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SOCIOECONOMIC POSITION AND HEALTH

Socioeconomic position and the risk of gastric and oesophageal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST)

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Objectives To evaluate the association of socioeconomic position with adenocarcinoma of the oesophagus and stomach.

Methods The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort comprises about 520 000 participants mostly aged 35–70 years. Information on diet and lifestyle was collected at recruitment. After an average follow-up of 6.5 years, 268 cases with adenocarcinoma of the stomach and 56 of the oesophagus were confirmed. We examined the effect of socioeconomic position on cancer risk by means of educational data and a computed Relative Index of Inequality (RII). In a nested case-control study, adjustment for Helicobacter pylori (*H. pylori*) infection was performed.

Results Higher education was significantly associated with a reduced risk of gastric cancer [vs lowest level of education, hazard ratio (HR): 0.64, 95% Confidence intervals (CI): 0.43–0.98]. This effect was more pronounced for cancer of the cardia (HR: 0.42, 95% CI: 0.20–0.89) as compared to non-cardia gastric cancer (HR: 0.66, 95% CI: 0.36–1.22). Additionally, the inverse association of educational level and gastric cancer was stronger for cases with intestinal (extreme categories, HR: 0.13, 95% CI: 0.04–0.44) rather than diffuse histological subtype (extreme categories, HR: 0.71 95% CI: 0.37–1.40). In the nested case-control study, inverse but statistically non-significant associations were found after additional adjustment for *H. pylori* infection [highest vs lowest level of education: Odds ratio (OR) 0.53, 95% CI: 0.24–1.18]. Educational level was non-significantly, inversely associated with carcinoma of the oesophagus.

Conclusion A higher socioeconomic position was associated with a reduced risk of gastric adenocarcinoma, which was strongest for cardia cancer or intestinal histological subtype, suggesting different risk profiles according to educational level. These effects appear to be explained only partially by established risk factors.

Keywords Socioeconomic position, gastric cancer, *Helicobacter pylori*, EPIC

Introduction

Over the past few decades, the incidence rate of gastric cancer has declined. However, it remains among the most common cancer sites world-wide.[1,2] In some countries, an increase in adenocarcinomas of the oesophagus, gastric cardia and the gastro-oesophageal junction (GEJ) was noticed.[3] It has been suggested that these three cancer sites form a single disease entity,[3] since they share the same epidemiological risk factors that are associated with a specific diet (low fruit and vegetable consumption), smoking habits, obesity, gastro-esophageal reflux disease and physical inactivity seen as typical for a western lifestyle.[4,5]

Socioeconomic inequalities were shown to be strongly associated with mortality and morbidity.[6–9] The risk of gastric and oesophageal cancers has also been associated with a lower socioeconomic position as measured by educational level,[10–14] occupation[12,14] or income.[10,15] The infection with Helicobacter pylori (*H. pylori*) bacterium is positively associated with gastric cancer. Since this infection is frequently acquired in childhood, education as a marker for childhood socioeconomic position may be of particular interest.[16] Most of these studies were case-control studies; however cohort studies have also found a higher educational level to be associated with a lower gastric cancer risk.[10,12]

The pathways through which the socioeconomic position influences gastric cancer risk are not established, but are likely to reflect differences in smoking,[17] diet[4,18] and infection with H. *pylori*.[19] Chronic gastritis is another potential risk factor for gastric cancer.[20,21] There is some evidence that the magnitude of these risk factors may differ by anatomical subtype.[3]

The aim of this study was to examine the association between socioeconomic position and the risk of adenocarcinomas of the stomach and oesophagus in the European Prospective Investigation into Cancer and Nutrition (EPIC), after taking into account other identified risk factors. *H. pylori* seroprevalence was assessed in a nested case-control study. In addition, differential effects by anatomical subsites and histological subtypes of gastric cancer were investigated.

Material and methods

Study subjects

EPIC is a multicentre prospective cohort study designed to investigate the relation between diet, lifestyle factors and risk of cancer. Approximately 520 000 subjects, mainly aged between 35 and 70 years, were recruited in 10 European Countries (Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom) between 1992 and 2000.

The study subjects were largely recruited from the general population residing in a given geographical area. Exceptions were the French cohort (members of the school health insurance and University employees), the Utrecht and the Florence cohorts (women attending breast cancer screening), part of the Italian and Spanish cohort (blood donors and their spouses), and most of the Oxford cohort (vegetarian volunteers and healthy eaters), details of which are provided elsewhere.[22,23] In brief, eligible subjects were invited to participate in the study by mail or by personal contact. Those who accepted gave informed consent and completed a lifestyle and dietary questionnaire. The majority of subjects also provided a blood specimen and had anthropometric measurements taken. Educational level was reported from 460 648 participants (7250 participants with missing data and 10 443 participants with non-assigned education were excluded). Furthermore, the Norwegian subcohort ($n = 35\,229$) was excluded due to the short follow-up and small number of incident cases, leaving 425 613 subjects (287 038 of whom were women) for the present analysis.

Since the French subcohort of 64 692 women consisted of educational employees only, this subcohort was only excluded from the analysis of the Relative Index of Inequality (RII), leaving 360 651 subjects (222 074 women) for this investigation.

Diet and lifestyle questionnaires

Habitual diet over the previous 12 months was measured at recruitment by a country-specific validated self- or interviewer-administered questionnaire. Most centres adopted a self-administered questionnaire, which comprised between 84 and 266 food items. Some centres additionally used 7- or 14-day dietary records. Lifestyle data were derived from questions on education, occupation, lifetime smoking and alcohol consumption, reproductive history, medical history and physical activity.

End points

Incident cancer cases were identified by population-based cancer registries (Denmark, Italy, The Netherlands, Spain, Sweden and the United Kingdom) or by active follow-up (France, Germany and Greece). Follow-up began at the date of recruitment and ended at either the date of diagnosis of gastric or oesophageal cancer, death or date of the last complete follow-up. A total of 400 incident stomach cancer and 67 oesophageal cancer cases had been reported to the central database at the International Agency for Research on Cancer (IARC) for the period up to December 1999, or September 2002, depending on the study centre. Cancer of the stomach included cancers coded as C16 according to the 10th Revision of the International Statistical Classification of Diseases, Injuries and Causes of Death (ICD). Validation of the diagnosis and classification of the tumours (according to ICD-O2 classification) was carried out by a panel of pathologists, details of which have been reported elsewhere.[23]

We excluded cases of gastric lymphomas ($n = 26$), gastric stump tumours ($n = 5$), other non-adenocarcinoma cases ($n = 11$), and other unspecified tumours of the stomach ($n = 8$). In addition, individuals who were in the top or bottom 1% of energy intake (seven cases) or with missing data on diet or educational attainment (75 cases) were excluded from the analysis. The Lauren classification was used to define histological subtypes, considering the two main subtypes (diffuse and intestinal) in further analyses.[24] For a number of reasons, some gastric cancer cases could not be classified by anatomical subsite or histological subtype. The analysis of cardia cancers included the 17 GEJ tumours in addition to the 68 cardia gastric cancer cases.

Nested case-control study

Design details of the nested case-control study, including the laboratory work, have been described extensively elsewhere.[25] In brief, for each newly diagnosed gastric cancer case with available blood sample for laboratory analysis ($n = 215$), four controls individually matched by centre, gender, age ($\pm$2.5 years) and blood donation date ($\pm$45 days) were randomly selected. Serum samples values above 100 arbitrary enzyme-linked immunosorbent assay units (EU) were considered as positive for anti-H. *pylori* immunoglobulin G (IgG) antibodies (84.2% of cases and 66.9% controls were positive).

Socioeconomic position

Educational level was used to characterize the participants for socioeconomic position. Four categories were used in the analyses defined as (i) primary school or less, (ii) vocational secondary education, (iii) other secondary education and (iv) college or university. Subjects without school attendance were assigned to the lowest educational level. In addition, the RII[26] was calculated. Comparisons of measures between socioeconomic indicators suffer from unequal group sizes. The RII was constructed to avoid the problem of large ratios of risk due to small groups at the edges. The classification is based on a hierarchical order of education. Assignment was performed by ranking the distribution of the educational level according to the proportion of participants within strata for study centres, 10-year age groups and sex. The midpoint of each class of the cumulative proportional distribution of educational level was used to calculate the score of the RII. For example, if within a stratum (centre, age group, sex) 40% of subjects have a low education level, the midpoint of this group was chosen and each cohort member in that stratum would be assigned a score of 20, corresponding to the proportion of population above this midpoint. If the proportion of subjects in the next educational group with a medium education level was 30%, the score would be 55 (40 plus 30/2). Accordingly, the remaining 30% of subjects in this stratum with high educational level would receive a score of 85 ($40 + 30 + 30/2$). Participants were assigned to a RII score of 1 (low), 2 (middle) or 3 (high) based on tertiles of the values.

Statistical methods

Cox proportional hazard regression models (SAS PHREG procedure) were used for the analyses of the cohort data. The analyses were stratified by sex, age and centre to control for potential confounding due to differences in follow-up procedures, questionnaire design and other centre-specific characteristics. Age was used as the time scale variable in all models. Time at entry into the study was defined as age at recruitment, and time at exit was defined as age of diagnosis (for cases) or age at censoring (for at-risk subjects). Crude and multivariate models were calculated. The following variables were considered for adjustment: height (m, continuous), weight (kg, continuous), smoking habits [never smoked, former smoker (ceased smoking ≥10 years, ceased <10 years, unknown), current smoker (<15, 15–25, ≥25, unknown cigarette/day), and unknown smoking status], lifelong average cigarette smoking (cigarette/day), duration of smoking (years), alcohol intake (g/day, quintiles), lifelong alcohol drinking (g/day quintiles, unknown), overall physical activity [metabolic equivalent of energy expenditure score (METs)], total energy intake (kcal/day, quintiles) consumption of meat and processed meat (g/day, quintiles), fruits (g/day, quintiles), and vegetables (g/day, quintiles). Initially, analyses were done for men and women separately, but because no substantial gender differences emerged, results are presented for both sexes combined. Analyses of gastric cancer using anatomical subsites and histological subtypes were performed.

We tested for heterogeneity of effect between different variables using Wald statistics.[27] Conditional logistic regression analysis (SAS PHREG procedure) was used to calculate the odds ratios (OR) and 95% confidence intervals (95% CI) in the nested case-control study, controlling for the variables as in the full cohort study as well as H. *pylori* seroprevalence. SAS statistical software 9.13 (SAS institute Inc, Cary, NC) was used for all statistical analyses.

Results

The cohort of 425 613 participants was followed for an average of 6.5 (SD = 1.8) years with a total of 2 765 038 person-years. Table 1 shows the number of incident cancer cases and person-years at risk in each participating country. In total, 268 cases of gastric adenocarcinoma, 56 cases of oesophageal adenocarcinoma, and 17 cases of cancers at the GEJ were identified. Cases were more likely to be smokers and to be older than non-cases (data not shown). The mean age of the subjects with gastric cancer was 58.8 years in men and 58.2 years in women.

Table 2 shows the distribution of baseline characteristics stratified by educational level in men and women separately. Subjects in the highest education category were leaner (only in women), had a higher lifelong intake of alcohol in women but a lower in men, higher vegetable intake (in women) and a lower intake of meat, lower duration of smoking and lower prevalence of high cigarette smokers than those in the lowest education category. Subjects in the highest education category also had a lower prevalence of *H. pylori* infections than those in the lowest education category. With regarding to fruit consumption, no clear educational gradient was found.

Overall,a higher educational level was significantly inversely associated with risk of gastric adenocarcinoma [highest vs lowest level of education: HR 0.64, 95% CI: 0.43–0.98] (Table 3). No statistically significant heterogeneity between countries was observed (data not shown). In the analysis by subsite of gastric cancer, a significant and strong negative association between education and cancer risk was observed for cases in the cardia subsite (highest vs lowest level of education HR 0.42, 95% CI: 0.20–0.89), while a non-significant negative association was observed for non-cardia gastric cancer (P for heterogeneity = 0.16). With histological subtype, a strong negative association was also observed for the intestinal type (highest vs lowest level of education HR 0.13, 95% CI: 0.04–0.44), while a non-significant negative association was observed for the diffuse type (P for heterogeneity = 0.42). Due to the low number of cases, further analysis by both subsite and subtype of gastric cancer was not possible.

In the nested case-control study (Table 4), an inverse but statistically non-significant association was found after additional adjustment for *H. pylori* infection (highest vs lowest level of education: OR 0.53, 95% CI: 0.24–1.18). A non-significant inverse association was also found for educational

Table 1 Description of the gastric and oesophageal adenocarcinoma cases in the EPIC cohort[a]

		Gastric adenocarcinoma (GAC)					Oesophageal adenocarcinoma (OAC)	Gastro-oesophageal junction (GEJ)
		All	Anatomical subsites[b]		Histological subtype[b]			
			Cardia	Non-cardia	Intestinal	diffuse		
Country	**Person-years (pys)**	*n*	*n*	*n*	*n*	*n*	*n*	*n*
France	547 495	8	3	3	2	2	0	0
Italy	263 316	43	6	25	18	15	2	2
Spain	255 800	26	3	19	9	11	0	1
United Kingdom	336 247	18	4	12	3	2	16	12
The Netherlands	230 742	24	6	8	2	12	4	0
Greece	94 604	16	2	4	4	9	0	0
Germany	288 983	38	9	20	13	21	2	1
Sweden	378 990	45	13	25	17	19	12	1
Denmark	368 861	50	22	15	12	8	20	0
SUM	2 765 038	268	68	131	80	99	56	17

[a] Norway excluded.

[b] Some GAC cases could not be classified by anatomical subsite or histological subtype.

Table 2 Baseline characteristics by educational level and gender of the EPIC-cohort[a]

	Men				**Women**			
	Primary school completed	Technical/professional school	Secondary school	University degree	Primary school completed	Technical/professional school	Secondary school	University degree
n	46 676	34 888	22 661	37 418	78 528	60 373	76 712	71 451
%	31.5	25.2	16.3	27.0	27.4	21.0	26.7	24.9
Number of gastric cancer cases	79	43	18	30	60	30	31	12
By anatomical subsite								
Cardia (GEJ incl.)	34	16	5	9	6	7	6	2
Non-cardia	30	19	7	11	34	12	13	5
By histological subtype								
Intestinal	32	16	7	5	16	2	8	0
Diffuse	19	13	5	11	28	13	10	4
Continuous variables	Median	Median	Median	Median	Median	Median	Median	Median
	Q1, Q3[b]	Q1, Q3[b]	Q1, Q3[b]	Q1, Q3[b]	Q1, Q3[b]	Q1, Q3[b]	Q1, Q3[b]	Q1, Q3[b]
Age (years)	57	52	49	51	56	52	51	48
	51, 62	45, 58	40, 56	43, 58	49, 61	44, 58	45, 57	42, 54
Height (m)	172	176	175	177	159	163	162	163
	167, 177	171, 180	170, 180	172, 182	154, 163	159, 168	158, 166	160, 168
Weight (kg)	80	80	79	80	67	65	62	61
	73, 89	73, 88	72, 87	73, 87	60, 76	59, 73	56, 69	56, 68
Total energy intake (kcal/day)	2435	2380	2460	2342	1877	1881	2004	1960
	1990, 2950	1966, 2856	2024, 2962	1953, 2779	1543, 2275	1571, 2250	1662, 2399	1629, 2337
Fruit consumption (g/day)	174	145	202	157	248	191	248	226
	86, 340	78, 260	102, 349	91, 272	136, 387	111, 298	148, 364	138, 335
Vegetable consumption (g/day)	152	142	145	157	182	158	210	217
	88, 272	90, 225	88, 235	103, 245	111, 294	106, 240	134, 311	141, 316
Red and processed meat consumption (g/day)	131	126	112	111	91	87	89	77
	90, 180	84, 172	75, 156	66, 158	63, 124	55, 119	56, 126	37, 116
Alcohol consumption (g/day)	12	13	12	15	2	5	4	6
	3, 32	4, 29	4, 29	6, 30	0, 8	1, 12	1, 13	2, 14
Lifelong alcohol consumption (g/day)	24	17	18	16	2	5	4	6
	10, 44	8, 32	8, 33	8, 29	0.1, 7	2,10	1, 10	2, 12
Duration of smoking (years)	24	22	19	20	20	19	15	15
	15, 33	14, 30	10, 28	13, 30	10, 31	10, 29	9, 23	8, 22
Lifelong cigarettes (cigarette/day)	17	15	16	14	10	10	10	10
	10, 21	10, 20	10, 20	8, 20	6, 15	6, 15	5, 15	8, 15

(continued)

Table 2 Continued

	Men				Women			
	Primary school completed	Technical/professional school	Secondary school	University degree	Primary school completed	Technical/professional school	Secondary school	University degree
Categorical variables	%	%	%	%	%	%	%	%
Smoking status								
Never smokers	27.3	30.0	35.0	40.2	64.9	49.9	58.3	56.9
Former smokers, ≥10 years ago	9.0	7.7	4.9	7.3	3.7	4.8	6.3	7.6
<10 years ago	4.3	4.0	2.8	3.5	2.1	2.6	2.9	3.2
Unknown quit	23.6	26.2	26.7	25.3	9.2	19.0	12.2	15.0
Current smokers, <15 cigarette/day	10.2	9.6	9.9	8.0	9.8	12.0	7.4	8.2
15–24 cigarette/day	12.2	11.2	10.1	6.5	7.3	8.7	5.5	4.5
≥25 cigarette/day	6.4	5.5	5.9	3.4	1.5	1.9	1.7	1.3
Unknown quantity	5.8	4.8	3.3	4.8	0.4	0.5	0.8	1.0
Unknown smoking status	1.2	0.9	1.4	1.0	1.1	0.4	2.7	2.4
Overall physical activity (METS, quartiles)								
Inactive	11.9	20.8	28.9	39.4	5.8	16.1	12.2	30.9
Moderately inactive	34.4	27.3	27.9	29.5	21.6	25.8	41.3	30.7
Moderately active	41.5	30.0	20.1	19.3	44.0	39.1	33.8	18.7
Active	8.8	11.0	5.7	4.4	23.8	13.2	7.3	14.0
Unknown	8.7	10.9	17.4	7.4	4.9	5.9	5.5	4.9
Nested case-control study								
n	385	226	104	169	220	128	103	67
H. pylori seropositive	76.9%	59.4%	65.4%	57.1%	82.9%	65.6%	66.7%	53.9%

[a] Norway excluded.
[b] Q1 Cut point of Quartile 1, Q3 Cut point of Quartile 3.

Table 3 Multivariate hazard ratios (HR) and 95% confidence intervals (95% CI) of gastric and oesophageal adenocarcinoma for educational level by anatomical site and histological type

	Primary school completed	Technical/professional school		Secondary school		University degree	
	HR	HR	95% CI	HR	95% CI	HR	95% CI
Gastric cancer	124	67		41		36	
Crude	1	1.04	0.75–1.42	0.82	0.55–1.21	0.63	0.43–0.94
Adjusted[a]	1	0.98	0.70–1.36	0.81	0.54–1.22	0.64	0.43–0.98
By anatomical subsite							
Cardia gastric cancer (incl. 17 GEJ)	40	23		11		11	
Adjusted[a]	1	0.78	0.44–1.37	0.70	0.33–1.47	0.42	0.20–0.89
Non-cardia gastric cancer	64	31		20		16	
Adjusted[a]	1	0.97	0.60–1.56	0.87	0.48–1.55	0.66	0.36–1.22
By histological subtype							
Intestinal	46	17		14		3	
Adjusted[a]	1	0.79	0.43–1.44	0.81	0.41–1.63	0.13	0.04–0.44
Diffuse	45	25		14		15	
Adjusted[a]	1	0.94	0.54–1.64	0.70	0.35–1.40	0.71	0.37–1.40
Oesophageal cancer	27	15		2		12	
Adjusted[a]	1	0.65	0.33–1.27	0.19	0.04–0.85	0.67	0.30–1.52

[a] Smoking habits (never smoked, former smoker ceased smoking ≥10 years, ceased <10 years, unknown time of ceasing smoking, current smoker <15, 15–25, ≥25, unknown cigarette/day, and unknown smoking status), lifelong average cigarette smoking (cigarette/day), duration of smoking (years), alcohol consumption (g/day, quintiles), lifelong alcohol drinking (g/day quintiles, unknown) height (m,cont.), weight (kg, cont.), total physical activity (METs, quartiles), total energy intake (kcal, quintiles), fruit intake (g/day, quintiles), vegetable intake (g/day, quintiles), meat/meat products intake (g/day, quintiles).

Table 4 Multivariate Odds ratios (OR) and 95% confidence intervals (95% CI) study of gastric and oesophageal adenocarcinoma according to educational level by anatomical site and histological type in the nested case-control study

	Primary school completed	Technical/professional school		Secondary school		University degree	
	OR	OR	95% CI	OR	95% CI	OR	95% CI
Gastric cancer cases	99	47		32		23	
Adjusted[a]	1	0.89	0.54–1.48	0.98	0.48–2.02	0.46	0.21–1.00
Adjusted[b]	1	1.02	0.60–1.72	0.98	0.47–2.04	0.53	0.24–1.18
By anatomical subsite							
Cardia gastric cancer (incl. GEJ)[b]	1	0.49	0.17–1.35	2.54	0.65–9.83	0.12	0.02–0.85
Non-cardia gastric cancer[b]	1	1.87	0.82–4.27	0.65	0.19–2.25	0.92	0.30–2.79
By histological subtype							
Intestinal[b]	1	0.92	0.37–2.31	0.99	0.29–3.40	0.06	0.01–0.63
Diffuse[b]	1	1.58	0.53–4.68	0.90	0.19–4.25	0.83	0.21–3.24

a Smoking habits (never smoked, former smoker ceased smoking ≥10 years, ceased <10 years, unknown time of ceasing smoking, current smoker <15, 15–25, ≥25, unknown cig/d, and unknown smoking status), lifelong average cigarette smoking (cig/d), duration of smoking (years), alcohol consumption (g/d,quintiles), lifelong alcohol drinking (g/d quintiles, unknown) height (m,cont.), weight (kg, cont.), total physical activity (METs, quartiles), total energy intake (kcal, quintiles), fruit intake (g/d, quintiles), vegetable intake (g/d, quintiles), meat/meat products intake (g/d, quintiles).

b Covariates as listed under # and additionally adjusted for H. *pylori*-seroprevalence.

level and risk of adenocarcinoma of the oesophagus (highest vs lowest level of education: HR 0.67: 95% CI: 0.30–1.52).

Table 5 shows the results of the association between RII and gastric cancer risk in the cohort and nested case-control study. Overall, RII score was associated with an inverse, but statistical non-significant risk of gastric adenocarcinoma (highest vs lowest RII score: HR 0.74, 95% CI: 0.53–1.05). Similar to the results obtained for educational level, the association between RII and gastric cancer risk was strongest for cardia (highest vs lowest RII score: HR 0.49, 95% CI: 0.27–0.90, P for heterogeneity = 0.22) and intestinal-type gastric cancers (highest vs lowest score: HR 0.33, 95% CI: 0.16–0.68, P for heterogeneity = 0.13).

Table 5 Association of Relative Index of Inequality (RII) with gastric and oesophageal adenocarcinoma according to anatomical site and histological type (Hazard ratio (HR) and 95% confidence interval (95% CI) for the cohort and odds ratio (OR) and 95% confidence interval (95% CI) for the nested case control study)

	Relative Index of Inequality RII				
		RII-2		RII-3	
	RII-1	HR	95% CI	HR	95% CI
Gastric cancer	110	90		60	
Crude	1	0.90	0.65–1.23	0.72	0.52–1.00
Adjusted[a]	1	0.89	0.64–1.24	0.74	0.53–1.05
By anatomical subsite					
Cardia gastric cancer (incl. GEJ)	41	23		18	
Adjusted[a]	1	0.62	0.35–1.10	0.49	0.27–0.90
Non-cardia gastric cancer	54	45		29	
Adjusted[a]	1	0.86	0.53–1.38	0.80	0.49–1.30
By histological subtype					
Intestinal type	37	31		10	
Adjusted[a]	1	0.86	0.49 –1.52	0.33	0.16–0.68
Diffuse type	43	31		23	
Adjusted[a]	1	0.77	0.44–1.35	0.76	0.43–1.33
Oesophageal cancer	29	15		12	
Adjusted[a]	1	0.60	0.30–1.19	0.59	0.28–1.24
Gastric cancer nested case control study					
	OR	OR	95% CI	OR	95% CI
Gastric cancer cases	99	47		32	
Adjusted[a]	1	0.99	0.60–1.62	0.74	0.40–1.37
Additionally adjusted for *H. pylori*-seroprevalence[b]	1	1.00	0.59–1.68	0.81	0.43–1.51

[a] Smoking habits (never smoked, former smoker ceased smoking ≥10 years, ceased <10 years, unknown time of ceasing smoking, current smoker < 15, 15–25, ≥25, unknown cigarette/day, and unknown smoking status), lifelong average cigarette smoking (cigarette/day), duration of smoking (years), alcohol consumption (g/day, quintiles), lifelong alcohol drinking (g/day, quintiles, unknown) height (m, cont.), weight (kg, cont.), total physical activity (METs, quartiles), total energy intake (kcal, quintiles), fruit intake (g/day, quintiles), vegetable intake (g/day, quintiles), meat/meat products intake (g/day, quintiles).

[b] Covariates as listed under a and additionally adjusted for *H. pylori*–seroprevalence.

In the nested case-control study, additional adjustment for *H. pylori* slightly attenuated the risk estimates. The OR between the RII-score and risk of gastric adenocarcinoma was 0.81 (95% CI: 0.43–1.51) with adjustment for *H. pylori* seroprevalence.

Discussion

A higher educational level was associated with a reduced risk of gastric adenocarcinoma, an effect that seems to be stronger for cardia and particularly for intestinal-type gastric cancers. No statistically significant heterogeneity between countries was observed. Differences in the distribution of known or potential risk factors for gastric cancer, such as smoking, alcohol consumption, obesity, physical activity or some dietary factors which are correlated with socioeconomic position, did not explain a considerable part of this effect. However, after adjustment for *H. pylori* seroprevalence, this association was attenuated and was no longer statistically significant. Consistent with other results, an inverse association between educational level and oesophageal adenocarcinoma was observed,[28] although it was not statistically significant and there were too few cases for reasonable interpretation.

Our findings are consistent with the results of other case-control studies[11,13–15,29–31] and cohort studies.[10,12] Only few risk factors, including smoking, obesity and low consumption of fruit and vegetables, are known to affect the risk of gastric and oesophageal cancers.[4] It is well established that differences in socioeconomic position are associated with inequalities in health[32] that may be mediated by differences in health-related behaviour.[33–35] This is in agreement with our observations that participants with a higher educational level were leaner, ate more vegetables and were less likely to be smokers at recruitment. Also in men, lifelong alcohol intake was lower in the highest educational categories. The correlation of these risk factors with socioeconomic position might help to explain the inverse association of the latter with gastric cancer incidence, but in previous cohort studies[10,12] a complete set of covariates was not always available.

H. pylori infection has been shown to be associated with lower social class.[36] Education may reflect childhood socioeconomic circumstances, such as family size and hygiene conditions of life, which correlate with the *H. pylori* infection rate.[35,37,38] This is in line with our observation, that educational attainment is correlated with the *H. pylori* seroprevalence, and as expected, further adjustment for *H. pylori* infections attenuated the risk estimates for non-cardia and gastric cancer overall. However, the findings from the present study suggest that these covariates, even the consideration of *H. pylori* infection, cannot fully explain the inverse association between socioeconomic factors and gastric cancer risk.

Few studies analysed the association between socioeconomic position and anatomical subsites or histological subtypes of gastric cancer.[12,14,39,40] Powell and McConkey[39] observed increasing incidence of cardia and decreasing incidence of pyloric gastric cancer cases in groups with high social position between 1961 and 1981 in the UK. In another registry based study, lower socioeconomic position was related to higher incidence of non-cardia gastric cancer, but no clear relationship was found with respect to cardia gastric cancer during 1987 to 1996 in Scotland.[41] In contrast, Wu-Williams *et al*.[40] found no association between socioeconomic position and risk of cardia cancer, although educational level was associated with distal gastric cancer in men aged 55 years and older. However, in their study neighbourhood controls were chosen, therefore direct comparability of their results with our data is limited. Another case-control study found higher socio-economic position to be associated with decreased risk of both cardia and non-cardia cancer cases.[14] Consistent with our observations, van Loon *et al*.[12] found a higher educational level to be associated with a lower risk of cardia cancer, although this association was attenuated after adjustment for lifestyle variables. Conflicting results between socioeconomic position and gastric cancer may be attributed to the changes in temporal pattern of site and type of gastric cancer.[39,41,42]

Since educational attainment may vary substantially across Europe, we additionally examined the association between the RII score and gastric cancer risk, a marker commonly used in social epidemiology, and which takes into account the age and sex distribution of the population in each centre.[26,43] However, both education level and the RII score showed similar inverse associations with gastric adenocarcinoma risk overall, and with anatomical and histological subtypes.

Some potential limitations of this study should be considered. Our study findings might have been affected by residual confounding and measurement error in the variables included in the models.[44] Dietary data are prone to measurement error.[45] In our data, however, the adjustment for known risk factors did not substantially change the association between educational level and gastric cancer risk. In the nested case-control study, a possible attenuation of risk may have occurred when *H. pylori* infection was close to the time of cancer diagnosis.[46] However, in our study the length of follow-up is still relatively short. Another source of error to be considered is residual confounding of other factors related to socioeconomic position that may determine gastric cancer risk. We did not take into account other measures for adulthood socioeconomic position such as occupation or income; however, measures of economic distress have been shown to be in good correlation with each other.[35] Rather than single indicators of socioeconomic position, multiple indicators covering life course may be necessary to create indicators which can better discriminate between social groups and identify risk factors.[35,47] Regarding socioeconomic position misclassification is unlikely to be a matter of concern. Since educational attainment applies for every person and is easily recordable, measurement error of the exposure variable is unlikely to have seriously biased our results. Period effects regarding the educational levels were considered by age-group stratified analyses. The participants of our cohort study are likely to be more educated than the general population, which may result in attenuated risk estimates and limit the generalizability of the results.

The strength of this study is the prospective study design, the consideration of relevant confounding variables including H. *pylori* infection, and the stratification by anatomical subsites and histological subtypes, for which the subclassification and verification for which was done by a panel of experienced pathologists, although these results by subtypes of gastric cancer should be confirmed in a larger study with more cases.

In this large prospective study, high educational level was associated with a reduced risk of gastric adenocarcinoma, which was strongest for cardia cancer and intestinal histological subtype. This gives support to the hypothesis that socioeconomic factors are diversely related to site and types of gastric cancer, a relationship that is not completely explained by differences in established risk factors for gastric cancer. Our observations emphasize the need of adjustment for socioeconomic position in studies evaluating risk factors for stomach cancer. Future investigations of the socioeconomic determinants of gastric adenocarcinoma should consider differential effects by subsites and subtypes. Emphasis should be put on studying correlates of socioeconomic position which can help explain the association with stomach cancer risk.

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KEY MESSAGES

- In this large European prospective study considering relevant risk factors for gastric cancer, high educational level was associated with reduced risk of gastric adenocarcinoma. By means of the calculated 'relative index of inequality' instead of the variable 'educational level' similar results were obtained.
- The risk reduction was strongest for tumours located in the cardia or with intestinal histological subtype.
- In a nested case-control, further adjustment for *H. pylori* seroprevalence attenuated the inverse relationship but a substantial yet unexplained part of variation remained, encouraging the search for further correlates of educational level that are linked to cancer development.

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