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ORIGINAL PAPER

Prospective study of physical activity and risk of primary adenocarcinomas of the oesophagus and stomach in the EPIC (European Prospective Investigation into Cancer and nutrition) cohort

José María Huerta · Carmen Navarro · María-Dolores Chirlaque · María-José Tormo · Karen Steindorf · Genevieve Buckland · Fátima Carneiro · Nina Føns Johnsen · Kim Overvad · Jakob Stegger · Anne Tjønneland · Marie-Christine Boutron-Ruault · Françoise Clavel-Chapelon · Sophie Morois · Heiner Boeing · Rudolf Kaaks · Sabine Rohrmann · Matthäus Vigl · Pagona Lagiou · Dimitrios Trichopoulos · Antonia Trichopoulou · H. Bas Bueno-de-Mesquita · Evelyn M. Monninkhof · Mattijs E. Numans · Petra H. Peeters · Amalia Mattiello · Valeria Pala · Domenico Palli · Rosario Tumino · Paolo Vineis · Antonio Agudo · Eva Ardanaz · Larraitz Arriola · Esther Molina-Montes · Laudina Rodríguez · Björn Lindkvist · Jonas Manjer · Roger Stenling · Eiliv Lund · Francesca L. Crowe · Timothy J. Key · Kay-Tee Khaw · Nicholas J. Wareham · Mazda Jenab · Teresa Norat · Dora Romaguera · Elio Riboli · Carlos A. González

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Abstract
Objective To analyse the association between types of physical activity (occupational, recreational and household, vigorous and overall) and risk of primary oesophageal (OAC) or gastric adenocarcinoma (GAC).
Methods From nine European countries, 420,449 participants were recruited between 1991 and 2000 and followed-up for a mean of 8.8 years to register incident GAC and OAC. Information on physical activity (PA), diet, lifestyle and health-related variables was obtained at baseline. *Helicobacter pylori* infection status was considered in a subset of 1,211 participants. Analyses were repeated by tumour site (cardia/non-cardia) and histological type (intestinal/diffuse).

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J. M. Huerta · C. Navarro · M.-D. Chirlaque · M.-J. Tormo · E. Ardanaz · L. Arriola · E. Molina-Montes
CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain

J. M. Huerta · C. Navarro · M.-D. Chirlaque · M.-J. Tormo
Epidemiology Department, Regional Council of Health and Consumer Affairs, Murcia, Spain

K. Steindorf
Unit of Environmental Epidemiology, German Cancer Research Center, Heidelberg, Germany

G. Buckland · A. Agudo · C. A. González
Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology, Barcelona (ICO-IDIBELL), Spain

F. Carneiro
Institute of Molecular Pathology and Immunology of the University of Porto and Medical Faculty, Porto, Portugal

N. F. Johnsen · A. Tjønneland
Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen, Denmark

K. Overvad · J. Stegger
Department of Cardiology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark

K. Overvad
Department of Clinical Epidemiology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark

M.-C. Boutron-Ruault · F. Clavel-Chapelon · S. Morois
INSERM (ERI20) & Paris XI University, Institut Gustave-Roussy, Villejuif, France

H. Boeing · M. Vigl
German Institute of Human Nutrition, Potsdam-Rehbücke, Germany

Results During the follow-up, 410 GAC and 80 OAC occurred. A lower risk of overall and non-cardia GAC was found for increasing levels of a PA index which combined occupational PA with weekly time spent in sports and cycling. The hazard ratio (HR) of GAC was 0.69, 95% CI: 0.50–0.94, for the comparison between active and inactive participants according to the PA index (HR = 0.44, 95% CI:0.26–0.74, for non-cardia GAC). No effect was found for cardia tumours or histological subtypes of GAC. PA of any kind was not associated with OAC.
Conclusions Overall and distal (non-cardia) gastric tumours were inversely associated with time spent on cycling and sports and a total PA index. No association was found for any type of PA and risk of cardia cancers of the stomach.

Keywords Physical activity · Stomach cancer · Oesophagus cancer · EPIC

Introduction

The overall incidence of stomach adenocarcinomas, which represent 95% of total gastric tumours, has been steadily declining for several decades [1]. Nevertheless, gastric cancer still remains as the fourth most common type of cancer worldwide with 934,000 estimated new cases per year [2]. Furthermore, whereas this declining trend regards the incidence of the most common distal (i.e., non-cardia) forms of gastric adenocarcinomas (GAC), tumours of the proximal region of the stomach (cardia) and those of the gastro-oesophageal junction (GEJ) are increasing in high-income countries [3, 4]. Oesophageal cancer appears to follow a similar pattern, with overall figures falling but drastic increases in incident oesophageal adenocarcinomas (OAC) in Europe and the United States [3–5].

This common rising pattern of adenocarcinomas of the oesophagus and proximal stomach in Western affluent areas might suggest the existence of a shared environmental background that would account for a common aetiology of these less frequent, albeit increasing, types of cancer. Among those lifestyle factors that have been studied in relation to the risk of cancer, there is physical activity (PA). Several tumours, especially those of the colon, breast, lung and endometrium have been shown to be associated with –and, to a variable extent, preventable by– PA to date [6–10]. But the association in relation to gastric or oesophageal cancer has been less studied, and the evidence for a protective role of PA is not yet conclusive [6, 11–17]. Furthermore, most of the studies did not show results by site or histological type of the tumours. According to recently published prospective data, the putative protection of PA on gastric

R. Kaaks · S. Rohrmann
Division of Cancer Epidemiology,
German Cancer Research Center, Heidelberg, Germany

P. Lagiou · A. Trichopoulou
Department of Hygiene and Epidemiology,
University of Athens Medical School, Athens, Greece

D. Trichopoulos
Department of Epidemiology, Harvard School of Public Health,
Boston, MA, USA

D. Trichopoulos
Bureau of Epidemiologic Research, Academy of Athens, Athens,
Greece

A. Trichopoulou
Hellenic Health Foundation, Athens, Greece

H. Bas Bueno-de-Mesquita
National Institute for Public Health and the Environment
(RIVM), Bilthoven, The Netherlands

H. Bas Bueno-de-Mesquita
Department of Gastroenterology and Hepatology,
University Medical Center Utrecht, Utrecht, The Netherlands

E. M. Monninkhof · M. E. Numans · P. H. Peeters
Julius Center for Health Sciences and Primary Care,
University Medical Center Utrecht, Utrecht, The Netherlands

P. H. Peeters · P. Vineis · T. Norat · D. Romaguera · E. Riboli
Department of Epidemiology and Public Health,
Imperial College, London, UK

A. Mattiello
Department of Clinical and Experimental Medicine,
Federico II University, Naples, Italy

V. Pala
Department of Preventive and Predictive Medicine, Nutritional
Epidemiology Unit, Fondazione IRCSS Istituto Nazionale dei
Tumori, Milan, Italy

D. Palli
Molecular and Nutritional Epidemiology Unit,
CSPO-Scientific Institute of Tuscany, Florence, Italy

R. Tumino
Cancer Registry and Histopathology Unit,
Civile M.P.Arezzo Hospital, Ragusa, Italy

P. Vineis
ISI Foundation, Torino, Italy

E. Ardanaz
Public Health Institute of Navarra, Pamplona, Spain

L. Arriola
Public Health Department of Gipuzkoa, Basque Government,
San Sebastian, Spain

cancer might be dependent on tumour site [18] and sex [19, 20]. The evidence for an association between PA and oesophageal cancer is even more scarce [15, 16, 20].

Since previous evidence is limited, our aim was to analyse the association of PA with GAC and OAC within EPIC (European Prospective Investigation into Cancer and Nutrition), a large-scale prospective study conducted in over half a million participants across ten European countries.

Subjects and methods

EPIC is an ongoing multi-centre prospective study carried out in 521,448 participants, mostly aged 25–70, recruited in 23 centres from 10 European countries between 1992 and 2000. The main aim of the EPIC study was the investigation of lifestyle (including diet), metabolic and genetic determinants of cancer and other chronic diseases, with a large-scale prospective epidemiological setting. Extensive dietary information of the previous year was gathered by means of validated questionnaires. Anthropometrical and lifestyle data were collected at recruitment, as well as information related to health issues, such as history of previous illness (cancer, diabetes, cardiovascular problems), or surgical operations. Blood samples were collected from approximately 74% of the EPIC participants. The rationale and detailed methodological issues of the study have been addressed in full in previous publications [21, 22].

Subjects were recruited from the general adult population residing in a given town or geographical area. In some centres (France, Utrecht—the Netherlands and Naples—Italy), only women were invited to participate, whereas half of the Oxford cohort consisted of non-meat eaters, and a large proportion of participants from Spain and the Italian centres Ragusa and Turin were blood donors. All participants gave their written informed consent. The protocols of the study were approved by the Ethical Review boards of the International Agency for Research on Cancer (IARC, Lyon) and the respective national/local Ethical Committees.

Prevalent cancer cases of any site according to baseline questionnaires were excluded for the present analysis ($n = 23{,}633$). Further exclusions included subjects lost to follow-up ($n = 2{,}041$), those lacking dietary information ($n = 6{,}839$) and participants for whom PA data were not available, including the whole cohorts from Norway ($n = 37{,}725$) and Umeå ($n = 13{,}297$). Eight participants initially diagnosed with cancer but not confirmed as cancer cases after examination were excluded for analyses. The final study sample consisted of 420,449 participants (130,087 men and 290,362 women) from 9 European countries: Denmark, France, Germany, Greece, Italy, Spain, Sweden, the Netherlands and United Kingdom).

Exposure assessment

Occupational activity

Participants were asked to choose the category that most accurately described the physical demand of their job, out of four possible options: sedentary occupation (e.g., office work), standing occupation (e.g., hairdresser, shop assistant, security guard), manual work (e.g., plumber, electrician, carpenter, cleaner, nurse) and heavy manual work (e.g., docker, bricklayer, miner). Due to small numbers, manual and heavy manual categories were combined in the analyses.

E. Molina-Montes
Andalusian School of Public Health, Granada, Spain

L. Rodríguez
Public Health Directorate, Asturias, Spain

B. Lindkvist
Department of Internal Medicine, Division of Gastroenterology and Hepatology, Sahlgrenska University Hospital, Gothenburg, Sweden

J. Manjer
Department of Surgery, Malmö University Hospital, Malmö, Sweden

R. Stenling
Department of Medical Biosciences, University of Umeä, Umeä, Sweden

E. Lund
Institute of Community Medicine, University of Tromsø, Tromsø, Norway

F. L. Crowe · T. J. Key
Cancer Epidemiology Unit, University of Oxford, Oxford, UK

K.-T. Khaw
Department of Public Health and Primary Care, Institute of Public Health, School of Clinical Medicine, University of Cambridge, Cambridge, UK

N. J. Wareham
MRC Epidemiology Unit, Institute of Metabolic Science, University of Cambridge, Cambridge, UK

M. Jenab
Lifestyle, Environment and Cancer Group, International Agency for Research on Cancer (IARC), Lyon, France

J. M. Huerta (✉)
Servicio de Epidemiología, Consejería Sanidad y Consumo, Ronda de Levante, 11, 30008 Murcia, Spain
e-mail: jmhuerta.carm@gmail.com

Leisure-time PA (recreational and household)

Detailed information was gathered on time spent (in hours/week) on several recreational activities, both in summer and winter: walking, cycling (either when going to work or as a recreational activity), gardening, do-it-yourself activities and sport (e.g., soccer, keep-fit, swimming, jogging, tennis, gym…). Household activity was also assessed as the total number of hours per week spent doing the housework (cleaning, doing the washing, cooking, taking care of children…), and the flights of stairs climbed per day were registered. A leisure-time physical activity variable was then computed weighing the time spent in each activity (walking, cycling, gardening, sport, do-it-yourself activities, housework and stair climbing) by its specific intensity score [23] and expressed as MET-h/week. For leisure-time activity, sex-specific quartiles were computed.

Vigorous PA

Participants were asked to declare the total amount of time (in hours/week) when the engaging in any of these activities had been vigorous enough as to cause sweating or a faster heartbeat. Vigorous PA was defined as none, $\leq$2 and $>$2 h/week.

Overall activity index

An overall PA index was computed (Cambridge/Bilthoven PA Index, CPAI) by combining occupational activity and time spent in sport and cycling, as previously described [24]. This index consists of four ordinal categories: inactive, moderately inactive, moderately active and active (see "Appendix"). Participants not working or with missing occupational data were ranked according to time spent in sports and cycling, only. The CPAI was validated against objectives measures of physical activity energy expenditure (PAEE) as determined by heart rate monitoring (Spearman's $\text{rho}_{\text{CPAI-PAEE}} = 0.27$, $p < 0.05$; Ulf Ekelund, personal communication).

Follow-up procedures and endpoint assessment

Incident gastric and oesophageal tumours were identified through population cancer registries, except in France, Germany, Greece and Naples where other methods, including health insurance records, cancer and pathology hospital registries or active follow-up were used. Mortality data were based in national or regional mortality registries. Participants were censored at the date of diagnosis of a first incident tumour, death, loss to follow-up due to emigration or other cause, or end of follow-up, whichever came first. Closing date was that of the last complete follow-up, between December 2002 and 2005, depending on the study centre.

The 2nd edition of the International Classification of Diseases for Oncology [25] was used to code site (C15.0–C15.9: oesophagus, C16.0: gastric cardia and GEJ; C16.1–C16.8: stomach, non-cardia) and morphology (adenocarcinoma codes 8140/3, 8144/3 and 8145/3). The histological type was classified as intestinal or diffuse following the Laurén Classification [26].

An expert panel of pathologists was in charge of the validation of diagnosis and classification of tumours. The panel included a representative from each country participating in EPIC and a coordinator. Almost 60% of gastric tumours ($n = 245$) were histologically confirmed as adenocarcinomas by the panel. Pathology reports and protocol forms were used for tumour classification in 23% of cases ($n = 97$), and 17% of gastric adenocarcinomas ($n = 68$) were classified according to the codes provided by the cancer registries to the IARC central database. For oesophageal adenocarcinomas, these figures were 69% ($n = 55$), 15% ($n = 12$) and 16% ($n = 13$), respectively. The methodological issues on the panel validation procedures and criteria have been detailed elsewhere [27].

Statistical analyses

Mean values (and standard deviations) or percentages were used as descriptive statistics (Kruskall–Wallis and χ^2 tests were used to assess statistical significance). The risks of incident adenocarcinomas of the stomach and oesophagus were modelled through proportional hazards Cox regression, with attained age as the underlying time variable [28]. Entry time was defined as age at recruitment and exit time as age at case diagnosis or censoring. Models were stratified on age (in 1-year categories), and centre, to control for differences in study design, diagnosis and follow-up procedures. All analyses were adjusted for sex, height (m), weight (kg), educational level (no studies, primary, technical/professional school, secondary, university and missing), smoking status (never smoker, former smoker who quit $\geq$10 years ago, former smoker who quit less than 10 years ago, former smoker of unknown quitting, current smoker of $<$15 cigarettes/day, current smoker of 15–25 cigarettes/day, current smoker of $\geq$25 cigarettes/day, current smoker of unknown amount of cigarettes/day and missing), alcohol consumption at recruitment (g/day), energy intake (kcal/day) and daily consumption of fruit, red meat and processed meat (in g/day).

Separate regression models were defined to evaluate specific risks of gastric cancer by site (cardia and non-cardia) and histology (intestinal and diffuse). The interaction of the physical activity index with age and body mass index was evaluated with two-sided likelihood ratio tests

comparing models with and without the interaction term. We explored the potential modifying effect of *Helicobacter pylori* infection on the association between PA and risk of GAC. For this purpose, we used data from a previous nested case–control study of *H. pylori* infection in regard to risk of gastric cancer carried out within the EPIC cohort [29]. Details on laboratory methods have been reported elsewhere [29]. Unconditional logistic regression was applied to derive odds ratios of incident stomach adenocarcinoma risks by PA separately by infection status in the subset of cases and non-cases not meeting the exclusion criteria.

Analyses of the physical activity index were repeated after exclusion of cases diagnosed within the first 2 years ($n = 93$) from the date of recruitment. Sensitivity analyses were also performed excluding subjects with self-reported diabetes or cardiovascular problems at baseline ($n = 90{,}371$).

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were taken into consideration in the writing of the manuscript [30].

Results

For the present analysis, mean follow-up time was 8.8 years completing 3.7 million person-years. A total of 410 first primary incident GAC cases (85% of total incident gastric cancer cases) and 80 OAC (78% of the total) occurred during this time. The distribution of adenocarcinoma cases of the stomach and oesophagus by participating country is presented in Table 1. Distal adenocarcinomas of the stomach were more frequent than those of the cardia region. A similar number of intestinal and diffuse tumours were found, overall. In regard to OAC, almost all incident cases were diagnosed in northern European countries (Denmark, Sweden and United Kingdom), with very low number of cases in the Mediterranean area.

Subjects in the highest quartile of recreational PA had the highest body mass index (BMI), the highest intake of fruit and vitamin C and the lowest consumption of alcohol, red meat and β-carotene (Table 2). These participants had also attained a lower educational level and were more likely to report diabetes or cardiovascular problems at baseline. Smoking status also differed by levels of PA. Most people in the upper PA quartile were never smokers, whereas the higher frequency of smokers of $\geq$15 cigarettes/day was found in the lowest PA quartile.

The main results of the evaluation of the prospective association between PA and risk of incident gastric and oesophageal adenocarcinomas are shown in Table 3. Levels of occupational activity were not related to GAC or OAC. No association was found for occupational or overall leisure-time PA and risk of GAC (neither all types nor site- or histological-specific tumours). Overall PA as estimated by the CPAI showed a significant reduction in GAC risk between 25 and 38% for different categories of PA when compared to the inactive group (hazard ratio (95% CI) = 0.69 (0.50–0.94) for active vs. inactive participants). This lower risk was consistent across categories with a statistically significant linear trend ($p = 0.006$). This result was restricted to non-cardia adenocarcinomas of the stomach, whereas it was not observed for intestinal or diffuse types. Vigorous PA was

Table 1 Summary of incident adenocarcinomas of the stomach and oesophagus, by country

Country	Cohort		Person-years	GAC							OAC
				All[a]	Site			Histology			
	Women	Men			Cardia[a]	Non-cardia	Unspecified	Intestinal	Diffuse	Unspecified	
Denmark	29,296	26,796	419,668	65	27	22	16	20	13	32	25
France[b]	69,426	–	755,957	17	4	9	4	6	6	5	1
Germany	28,478	22,022	409,553	55	13	31	11	20	29	6	5
Greece	15,313	10,812	185,459	25	3	10	12	10	10	5	0
Italy[b]	31,106	14,299	383,574	62	11	34	17	23	23	16	2
Spain	25,357	15,452	403,052	55	8	32	15	23	19	13	1
Sweden	14,394	10,441	247,477	40	15	21	4	16	16	8	11
the Netherlands[b]	24,269	7,723	265,869	29	9	12	8	7	13	9	3
United Kingdom	52,723	22,542	631,757	62	33	17	12	23	10	29	32
Total	290,362	130,087	3,702,365	410	123	188	99	148	139	123	80

GAC gastric adenocarcinoma, *OAC* oesophageal adenocarcinoma

[a] Include tumours of the gastro-oesophageal junction

[b] The cohorts from France, Naples (Italy) and Utrecht (the Netherlands) were comprised of women only

Table 2 Distribution of variables of interest according to sex-specific quartiles (Q_1–Q_4) of leisure-time physical activity

	Q_1 $n = 105{,}274$	Q_2 $n = 105{,}155$	Q_3 $n = 105{,}025$	Q_4 $n = 104{,}995$
	Mean (standard deviation)			
Age at recruitment (year)	51.7 (9.4)	51.8 (10.0)	52.1 (10.4)	51.8 (10.4)
Height (cm)	165.6 (8.5)	166.1 (8.7)	165.6 (9.2)	164.9 (9.6)
Weight (kg)	69.3 (14.6)	69.6 (14.0)	70.5 (13.7)	71.3 (13.2)
Body mass index (kg/m^2)	25.2 (4.4)	25.1 (4.2)	25.7 (4.3)	26.2 (4.4)
Energy intake (kcal/d)	2,139.1 (686.5)	2,131.5 (659.2)	2,129.2 (665.9)	2,163.3 (704.9)
Alcohol intake (g/d)	14.3 (19.7)	14.0 (18.6)	13.1 (18.7)	11.9 (18.8)
Vegetable intake (g/d)	224.3 (146.8)	223.5 (146.8)	225.5 (153.5)	228.5 (162.0)
Fruit intake (g/d)	235.8 (191.2)	239.2 (191.3)	256.1 (203.4)	276.3 (226.3)
Red meat intake (g/d)	51.0 (39.6)	47.6 (38.1)	46.0 (37.2)	45.9 (36.5)
Processed meat intake (g/d)	31.1 (31.9)	31.0 (32.0)	31.0 (33.1)	31.0 (34.1)
Beta-carotene intake (microg/d)	3,447.7 (2,785.8)	3,549.7 (2,821.9)	3,467.6 (2,835.0)	3,304.8 (2,637.5)
Vitamin C intake (mg/d)	126.8 (69.9)	131.2 (70.8)	137.6 (74.2)	144.3 (81.0)
Fibre intake (g/d)	23.0 (8.8)	23.5 (8.6)	23.9 (8.7)	24.7 (9.2)
	N (%)			
Smoking status				
Never smoker	50,905 (48.4)	51,635 (49.1)	52,633 (49.6)	54,287 (51.7)
Former, quit $\geq$10 years ago	16,529 (15.7)	18,221 (17.3)	19,384 (18.3)	17,665 (16.8)
Former, quit <10 years ago	9,532 (9.1)	9,720 (9.2)	9,485 (8.9)	9,081 (8.6)
Former, quitting unknown	1,145 (1.1)	1,178 (1.1)	1,041 (1.0)	888 (0.8)
Current, <15 cigarettes/day	9,573 (9.1)	9,526 (9.1)	10,020 (9.5)	10,077 (9.6)
Current, 15–25 cigarettes/day	8,741 (8.3)	7,972 (7.6)	7,583 (7.2)	7,782 (7.4)
Current, $\geq$25 cigarettes/day	4,012 (3.8)	2,880 (2.7)	2,639 (2.5)	2,513 (2.4)
Current, unknown amount	2,384 (2.3)	2,250 (2.1)	2,081 (2.0)	1,967 (1.9)
Missing	2,453 (2.3)	1,773 (1.7)	1,159 (1.1)	735(0.7)
Educational level				
None	3,052 (2.9)	2,815 (2.7)	5,414 (5.2)	7,871 (7.5)
Primary school completed	21,700 (20.6)	21,452 (20.4)	25,058 (23.9)	29,756 (28.3)
Technical/professional school	18,164 (17.3)	22,516 (21.4)	24,090 (22.9)	24,444 (23.3)
Secondary school	29,193 (27.7)	24,466 (23.3)	20,521(19.5)	18,528 (17.6)
Longer (incl. University)	29,398 (27.9)	30,121 (28.6)	25,508 (24.3)	19,027 (18.1)
Missing	3,767 (3.6)	3,785 (3.6)	4,434 (4.2)	5,369 (5.1)
Cardiovascular problems reported				
No	73,939 (70.2)	72,056 (68.5)	69,907 (66.6)	71,493 (68.1)
Yes	19,572 (18.6)	19,851 (18.9)	21,759 (20.7)	23,002 (21.9)
Missing	11,763 (11.2)	13,248 (12.6)	13,359 (12.7)	10,500 (10.0)
Diabetes reported				
No	98,644 (93.7)	99,816 (94.9)	99,708 (94.9)	99,884 (95.1)
Yes	2,969 (2.8)	2,753 (2.6)	3,063 (2.9)	3,331 (3.2)
Missing	3,661 (3.5)	2,586 (2.5)	2,254 (2.1)	1,780 (1.7)

Sex-specific cut-off points ($Q1$–$Q2$: 51.1 (women), 34.0 (men); $Q2$–$Q3$: 82.5 (women), 56.6 (men); $Q3$–$Q4$: 123.3 (women), 87.0 (men)
All differences significant at $p < 0.001$ level

not associated with cancer risk in this analysis. For any variable studied, no effect of PA on the risk of developing OAC was found. Nevertheless, a closer analysis of different recreational activities revealed that participants regularly engaging in cycling and sport were less prone to develop GAC, especially at distal locations, whereas

Table 3 Hazard ratio of gastric adenocarcinoma, by tumour site and histology, and overall oesophageal adenocarcinoma according to levels of physical activity in the EPIC cohort

	Person-years	Gastric adenocarcinoma															Oesophageal adenocarcinoma		
		All			Site						Histology								
					Cardia			Non-cardia			Intestinal			Diffuse					
		n	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI
Physical activity at work																			
Sedentary occupation	1,018,685	76	1		23	1		35	1		26	1		28	1		15	1	
Standing occupation	961,691	75	1.27	0.91–1.77	21	1.42	0.77–2.61	36	1.18	0.73–1.90	23	1.08	0.60–1.92	27	1.11	0.64–1.92	14	1.61	0.77–3.41
Manual work	380,532	42	0.92	0.62–1.37	11	0.70	0.33–1.48	16	0.82	0.44–1.52	15	0.84	0.43–1.63	14	1.07	0.54–2.11	10	0.95	0.41–2.20
p for trend			0.827			0.489			0.852			0.938			0.739			0.953	
Recreational and household physical activity[a]																			
Low	969,141	95	1		26	1		43	1		40	1		24	1		22	1	
Medium	933,323	91	0.98	0.73–1.31	33	1.21	0.72–2.03	37	0.89	0.57–1.38	31	0.84	0.52–1.35	31	1.34	0.78–2.29	18	0.74	0.40–1.40
High	906,320	104	0.97	0.73–1.30	33	1.13	0.67–1.92	47	0.94	0.61–1.45	34	0.83	0.51–1.32	41	1.43	0.85–2.43	23	0.93	0.51–1.69
Very high	893,580	120	1.07	0.80–1.43	31	0.97	0.56–1.69	61	1.15	0.76–1.76	43	0.97	0.61–1.54	43	1.42	0.83–2.43	17	0.63	0.32–1.22
p for trend			0.513			0.786			0.358			0.752			0.399			0.184	
Vigorous physical activity																			
None	1,672,058	198	1		51	1		92	1		73	1		72	1		31	1	
≤2 h/week	780,548	61	0.90	0.66–1.23	16	0.68	0.38–1.24	30	1.15	0.73–1.81	22	1.06	0.63–1.78	19	0.74	0.43–1.27	13	0.70	0.35–1.39
>2 h/week	613,931	58	0.92	0.67–1.23	25	1.14	0.68–1.91	23	0.98	0.60–1.60	23	1.10	0.66–1.81	16	0.74	0.42–1.32	13	0.72	0.36–1.42
p for trend			0.601			0.732			0.997			0.635			0.299			0.319	
Cambridge physical activity index																			
Inactive	842,268	140	1		34	1		72	1		55	1		42	1		24	1	
Moderately inactive	1,287,380	132	0.75	0.59–0.97	41	1.05	0.65–1.70	63	0.67	0.47–0.96	46	0.78	0.51–1.17	45	0.74	0.48–1.15	25	1.08	0.60–1.95
Moderately active	904,799	69	0.62	0.46–0.84	23	0.93	0.53–1.63	31	0.54	0.34–0.84	26	0.74	0.45–1.21	29	0.74	0.45–1.23	16	1.05	0.54–2.07
Active	667,918	69	0.69	0.50–0.94	25	1.05	0.59–1.86	22	0.44	0.26–0.74	21	0.67	0.39–1.16	23	0.69	0.40–1.20	15	0.98	0.48–2.01
p for trend			0.006			0.994			0.001			0.130			0.202			0.951	

Analyses stratified on centre and age, and adjusted for sex, height, weight, educational level, smoking status, alcohol consumption and daily intake of total energy, fruit, red meat and processed meat

Numbers in subgroup analyses by site and histology do not add up because of cases with mixed or unspecified location or histological type

[a] Sex-specific quartiles. Tests for trend based on median MET-h/week values within quartiles: Low: 36.0 (women), 22.0 (men); Medium: 66.4 (women), 45 (men); High: 100.6 (women), 70.0 (men); Very high: 153.7 (women), 114.1 (men)

Table 4 Hazard ratio of gastric adenocarcinoma, by tumour site and morphology, and overall oesophageal adenocarcinoma according to levels of recreational physical variables in the EPIC cohort

	Person-years	Gastric adenocarcinoma																Oesophageal adenocarcinoma		
		All			Site						Histology									
					Cardia			Non-cardia			Intestinal			Diffuse						
		n	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI
Walking (MET-h/week)																				
Never	272,095	23	1		8	1		12	1		10	1		7	1		10	1	
T1	1,265,080	148	1.69	1.07–2.66	49	1.67	0.78–3.60	66	1.51	0.80–2.88	57	1.61	0.80–3.21	49	1.79	0.78–4.09	28	0.81	0.38–1.74
T2	1,213,274	120	1.42	0.89–2.27	32	1.24	0.56–2.77	56	1.33	0.69–2.56	45	1.25	0.61–2.56	38	1.41	0.60–3.30	24	0.83	0.38–1.81
T3	951,915	119	1.57	0.98–2.52	34	1.38	0.62–3.10	54	1.45	0.74–2.84	36	1.03	0.49–2.17	45	1.94	0.83–4.56	18	0.73	0.32–1.67
All active[a]	3,430,269	387	1.57	1.01–2.44	115	1.47	0.70–3.08	176	1.44	0.77–2.67	138	1.34	0.69–2.62	132	1.70	0.76–3.79	70	0.80	0.39–1.62
p for trend across categories			0.655			0.863			0.769			0.162			0.291			0.590	
p for trend (continuous)			0.372			0.784			0.339			0.268			0.291			0.719	
Gardening (MET-h/week)																				
Never	1,493,992	160	1		36	1		80	1		65	1		50	1		26	1	
T1	917,591	91	1.15	0.88–1.51	26	1.12	0.66–1.90	39	1.10	0.74–1.65	28	0.93	0.59–1.49	35	1.63	1.03–2.58	22	1.04	0.58–1.88
T2	600,032	66	0.89	0.66–1.20	27	1.13	0.67–1.91	28	0.92	0.59–1.44	20	0.64	0.38–1.07	26	1.46	0.89–2.40	17	0.72	0.38–1.36
T3	690,749	33	0.97	0.74–1.28	34	1.10	0.66–1.84	41	1.04	0.70–1.56	35	0.79	0.50–1.23	28	1.25	0.76–2.04	15	0.49	0.25–0.97
All active[a]	2,208,373	190	1.01	0.81–1.25	87	1.12	0.73–1.70	108	1.03	0.75–1.41	83	0.79	0.55–1.12	89	1.45	1.00–2.10	54	0.74	0.44–1.23
p for trend across categories			0.707			0.712			0.922			0.356			0.421			0.035	
p for trend (continuous)			0.585			0.406			0.221			0.385			0.753			0.435	
Cycling (MET-h/week)																				
Never	2,183,472	259	1		70	1		128	1		97	1		84	1		42	1	
T1	545,646	51	0.79	0.58–1.09	19	1.06	0.62–1.81	19	0.57	0.35–0.95	17	0.84	0.49–1.44	15	0.65	0.37–1.16	12	1.26	0.64–2.49
T2	515,350	52	0.76	0.56–1.05	14	0.71	0.39–1.30	26	0.76	0.48–1.19	19	0.88	0.52–1.49	22	0.90	0.54–1.50	13	1.28	0.66–2.50
T3	457,897	48	0.74	0.53–1.03	20	1.12	0.65–1.95	15	0.47	0.26–0.83	15	0.76	0.42–1.36	18	0.74	0.42–1.30	13	1.37	0.69–2.71
All active[a]	1,518,892	151	0.76	0.61–0.96	53	0.95	0.64–1.43	60	0.61	0.43–0.85	51	0.83	0.57–1.22	55	0.76	0.52–1.13	38	1.30	0.79–2.15
p for trend across categories			0.066			0.879			0.014			0.348			0.423			0.368	
p for trend (continuous)			0.228			0.975			0.174			0.855			0.270			0.969	
Sport (MET-h/week)																				
Never	1,886,756	269	1		72	1		128	1		99	1		84	1		56	1	
T1	683,401	68	0.97	0.74–1.27	23	1.31	0.81–2.13	29	0.90	0.59–1.36	23	1.06	0.66–1.69	31	1.31	0.86–2.01	10	0.74	0.37–1.47
T2	584,221	35	0.66	0.46–0.95	11	0.80	0.42–1.54	18	0.72	0.43–1.19	15	0.93	0.53–1.62	11	0.61	0.32–1.16	9	0.80	0.39–1.63
T3	547,986	38	0.75	0.53–1.06	17	1.27	0.73–2.18	13	0.58	0.32–1.03	11	0.71	0.37–1.34	13	0.77	0.42–1.40	5	0.47	0.19–1.20
All active[a]	1,815,609	141	0.81	0.66–1.01	51	1.14	0.78–1.67	60	0.75	0.54–1.04	49	0.92	0.64–1.32	55	0.95	0.66–1.36	24	0.68	0.41–1.12

Table 4 continued

	Person-years	Gastric adenocarcinoma												Oesophageal adenocarcinoma		
		All			Site				Histology							
					Cardia			Non-cardia		Intestinal		Diffuse				
	n	*n*	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI	*n*	HR	95% CI
p for trend across categories			0.043			0.522			0.037			0.357			0.293			0.119	
p for trend (continuous)			0.188			0.259			0.220			0.387			0.631			0.099	

Analyses stratified on centre and age, and adjusted for sex, height, weight, educational level, smoking status, alcohol consumption and daily intake of total energy, fruit, red meat and processed meat

Numbers in subgroup analyses by site and histology do not add up because of cases with mixed or unspecified location or histological type

T1, T2, T3: sex-specific tertiles among practisers

Tests for trend across categories based on the sex-specific median values within tertiles

[a] (T1 + T2 + T3) versus Never

the habit of walking was associated with an increased GAC risk (Table 4).

In our analyses involving $n = 1{,}211$ participants of a prior nested case–control study [22], *Helicobacter pylori* was detected in 83.2% of cases ($n = 163$) and 68.7% of non-cases ($n = 697$). In this subset of participants, a significant interaction was detected between *H. pylori* infection with type of occupation and recreational PA (Table 5). Nevertheless, there were no significant associations or a clear trend in regard to GAC in separate analyses for infected and not infected participants. The association between the total PA index and GAC persisted when adjusting for *H. pylori* seroprevalence.

Discussion

Overall physical activity (PA) was associated with a significant reduction in risk of developing total and non-cardia gastric adenocarcinomas in this study. No association overall was seen for increased PA in regard to OAC. Even when previous epidemiological data suggested the possibility of an independent association between physical activity and risk of tumours of the stomach and the oesophagus [11, 15, 16], the analysis of such relationship had not been sufficiently addressed in the context of large prospective studies until recently. Our study provides valuable results for gaining insight into this association [17–20].

Physical activity at work

A sizeable amount of the daily PA among workers is determined by the physical demand of their job. A sedentary job might add to a sedentary lifestyle in the promotion of overweight and obesity [6]. Nevertheless, we did not find a significant risk reduction in those subjects with manual or standing occupations when compared to sedentary workers, in regard to GAC or OAC. These null results agree with previous existing literature [15, 22] and do not support the finding by Severson et al. [14] relating gastric cancer risk with moderate or heavy working activities.

Leisure-time activity

The daily amount of recreational PA, probably the most variable component of energy expenditure, largely reflects individual preferences and health-based decisions (household activities are less subject to free choice). As such, recreational activity represents the key PA component in terms of prevention [31]. Whereas our study does not support an overall protective role for leisure-time PA

Table 5 Odds ratio of incident gastric adenocarcinoma (GAC) by physical activity levels, according to *Helicobacter pylori* infection status

	H. pylori-negative GAC			*H. pylori*-positive GAC			All GAC[a]		
	Non-cases/cases	OR	95% CI	Non-cases/cases	OR	95% CI	Non-cases/cases	OR	95% CI
Physical activity at work									
Sedentary occupation	96/5	1		124/29	1		220/34	1	
Standing occupation	37/8	5.37	1.13–25.57	110/24	1.06	0.55–2.04	147/32	1.36	0.77–2.42
Manual work	34/3	1.03	0.16–6.46	87/16	0.83	0.40–1.74	121/19	0.89	0.46–1.73
p for trend	0.434			0.634			0.649		
			p for interaction = 0.049						
Recreational and household physical activity[b]									
Low	54/6	1		138/35	1		192/41	1	
Medium	71/11	2.99	0.68–13.12	151/37	0.92	0.53–1.60	222/48	1.01	0.62–1.64
High	88/12	2.55	0.63–10.40	189/39	0.76	0.44–1.32	277/51	0.88	0.54–1.43
Very high	105/4	0.50	0.09–2.62	219/52	0.90	0.53–1.53	324/56	0.89	0.55–1.43
p for trend	0.203			0.709			0.526		
			p for interaction = 0.040						
Vigorous physical activity									
None	137/10	1		369/84	1		506/94	1	
≤2 h/week	42/9	3.29	0.77–14.05	75/24	1.29	0.72–2.32	117/33	1.54	0.93–2.58
>2 h/week	60/4	0.74	0.14–3.95	74/21	1.15	0.62–2.11	134/25	1.03	0.60–1.78
p for trend	0.916			0.752			0.778		
			p for interaction = 0.297						
Cambridge physical activity index									
Inactive	82/10	1		220/56	1		302/66	1	
Moderately inactive	104/11	0.94	0.26–3.42	213/60	1.00	0.65–1.56	317/71	0.99	0.67–1.47
Moderately active	70/9	1.77	0.45–6.93	147/23	0.56	0.32–0.98	217/32	0.64	0.39–1.05
Active	62/3	0.22	0.04–1.27	177/24	0.70	0.39–1.27	179/27	0.60	0.36–1.05
p for trend	0.229			0.072			0.024		
			p for interaction = 0.101						

$n = 1{,}211$

Unconditional logistic regression adjusted for age, sex, centre, height, weight, educational level, smoking status, alcohol consumption and daily intake of total energy, fruit, red meat and processed meat

p for interaction between categories of physical activity and *H. pylori* infection status was based on the likelihood ratio test between models with and without the interaction term

[a] Additionally adjusted for *H. pylori* seroprevalence

[b] Sex-specific quartiles. Tests for trend based on median MET-h/week values within sample quartiles: low: 36.0 (women), 22.0 (men); medium: 66.4 (women), 45 (men); high: 100.6 (women), 70.0 (men); very high: 153.7 (women), 114.1 (men)

(neither household nor recreational PA separately; data not shown), a more in-depth analysis suggested an inverse association for cycling and sporting activities (but direct for walking) and risk of GAC (Table 4). This association was site-specific, restricted to distal tumours, but unrelated to the histological type. It could be speculated that only physiologically demanding activities would be of a sufficient magnitude as to exert a relevant health effect [11, 32], but our data do not fully support this speculation. On the one hand, only those activities with high MET values were inversely associated with GAC ($MET_{cycling/sport} = 6$). On the other hand, the amount of vigorous PA was not associated with risk of GAC or OAC. This finding is in disagreement with previous evidence [16]. However, reported vigorous PA would not necessarily be expected to decrease the risk of the disease. An exercise would cause sweating or increased heartbeat when the intensity is high, but also when the physical fitness of the individual is poor, which would have a very different meaning in relation to cancer risk. Besides, high-intensity PA may be less prone to misclassification than other activities of light or moderate intensity (e.g., walking). Our results would support the practice of regular exercise of moderate to high intensity rather than episodes of exhausting activity.

Overall physical activity

The CPAI (see "Appendix") was designed to capture relevant variability in overall PA by combining PA at work and recreational activities (sports and cycling), so that the ranking of participants reflected actual differences in PA [22]. Our results suggest a protective role of PA against GAC (but not OAC), showing a significant decrease in risk of non-cardia tumours by increasing PA categories of the index. The hazard ratio (HR) for the 'active' relative to the 'inactive' group was 0.44 (95% CI: 0.26–0.74; p for trend = 0.001). For total GAC, this HR was 0.69 (95% CI: 0.50–0.94). Few studies have analysed the effect of PA and risk of gastric cancer separately by site or histological type. A previous case–control study conducted in Canada estimated average lifetime PA of the participants and found this measure to be inversely associated with risk of total and cardia gastric cancer risk [11]. For non-cardia tumours, the age- and sex-adjusted inverse association found was weakened after controlling for a series of confounders in multivariate models. All those variables were controlled for in our analyses, except the Western dietary pattern. Nevertheless, we adjusted for those elements of this pattern of greater relevance for gastric or oesophageal cancer risk, such as consumption of red and processed meat, fruit, alcohol and total energy intake [6, 33, 34]. Other potential confounders tested (such as vegetable and fibre intake) had no significant effect on the associations under study (<5% coefficient change) and were finally discarded due to efficiency reasons. Therefore, it is not likely that the discrepant results could be attributed to residual confounding by diet. Only two previous prospective studies have reported results by site [18, 20]. In the first, recreational PA was associated with a significant reduction in non-cardia cancer risk [18]. Unfortunately, the authors did not include cardia tumours in their analysis. The second one showed an independent association for non-cardia adenocarcinomas only [20]. According to the available evidence, PA may be regarded as protective in relation to distal (non-cardia) forms of gastric cancer, although an effect would be more expected to be observed at cardia locations, which are probably associated with obesity [35]. Further prospective evidence might be needed before these results can be considered as conclusive.

The mechanisms by which increased physical activity could affect the risk of gastric or other types of cancer are largely unknown. Both generalised and site-specific effects have been alleged to account for a protection of PA on overall cancer risk [6, 31, 36–38]. An effect on chronic inflammation or the modulation of oxidative stress would be plausible mechanisms, but it is unclear whether PA is able to inhibit any (or both) of them. In our study, we did not find indications that the significant association of PA and stomach cancer risk could be mediated by an effect of PA on body fat deposition (adjustment or stratification by BMI categories did not reveal significant interactions). The same was reported by others for overall [18] and non-cardia GAC [20]. Although a potential influence of sex-related factors cannot be discarded, we found no significant interactions by sex overall (data not shown). Of interest is that, recently, increased physical activity has been associated with the methylation level of CACNA2D3, a gene involved in the regulation of cell cycle [39]. This gene was found to be hypermethylated (i.e., silenced) in cultured gastric cancer cell lines [40]. Whether PA would be capable of epigenetic silencing of CACNA2D3 would first need to be established.

We studied the potential modulation of the PA effect on gastric cancer due to infection by *H. pylori*. Chronic inflammation of the gastric mucosa is an early event in *H. pylori*-associated gastric tumorigenesis. Our results do not clearly support that infection by *H. pylori* would be able to modulate the effect of PA on GAC risk. Although interactions by infection status were significant for different types of PA, the low number of cases analysed does not allow us to draw firm conclusions on this topic. Since no other study has taken into consideration *H. pylori* seroprevalence when analysing PA and GC risk, further research is needed to elucidate this point.

The EPIC study provides a unique epidemiological framework for testing PA and cancer interactions. The size and geographical distribution of the cohort was aimed at maximising the variability in exposures and confounders, and the prospective design makes it possible to assess the long-term effect of PA. The CPAI has been validated against measurements of energy expenditure based in heart rate monitoring. Although the correlation was not impressive ($r = 0.27$), the index was consistent across centres and suitable for ranking individuals (Ulf Ekelund, personal communication). Another strength is that bias due to outcome misclassification has largely been eliminated because the majority of cases were confirmed by a panel of expert pathologists. Further considerations apply when interpreting these results. First of all, the limited statistical power due to the low number of endpoint cases, in spite of the long follow-up period. The assessment of PA was indirect, based on an administered questionnaire, and some degree of misclassification may exist. Medical advice to increase PA could have occurred in participants with chronic disease at baseline. We therefore performed sensitivity analyses excluding those participants reporting diabetes or cardiovascular problems at recruitment. Neither the exclusion of these patients nor the GAC cases diagnosed within the first 2 years of follow-up modified the results noticeably. In spite of reported differences in recreational PA [41] and prevalence of *H. pylori* infection [42] across

Table 6 Classification of physical activity based on occupational activity and practice of sports and cycling (Cambridge Physical Activity Index, CPAI)

	Leisure-time physical activity (Duration of sport and cycling in hours/week)			
Work activity	No	≤3.5	>3.5 and ≤7.0	>7.0
Sedentary	Inactive	Moderately inactive	Moderately active	Active
Standing	Moderately inactive	Moderately active	Active	Active
Manual	Moderately active	Active	Active	Active
Heavy manual	Active	Active	Active	Active
Non-worker/unknown	Inactive	Moderately inactive	Moderately active	Active

European countries, we found no significant heterogeneity by region (North vs. South; data not shown). The use of sex-specific cut-offs and the stratification by study centre should account for the variability in leisure-time PA by sex and country. A concern in relation to age arises when considering that 'inactive' participants were much older, on average, than those classified in any other PA category. While not an unexpected finding (older people reporting less PA), it is a disturbing one if taking into account that the 'inactive' group was set as the reference category for analyses. We cannot discard here the possibility of reverse causation if older people suffering from chronic gastritis (precursor of GAC) would have reduced their level of PA. In order to control for its effect in Cox models, we defined age as the underlying time variable and further stratified the models by 1-year categories, allowing comparisons within age strata instead of simply controlling for its effect in a cohort-wide model. In stratified analyses, the association with the CPAI remained significant only in the 55- to 60-year-old group, although there was no heterogeneity overall (data not shown). Finally, as in any observational study, the possibility of residual confounding cannot be totally discarded.

In conclusion, we present prospective data showing a decreased risk of gastric adenocarcinoma associated with higher levels of PA. This association manifested principally in non-cardia tumours, whereas no effect was found for PA in relation to intestinal/diffuse forms of GAC or OAC. Further studies should be aimed at clarifying whether these associations would be causal.

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Appendix

See Table 6.

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