Education and gastric cancer risk – An individual participant data meta-analysis in the StoP project consortium

Short title: Education and gastric cancer risk

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NOVELTY AND IMPACT: Which is the impact of education on gastric cancer risk? An updated quantification came from the analysis of the "Stomach cancer Pooling (StoP) Project", a large international consortium of case-control studies. A ~40% decreased risk of gastric cancer emerged among intermediate/highly educated subjects as compared to less educated ones. The association was evident both among *H. pylori* negative and positive subjects.

ABSTRACT

Low socioeconomic position (SEP) is a strong risk factor for incidence and premature mortality from several cancers. This study aimed at quantifying the association between SEP and gastric cancer (GC) risk through an individual participant data meta-analysis within the "Stomach cancer Pooling (StoP) Project".

Educational level and household income were used as proxies for the SEP. We estimated pooled odds-ratios (ORs) and the corresponding 95% confidence intervals (CIs) across levels of education and household income by pooling study-specific ORs through random-effects meta-analytic models. The relative index of inequality (RII) was also computed.

A total of 9,773 GC cases and 24,373 controls from 25 studies from Europe, Asia and America were included. The pooled OR for the highest compared to the lowest level of education was 0.60 (95% CI, 0.44-0.84), while the pooled RII was 0.45 (95% CI, 0.29-0.69). A strong inverse association was observed both for non-cardia (OR 0.39, 95% CI, 0.22-0.70) and cardia GC (OR 0.47, 95% CI, 0.22-0.99). The relation was stronger among *H. pylori* negative subjects (RII 0.14, 95% CI, 0.04-0.50) as compared to *H. pylori* positive ones (RII 0.35, 95% CI, 0.12-1.05), in the absence of a significant interaction (p=0.28). The highest household income category showed a pooled OR of 0.65 (95% CI, 0.48-0.89), the corresponding RII being 0.40 (95% CI, 0.22-0.72).

Our collaborative pooled-analysis showed a strong inverse relationship between SEP indicators and GC risk. Our data call for public health interventions to reduce GC risk among the more vulnerable groups of the population.

INTRODUCTION

National and international agencies are implementing strategies to guarantee health and wellbeing for all people by targeting sustainable development goals like education, gender equality and poverty reduction [1]. Worldwide, there is increasing awareness and evidence that low socioeconomic position (SEP) is a strong determinant of morbidity and premature mortality from selected non-communicable diseases, including a number of cancers [2, 3].

SEP reflects the availability of cultural, material and social resources that translates into advantages in terms of decision making, social network, lifestyle habits and also access to health services. SEP can be measured by a series of indicators, including education, occupation and income. These indicators are correlated but each of them measures different aspects of the socioeconomic stratification [4]. Education captures the intellectual assets of individuals besides the socioeconomic conditions in childhood and adolescence, and also represents the opportunity to access to higher level jobs. Occupation reflects the privileges related to social standing, material resources and job-related risk factors; income reflects the material component, but it is also related to better living conditions and healthy environment.

Gastric cancer (GC) is one of the neoplasms most strongly associated with low SEP [5-8] . Almost one million new GC cases are diagnosed every year worldwide, and despite a steady fall in incidence over the last several decades, GC is still the third leading cause of cancer mortality [9].

Thus, an accurate quantification of the impact of SEP on GC risk is of major importance to plan public health interventions aimed to reduce GC incidence and socioeconomic disparities [1].

This study aimed at improving previously published estimates of the association between low SEP and GC risk through an individual participant data meta-analysis within the “Stomach cancer

Pooling (StoP) Project", a recently established consortium of case-control or nested cohort studies from various areas of the World [10]. The StoP consortium, with its powered gold standard approach typical of individual participant data meta-analyses [11], allows to study the relation between SEP and GC according to cancer subsite and histological subtype, as well as to consider it in strata of geographic area or macroeconomic measure of income inequality of the country where the study was conducted.

MATERIALS AND METHODS

Characteristics of the included studies

Policies of the StoP consortium and study inclusion criteria have been previously published [10]. The participating studies 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). All identifying information was removed before data were pooled at the study coordinating center located at the University of Milan.

A total of 25 out of 30 studies included in the StoP dataset (release version 2.0) collected data on SEP and GC risk (Supplementary Table 1). Eleven studies [12-21] - two of which were nested case-control studies within the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM) [20] - were from European countries, six were from Asia [22-27], three studies, including one with unpublished data, were from North America [28, 29], and five studies were from Central and South America [30-34]. Out of the 25 included studies, 2 were nested in a cohort [20], twelve selected controls from the general population [15, 16, 18, 21, 23-27, 32-34] and 11 (one of which with unpublished data) were hospital-based case-control studies [12-14, 17, 19, 22, 28-31]. In the latter [12-14, 17, 19, 22, 28-31],

controls were patients admitted to the same hospital network as cases for a wide spectrum of acute, non-neoplastic conditions unrelated to risk factors for stomach cancer, including among the others, traumas and orthopaedic conditions, eye and ear, nose and throat diseases.

Cases had histologically confirmed diagnosis of gastric cancer that were classified and harmonized across studies using the International Classification of Diseases 10th Revision (ICD-10 codes C16.0-C16.9). For the aims of the stratified analysis by anatomical subsite, GCs were classified into gastric cardia cancer (ICD-10 C16.0) and non-cardia cancers (ICD-10 C16.1-C16.9). When available, the histological subtype was classified using Lauren's classification into intestinal and diffuse.

We classified each study into low, middle and high according to the Gross National Income (GNI) per capita at the time of the study conduction, a macroeconomic measure of income inequality estimated by the World Bank Atlas method [35].

Definition of SEP

SEP is a complex concept which involves several dimensions including education, work experience, access to material resources, prestige and social position [4]. In the StoP project, we used the level of education and household income as proxies for the SEP [36].

Education was standardized across studies using the International Standard Classification of Education (ISCED 2011) [36] of the UNESCO, an international reference classification that facilitates comparisons of education systems across countries. We defined three categories: i) *low education level*, including early childhood and primary education (ISCED 0-1); ii) *intermediate education level*, including secondary education (lower and upper) and post-secondary non tertiary education (ISCED 2 to 4); iii) *high education level*, including tertiary vocational education, often designed to

provide participants with professional knowledge, skills and competencies, and education leading to a university degree (ISCED 5-6). ISCED 2 was considered an intermediate level of education since the majority of subjects were born between 1930s and 1950s. A sensitivity analysis was carried out considering ISCED 0 to 2 as a low education level, ISCED 3-4 and 5-6 as intermediate and high education levels, respectively.

Household income was available in a subset of studies [17, 22, 23, 27, 28, 30, 31] (Supplementary Table 1). It was either collected through questionnaire based pre-defined categories [17, 27, 28] or through income volumes [22, 23, 30, 31] (as a continuous variable). For the latter studies, we provided to define standardized categories through study-specific quartiles in order to merge the two definitions.

Statistical analysis

A two-stage approach was adopted [37]. To analyse the association of education and household income with GC risk, we firstly estimated study-specific odds ratios (ORs) and the corresponding 95% CIs using multivariable unconditional logistic regression models. Polytomous unconditional logistic regression models were fitted when analysing the association by cancer subsite and histological type.

To facilitate comparison with results from different studies, we also estimated the relative index of inequality (RII) for both education and household income. The RII is a unique regression-based summary measure of social inequality that allows comparisons across countries with different distributions of the socioeconomic variables. It takes into account the size of the population in each socioeconomic level, and their relative position in the socioeconomic scale [38]. The RII was defined as follows. Within each study, for each of the k ordered levels (i = 1, …, k) of the SEP variable (i.e.,

education or household income), let c_i be the proportion of study subjects in class i or lower (with c_0=0 and c_k=1). Then, for each class i = 1, …, k, let define $x_i=(c_i+c_{i-1})/2$ as the mean rank, i.e. the midpoint between the proportion of study subjects in class i (c_i) and those in the previous one (c_{i-1}). The RII was then estimated by including the mean rank x_i as explanatory variable in the models used to derive the ORs instead of the original SEP variable. The RII can be interpreted as the GC risk of subjects at the highest level of the socioeconomic hierarchy as compared to those in the lowest one. A RII<1 indicates a lower risk among subjects in the highest level of the socioeconomic scale, whereas a RII>1 indicates an increased risk.

Two different models were fitted: a simple model adjusted for age (<40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74 and ≥75 years) and sex, and a model further adjusted for alcohol drinking (never, ≤ 1 drink per day, >1 to ≤ 4 drinks/day and > 4 drinks/day), tobacco smoking (never, former, current ≤10 cigarettes/day, >10 to 20 cigarettes/day and >20 cigarettes/day), race/ethnicity (White, Hispanic/Latino, Black/African American, other), fruit and vegetable consumption (study-specific tertiles) and study centre (for multicentre studies).

To avoid data loss due to sporadically missing values in study-specific confounders, we applied multiple imputation using full chained equations [39]. Under the missing at random assumption, five imputed datasets were generated for each study, with missing values filled in with a set of plausible values drawn from the posterior predictive distribution of the missing data, conditional on the observed data. The imputation models were congenial with the analysis models, and included the same set of covariates plus the case/control status. Study specific regression coefficients and their standard errors were obtained through the Rubin's rule.

In the second stage, summary (pooled) effect estimates for education and household income were computed using a random-effect model [40]. Heterogeneity between studies was evaluated using the Q test statistics and quantified using I^2, i.e., the proportion of total variation contributed by between-study variance [41]. The Galbraith plot was used to graphically assess and visualize the impact of individual studies on overall heterogeneity.

We carried out several stratified analyses to investigate the effect of education across strata of selected covariates: geographic region of the study (Europe, Asia, North America, Central/South America), per capita GNI of the country where the study was conducted (Low, Middle, High), study period (before and after 2000), type of controls (hospital-based, population-based; controls from the two nested case-control studies were considered together with the latter), age (≤55, >55 to 65, >65), sex, cigarette smoking (never, former, current), alcohol drinking (never, ever) and *H. pylori* infection status (positive, negative).

The interaction between educational level and the above reported potential effect modifiers was tested through a meta-regression model using the RII.

Analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The main characteristics of the study subjects - 9,773 GC cases and 24,373 controls - are presented in Table 1. About two-thirds of GC cases (6,354 out of 9,773) were men, while this percentage was around 58% in controls. Half of the cases and controls were from European studies. A total of 6,373 cases (65%) and 18,762 controls (77%) were from countries with a high per capita GNI at the time of study conduction (see Supplementary Table 1 for details). Cases were somewhat older (median

age 64 years) than controls (median age 62 years). Among men, 12% of GC cases had a high educational level (ISCED 5-6) compared to 7.4% among women. Overall, GC cases were less educated and had a lower household income than controls. In fact, 10.5% of cases as compared to 18.5% of controls had a high educational level (ISCED 5-6), and 3.5% of cases and 5.2% of controls had a high household income.

Table 2 reported the pooled ORs of GC according to educational level. Compared to low educational level (ISCED 0-1), both intermediate (ISCED 2-4) and high (ISCED 5-6) educational levels were significantly inversely associated with GC risk, being the ORs from the fully adjusted models 0.68 (95% CI, 0.55-0.84) and 0.60 (95% CI, 0.44-0.84), respectively. The corresponding pooled RII was equal to 0.45 (95% CI, 0.29-0.69). No substantial differences emerged between minimally adjusted (i.e., age and sex) and fully adjusted ORs estimates. Similar results emerged in the sensitivity analysis considering ISCED 0 to 2 as a low education level (Supplementary Table 2). A significant between-study heterogeneity was evident, as shown by study-specific estimates for the high educational level (I^2=85.5%, p<.01) displayed in Figure 1. The Galbraith plot (Supplementary Figure 1) identified the study conducted in Portugal [16] as a potential source of heterogeneity. However, between-study heterogeneity did not substantially decreased (I^2=76.1%, p<.01) after removing that study [16].

In the analysis by cancer subsite, a strong inverse association was observed both for non-cardia (highest vs lowest level education: OR 0.50, 95% CI, 0.32-0.78) and cardia GC (OR 0.65, 95% CI, 0.41-1.03). Similar findings emerged across histological subtypes, as higher level of education was inversely associated with both diffuse (OR 0.62, 95% CI, 0.22-1.11) and intestinal-type (OR 0.54, 95% CI, 0.32-0.91) GC risk.

Results of the stratified analyses reported in terms of education-based RII are shown in Figure 2 (see Supplementary Table 3 for full results). The risk of GC was strongly associated with lower educational attainment in European (RII 0.37, 95% CI, 0.18-0.75) and Asian (RII 0.27, 95% CI, 0.09-0.75) studies, while the inverse association was not significant in studies from North America (RII 0.58, 95% CI, 0.23-1.41). There was a null association when considering the studies from Central/South America (RII 1.07, 95% CI, 0.46-2.48). There was a strong significant inverse relation between educational attainment and GC risk in studies from countries with low (RII 0.31, 95% CI, 0.14-0.70) and high (RII 0.43, 95% CI, 0.24-0.79) per capita GNI, while the association was less strong in studies with a middle per capita GNI (RII 0.74, 95% CI, 0.28-1.92), in the absence of a significant interaction (p=0.37). Socioeconomic inequality due to educational attainment was statistically significant only in studies conducted after 2000 (RII 0.31, 95% CI, 0.09-1.10) and when considering those with controls from the general population (RII 0.36, 95% CI, 0.18-0.70).

No significant differences in risk estimates were observed across strata of age, sex, cigarette smoking and drinking. Among the 11 studies who collected data on *H. pylori* infection, the relation was stronger among *H. pylori* negative subjects (RII 0.14, 95% CI, 0.04-0.50) as compared to positive ones (RII 0.35, 95% CI, 0.12-1.05), in the absence however of a significant interaction (p=0.28).

When using household income as a proxy for the SEP (Supplementary Table 4), a significantly reduced GC risk emerged in the highest as compared to the lowest household income category (OR 0.65, 95% CI, 0.48-0.89, Supplementary Figure 2). The corresponding RII was 0.40 (95% CI, 0.22-0.72).

Similar associations emerged across anatomic subsites and histological subtypes.

DISCUSSION

This uniquely large individual participant data meta-analysis provides a precise estimate of the strong inverse relationship between SEP and GC risk. We found a decreased GC risk among individuals with intermediate and high education levels as compared to those in the lowest level. The magnitude of the association was similar across anatomic tumor subsites and histological subtypes. Similar results emerged when we used household income as a proxy for the SEP.

Our results are in agreement with previous case-control and cohort studies [6, 8, 42, 43] investigating the relation between SEP and GC risk. In the EPIC cohort study, higher education was associated with a 36% reduced risk of GC (hazard ratio, HR 0.64, 95% CI, 0.43-0.98), and the effect was more pronounced for cardia (HR 0.42, 95% CI, 0.20-0.89) as compared to non-cardia cancers (HR 0.66, 95% CI, 0.36-1.22) [6]. In a large cohort in the US (NIH–AARP Diet and Health Study), less educated men had a nearly 70% increased risk of GC (relative risk, RR, 1.67, 95% CI, 1.20-2.33) as compared to highly educated ones, while there was no significant association in women (RR 0.92, 95% CI, 0.44-1.92) [43]. A Swedish cohort study including more than 4.7 million participants from 1991 to 2010 found a decreased incidence of cardia (incidence rate ratio, IRR, 0.74, 95% CI, 0.63-0.87) and non-cardia GC (IRR 0.59, 95% CI, 0.54-0.66) among highly educated men, and among those above the highest quintile of household income (IRR 0.75, 95% CI, 0.65-0.86 for cardia GC, and IRR 0.79, 95% CI, 0.73-0.86 for non-cardia GC), while in women the association emerged only for education, and was limited to non-cardia GC (IRR 0.64, 95% CI, 0.56-0.73) [42]. A strong inverse association emerged also in a recent large longitudinal Italian census-based study reporting a reduced mortality among highly educated individuals in both sexes, with

standardized mortality ratio of 0.41 in men and 0.50 in women for the highest compared to the lowest level of education [8].

The causative pathway linking high SEP to low risk of GC has not been fully established. The disparities in GC risk among socioeconomic classes have been attributed to the uneven distribution of lifestyle risk factors for GC that favours people in the highest SEP, with differences in smoking [44], alcohol drinking [45] and dietary habits [46] being thought to play a major role. However, when we adjusted for these risk factors, the magnitude of the association remained strong, suggesting that the reduced risk of GC associated with a high SEP operates through more complex pathways than those related to modifiable risk factors. *H. pylori* infection is associated with an increased non-cardia GC risk, and it is more common in subjects from low SEP [47]. Although only half of the studies included in the StoP consortium collected data on *H. pylori* infection, we found a nearly 40% decreased GC risk in highly educated *H. pylori* positive subjects.

The stratified analysis according to type of controls showed that the relationship between education and GC risk was stronger, but not significantly different, among population-based than hospital-based controls. Hospital-based case-control studies may be more prone to selection bias, being less educated people more likely to be hospitalized for chronic conditions as compared to controls selected from the general population.

Our findings surprisingly evidenced a lack of association between educational attainment and GC risk in the stratified analysis of the five studies [30-34] from Central and Southern America, two of which from Brazil [30, 31] and three from Mexico [32-34]. Among these studies [30-34], the only one showing a significant inverse association was carried out among Japanese Brazilians in Sao Paulo [31]. The Mexican study by Ward et al. [33] separately reported a lack of association between

educational level and GC risk, too. This raised concerns about the reliability of education as a proxy for the SEP in Mexico, where the education system is problematic and part of the population fails to achieve even basic education [48]. In fact, a very small fraction of study participants gained higher education in such studies [32-34]. Moreover, these studies were from countries having a middle per capita GNI [35] at the time of conduction. Low and middle income countries account for substantial inequalities as wealth remains concentrated in the hands of the rich, whilst the vast majority of the population remains poor, with limited access to education, and thus to potentially better life conditions in the future. This may have attenuated the results towards the null, as in stratified analyses according to per capita GNI, the decreased GC risk in highly educated as compared to less educated subjects was not significant in either low (OR 0.73, 95% CI 0.46-1.16) or in middle GNI countries (OR 0.83, 95% CI 0.40-1.75).

With reference to study limitations, we found a considerable heterogeneity across studies that was not explained by age, sex, cigarette smoking, alcohol drinking and geographic area of the study. The study conducted in Portugal [16] was a potential source of heterogeneity, being the OR estimate for high vs low education really low. This may be explained by selection bias, as there was no perfect match between the populations from which controls (Porto dwellers) and cases (selected in two hospitals that received patients from the north, including also poorer regions than Porto) were selected. However, the exclusion of such Portuguese study [16] did not lead to a reduction in heterogeneity. In the StoP consortium, a huge effort has been done to harmonize data according to a pre-specified format in order to ensure standardization of case-definition and confounders [10]. Despite this, we cannot rule out uncontrolled confounders such as salt or salty foods consumption (e.g., processed meat) and food preservation, including refrigerator use. The use of random-effects

models allows to account for, but not resolve, heterogeneity. We adopted the two-stage approach, which gives similar results with respect to the one-stage approach, even in the presence of heterogeneity, and when several covariates must be concurrently considered [37]. However, as a sensitivity analysis, we also performed a one-stage analysis, that gave materially unchanged results.

In this work, we considered two of the most common proxy variables of the SEP, educational attainment and household income. However, we could not evaluate the relationship between occupational-based social class and GC risk since we were unable to have a uniform definition of occupational position among the included studies. This indicator could be a better proxy for the SEP. We decided to standardize educational attainment across studies using the UNESCO ISCED 2011 classification [36], a recognized and comprehensive framework that allows the comparison of national education systems across countries. However, the meaning of educational level varies according to birth cohort, as over recent decades there have been increasing opportunities to get proper education even for minorities and individuals of low social status. This means that in today's young generations, low education may reflect a worse life, health and psychiatric conditions.

The "StoP Project" includes original and individual data on risk factors for GC on about 10,000 cancer cases and 24,000 controls, providing us a unique opportunity to investigate and accurately quantify the magnitude of the association between two proxy variables for the SEP, educational attainment and household income, and GC risk, overall and according to anatomical subsites, histology, geographic area, per capita GNI of the country where the study was conducted, and other selected potential confounders. The individual level approach has the undoubted advantage of the availability of detailed and uniform information on important covariates as compared with meta-analysis based on published data, allowing to adjust for recognized GC risk

factors [11]. However, despite the use of multivariable adjusted models, residual confounding cannot be completely ruled out.

We computed the RII [38] for both education and household income. This index has the advantage of providing a unique measure of the magnitude of inequality that can be compared across different countries, studies and diseases [38]. Our estimates of the RII are in line with that reported in a census-based Spanish study based on GC deaths registered between 2001 and 2008 [49], and with the results of the Turin Longitudinal study based on the Piedmont cancer registry collecting data between 1985-1999 [50]. In these studies, the RII ranged between 1.96 in Spanish men and 3.24 in Italian men, i.e. people in the highest rank of the socioeconomic hierarchy had a 30% to 50% reduction in GC mortality as compared to those in the lowest class.

The StoP project included seven case-control studies [17, 22, 23, 27, 28, 30, 31] who collected household income data. Household income was standardized as far as possible to ensure comparability across studies. Despite that, household income may have varied over the time span of the included studies.

In conclusion, SEP is a strong determinant of GC. Effective interventions to reduce socio-economic inequalities at local, national and international level are needed to reduce GC risk among the more vulnerable groups of the population. Being GC strictly related to low SEP, these interventions will reduce the burden of the disease in the whole population.

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Table 1. Distribution of StoP consortium gastric cancer cases and controls by selected characteristics, overall and according to sex.

		Women				Men				All				P
		Controls (n=10302)		Cases (n=3419)		Controls (n=14071)		Cases (n=6354)		Controls (n=24373)		Cases (n=9773)		
		n	%	n	%	n	%	n	%	n	%	n	%	
Geographic area	Europe	5284	51.3	1853	54.2	6936	49.3	3066	48.3	12220	50.1	4919	50.3	<.01
	Asia	942	9.1	568	16.6	1848	13.1	1251	19.7	2790	11.4	1819	18.6	
	North America	3065	29.8	587	17.2	4188	29.8	1427	22.5	7253	29.8	2014	20.6	
	Central/South America	1011	9.8	411	12.0	1099	7.8	610	9.6	2110	8.7	1021	10.4	
Per capita Gross National Income (GNI) study classification[a]	Low	1260	12.2	770	22.5	2141	15.2	1499	23.6	3401	14.0	2269	23.2	<.01
	Middle	1062	10.3	464	13.6	1148	8.2	667	10.5	2210	9.1	1131	11.6	
	High	7980	77.5	2185	63.9	10782	76.6	4188	65.9	18762	77	6373	65.2	
Study period	Before 2000	6693	65.0	2494	72.9	9439	67.1	4710	74.1	16132	66.2	7204	73.7	<.01
	After 2000	3609	35.0	925	27.1	4632	32.9	1644	25.9	8241	33.8	2569	26.3	
Type of controls														
	Population based	7612	73.9	2175	63.6	9340	66.4	3987	62.7	16952	69.6	6162	63.1	
	Hospital based	2302	22.3	1007	29.5	4322	30.7	2061	32.4	6624	27.2	3068	31.4	
	Mixed	388	3.8	237	6.9	409	2.9	306	4.8	797	3.3	543	5.6	
Age (years)	<40	763	7.4	188	5.5	997	7.1	179	2.8	1760	7.2	367	3.8	<.01
	40-44	713	6.9	135	3.9	742	5.3	230	3.6	1455	6.0	365	3.7	
	45-49	992	9.6	237	6.9	966	6.9	378	5.9	1958	8.0	615	6.3	
	50-54	1124	10.9	276	8.1	1267	9.0	622	9.8	2391	9.8	898	9.2	

	55-59	1203	11.7	372	10.9	1606	11.4	857	13.5	2809	11.5	1229	12.6	
	60-64	1428	13.9	490	14.3	2282	16.2	1053	16.6	3710	15.2	1543	15.8	
	65-69	1619	15.7	638	18.7	2402	17.1	1167	18.4	4021	16.5	1805	18.5	
	70-74	1398	13.6	627	18.3	2235	15.9	1107	17.4	3633	14.9	1734	17.7	
	≥75	1058	10.3	456	13.3	1570	11.2	761	12.0	2628	10.8	1217	12.5	
	missing	4	0.0	--	--	4	0.0	--	--	8	0.0	--	--	
Education (ISCED)[b]	Low (0-1)	4680	45.4	2163	63.3	5995	42.6	3599	56.6	10675	43.8	5762	59.0	<.01
	Intermediate (2-4)	3721	36.1	927	27.1	5234	37.2	1891	29.8	8955	36.7	2818	28.8	
	High (5-6)	1784	17.3	252	7.4	2725	19.4	775	12.2	4509	18.5	1027	10.5	
	missing	117	1.1	77	2.3	117	0.8	89	1.4	234	1.0	166	1.7	
Household income[c]	Low	562	5.5	206	6.0	638	4.5	357	5.6	1200	4.9	563	5.8	<.01
	Lower middle	665	6.5	229	6.7	845	6.0	503	7.9	1510	6.2	732	7.5	
	Upper middle	863	8.4	251	7.3	1134	8.1	460	7.2	1997	8.2	711	7.3	
	High	450	4.4	75	2.2	809	5.7	248	3.9	1259	5.2	323	3.3	
	missing	7762	75.4	2658	77.8	10645	75.6	4786	75.4	18407	75.5	7444	76.2	
Tobacco smoking	Never	6825	66.2	2488	72.8	4098	29.1	1620	25.5	10923	44.8	4108	42.0	<.01
	Former	1596	15.5	363	10.6	5234	37.2	2313	36.4	6830	28.0	2676	27.4	
	Current ≤10 cig/day	790	7.7	210	6.1	1284	9.1	495	7.8	2074	8.5	705	7.2	
	Current 10-20 cig/day	622	6.0	182	5.3	1698	12.1	902	14.2	2320	9.5	1084	11.1	
	Current >20 cig/day	281	2.7	67	2.0	1468	10.4	803	12.6	1749	7.2	870	8.9	
	missing	188	1.8	109	3.2	289	2.1	221	3.5	477	2.0	330	3.4	
Alcohol drinking	Never	3849	37.4	1304	38.1	2544	18.1	1067	16.8	6393	26.2	2371	24.3	<.01
	≤1 drink/day	3415	33.1	848	24.8	4254	30.2	1470	23.1	7669	31.5	2318	23.7	
	>1 to <4 drinks/day	1277	12.4	602	17.6	3377	24.0	1631	25.7	4654	19.1	2233	22.8	
	>4 drinks	171	1.7	62	1.8	1940	13.8	1075	16.9	2111	8.7	1137	11.6	

	missing	1590	15.5	603	17.6	1956	13.9	1111	17.5	3546	14.5	1714	17.6	
Family history of GC	No	4516	43.8	1465	42.8	6160	43.8	2765	43.5	10676	43.8	4230	43.3	<.01
	Yes	394	3.8	383	11.2	530	3.8	521	8.2	924	3.8	904	9.2	
	missing	5392	52.3	1571	46.0	7381	52.5	3068	48.3	12773	52.4	4639	47.5	
Fruit/vegetables consumption	Low	2340	22.7	924	27.0	3523	25.0	1783	28.1	5863	24.1	2707	27.7	<.01
	Intermediate	3083	29.9	976	28.5	3887	27.6	1860	29.3	6970	28.6	2836	29.0	
	High	3580	34.8	1106	32.3	4174	29.7	1856	29.2	7754	31.8	2962	30.3	
	missing	1299	12.6	413	17.6	2487	17.6	855	13.5	3786	15.5	1268	13.0	
***H. pylori* infection**														<.01
	No	677	6.6	300	8.8	761	5.4	445	7.0	1438	5.9	745	7.6	
	Yes	2203	21.4	729	21.3	2921	20.8	1350	21.2	5124	21.0	2079	21.3	
	missing	7422	72.0	2390	69.8	10389	73.8	4559	71.7	17811	73.0	6949	71.1	

[a] According to the Gross National Income (GNI) per capita historical classification computed by the World Bank atlas method [35].

[b] Education was standardized using the International Standard Classification of Education (ISCED 2011) [36]. Low education corresponds to ISCED 0-1, Intermediate education to ISCED 2-4 and High education to ISCED 5-6.

[c] Data on household income was available for the following studies: China (Harbin) [22], Canada (eight provinces) [28], China (Taixing, Jiangsu) [23], Russia (Moscow) [17], Iran (Ardabil) [27], Brazil (São Paulo) [30], Brazil (São Paulo) [31].

Table 2. Pooled ORs and 95% CIs of gastric cancer by anatomical subsite and histological subtype according to education level[a] in the StoP consortium.

	Cases	Controls	Age and sex adjusted OR (95% CI)	Fully adjusted[b] OR (95% CI)	I^2, p for heterogeneity
All gastric cancer					
Low	5762	10675	1 (ref)	1 (ref)	
Intermediate	2818	8955	0.66 (0.53-0.82)	0.68 (0.55-0.84)	84.5%, <.01
High	1027	4509	0.56 (0.39-0.79)	0.60 (0.44-0.84)	85.5%, <.01
Relative Index of Inequality (RII)	*9607*	*24139*	*0.43 (0.28-0.67)*	*0.45 (0.29-0.69)*	*90.9%, <.01*
By anatomical subsite					
Cardia gastric cancer					
Low	575	8572	1 (ref)	1 (ref)	
Intermediate	448	7966	0.81 (0.58-1.14)	0.80 (0.55-1.15)	42.5%, .05
High	265	4374	0.66 (0.42-1.04)	0.65 (0.41-1.03)	47.6%, .05
Relative Index of Inequality (RII)	*1288*	*20912*	*0.49 (0.23-1.06)*	*0.47 (0.22-0.99)*	*78.2%, <.01*
Non-cardia gastric cancer					
Low	2945	8572	1 (ref)	1 (ref)	
Intermediate	921	7966	0.63 (0.47-0.83)	0.62 (0.46-0.83)	77.6%, <.01
High	329	4374	0.53 (0.34-0.83)	0.50 (0.32-0.78)	82.4%, <.01
Relative Index of Inequality (RII)	*4195*	*20912*	*0.38 (0.21-0.69)*	*0.39 (0.22-0.70)*	*86.6%, <.01*
By histological subtype					
Diffuse-type					
Low	1020	6907	1 (ref)	1 (ref)	
Intermediate	332	5904	0.72 (0.51-1.00)	0.73 (0.53-1.00)	65.0%, <.01
High	131	3320	0.59 (0.34-1.04)	0.62 (0.35-1.11)	76.5%, <.01
Relative Index of Inequality (RII)	*1483*	*16131*	*0.44 (0.21-0.96)*	*0.46 (0.22-0.98)*	*83.0%, <.01*
Intestinal-type					
Low	1790	6907	1 (ref)	1 (ref)	
Intermediate	361	5904	0.59 (0.41-0.86)	0.62 (0.43-0.90)	75.9%, <.01
High	149	3320	0.49 (0.29-0.82)	0.54 (0.32-0.91)	75.4%, <.01
Relative Index of Inequality (RII)	*2300*	*16131*	*0.32 (0.16-0.67)*	*0.35 (0.17-0.70)*	*83.6%, <.01*

[a] Education was standardized using the International Standard Classification of Education (ISCED 2011) [36]. Low education corresponds to ISCED 0-1, Intermediate education to ISCED 2-4 and High education to ISCED 5-6.

[b] Adjusted for age, sex, alcohol drinking, tobacco smoking, race/ethnicity, fruit and vegetable consumption and study centre (for multicentre studies).

FIGURE LEGENDS

Figure 1. Study-specific and pooled ORs and corresponding 95% CIs of gastric cancer risk for high (ISCED 5-6) as compared to low (ISCED 0-1) educational level in the Stomach cancer Pooling (StoP) Project consortium. RE: random effect.

Figure 2. Pooled education-based RIIs and 95% CIs for gastric cancer risk in strata of geographic area, per capita GNI of the country where the study was conducted, study period, type of controls, age, sex, cigarette smoking, alcohol drinking and *H. pylori* infection in the Stomach cancer Pooling (StoP) Project consortium.