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

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Low socioeconomic position (SEP) is a strong risk factor for incidence and premature mortality from several cancers. Our 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 noncardia (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, 0.04–0.48) as compared to *H. pylori* positive ones (RII 0.29, 95% CI, 0.10–0.84), 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), while the corresponding RII was 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.

What's new?

Gastric cancer is associated with low socioeconomic position but the precise impact of education on gastric cancer risk needs to be quantified. Here the authors provide an updated quantification through the analysis of the Stomach cancer Pooling (StoP) Project, a large international consortium of case-control studies. They observe a ~40% decreased risk of gastric cancer among individuals with intermediate/high education status as compared to less educated study subjects. The association was evident regardless of *Helicobacter pylori* infection, underscoring the need for public health interventions to reduce gastric cancer risk.

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 noncommunicable diseases, including several cancers.[2,3]

SEP reflects the availability of cultural, material and social resources that translate 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 1 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.

Our 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 described.[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 (Supporting Information Table S1). Studies were grouped into geographic regions on the basis of the classification of the Statistics Division of the United Nations. 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] 12 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 these latter ones, controls were patients admitted to the same hospital networks as cases for a wide spectrum of acute, nonneoplastic conditions unrelated to risk factors for stomach cancer, including among the others, traumas and orthopedic 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 stratified analysis by anatomical subsite, GCs were classified into gastric cardia cancer (ICD-10 C16.0) and noncardia cancers (ICD-10 C16.1–C16.9). When available, the histological subtype was classified using Lauren's classification into intestinal and diffuse.

We grouped each study into categories (low, middle and high) of 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.

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 postsecondary non tertiary education (ISCED 2–4); (*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 0–2 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] (Supporting Information Table S1). It was either collected through questionnaire-based predefined categories[17,27,28] or through income volumes[22,23,30,31] (as a continuous variable). For the latter studies, we defined standardized categories through study-specific quartiles in order to merge the two definitions.

Statistical analysis

A two-stage approach was adopted.[37] To analyze the association of education and household income with GC risk, we first 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 analyzing 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 ($i = 1, \ldots, k$) 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 $i = 1, \ldots, k$, let define $x_i = (c_i + c_{i-1})/2$ as the mean rank, that is, 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 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 center (for multicenter studies).

To avoid data loss due to sporadically missing values in study-specific confounders, we applied multiple imputations 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, that is, 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) 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 Supporting Information Table S1 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 3.3% of cases and 5.2% of controls had a high household income.

Table 2 reports 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 associated with reduced 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 0–2 as a low education level (Supporting Information Table S2).

A significant between-study heterogeneity was evident, as shown by study-specific estimates for the high educational level (I^2 = 85.5%, p < 0.01) displayed in Figure 1. The Galbraith plot (Supporting Information Fig. S1) identified the study conducted in Portugal[16] as a potential source of heterogeneity. However, between-study heterogeneity did not substantially decrease (I^2 = 76.1%, p < 0.01) after removing that study.

In the analysis by cancer subsite, a strong inverse association was observed both for noncardia (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, 0.35–1.11) 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 Supporting Information Table S3 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). The association was null when considering the studies from Central/South America (RII 1.07, 95% CI, 0.46–2.48). There was a strong significant inverse relationship 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 before 2000 (RII 0.56, 95% CI, 0.40–0.79) and when considering those using 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 that collected data on *H. pylori* infection, the relation was stronger among *H. pylori* negative subjects (RII 0.14, 95% CI, 0.04–0.48) as compared to positive ones (RII 0.29, 95% CI, 0.10–0.84), in the absence however of a significant interaction (p = 0.28).

When using household income as a proxy for the SEP (Supporting Information Table S4), a significantly reduced

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

	Women				Men				All				
	Controls (*n* = 10,302)		Cases (*n* = 3,419)		Controls (*n* = 14,071)		Cases (*n* = 6,354)		Controls (*n* = 24,373)		Cases (*n* = 9,773)		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*p*
Geographic area[1]													
Europe	5,284	51.3	1,853	54.2	6,936	49.3	3,066	48.3	12,220	50.1	4,919	50.3	<0.01
Asia	942	9.1	568	16.6	1,848	13.1	1,251	19.7	2,790	11.4	1,819	18.6	
North America	3,065	29.8	587	17.2	4,188	29.8	1,427	22.5	7,253	29.8	2,014	20.6	
Central/South America	1,011	9.8	411	12.0	1,099	7.8	610	9.6	2,110	8.7	1,021	10.4	
Per capita Gross National Income (GNI) study classification[2]													
Low	1,260	12.2	770	22.5	2,141	15.2	1,499	23.6	3,401	14.0	2,269	23.2	<0.01
Middle	1,062	10.3	464	13.6	1,148	8.2	667	10.5	2,210	9.1	1,131	11.6	
High	7,980	77.5	2,185	63.9	10,782	76.6	4,188	65.9	18,762	77.0	6,373	65.2	
Study period													
Before 2000	6,693	65.0	2,494	72.9	9,439	67.1	4,710	74.1	16,132	66.2	7,204	73.7	<0.01
After 2000	3,609	35.0	925	27.1	4,632	32.9	1,644	25.9	8,241	33.8	2,569	26.3	
Type of controls													
Population-based	7,612	73.9	2,175	63.6	9,340	66.4	3,987	62.7	16,952	69.6	6,162	63.1	<0.01
Hospital-based	2,302	22.3	1,007	29.5	4,322	30.7	2,061	32.4	6,624	27.2	3,068	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	1,760	7.2	367	3.8	<0.01
40–44	713	6.9	135	3.9	742	5.3	230	3.6	1,455	6.0	365	3.7	
45–49	992	9.6	237	6.9	966	6.9	378	5.9	1,958	8.0	615	6.3	
50–54	1,124	10.9	276	8.1	1,267	9.0	622	9.8	2,391	9.8	898	9.2	
55–59	1,203	11.7	372	10.9	1,606	11.4	857	13.5	2,809	11.5	1,229	12.6	
60–64	1,428	13.9	490	14.3	2,282	16.2	1,053	16.6	3,710	15.2	1,543	15.8	
65–69	1,619	15.7	638	18.7	2,402	17.1	1,167	18.4	4,021	16.5	1,805	18.5	
70–74	1,398	13.6	627	18.3	2,235	15.9	1,107	17.4	3,633	14.9	1,734	17.7	
≥75	1,058	10.3	456	13.3	1,570	11.2	761	12.0	2,628	10.8	1,217	12.5	
Missing	4	0.0	–	–	4	0.0	–	–	8	0.0	–	–	
Education (ISCED)[3]													
Low (0–1)	4,680	45.4	2,163	63.3	5,995	42.6	3,599	56.6	10,675	43.8	5,762	59.0	<0.01
Intermediate (2–4)	3,721	36.1	927	27.1	5,234	37.2	1,891	29.8	8,955	36.7	2,818	28.8	
High (5–6)	1,784	17.3	252	7.4	2,725	19.4	775	12.2	4,509	18.5	1,027	10.5	
Missing	117	1.1	77	2.3	117	0.8	89	1.4	234	1.0	166	1.7	
Household income[4]													
Low	562	5.5	206	6.0	638	4.5	357	5.6	1,200	4.9	563	5.8	<0.01
Lower middle	665	6.5	229	6.7	845	6.0	503	7.9	1,510	6.2	732	7.5	
Upper middle	863	8.4	251	7.3	1,134	8.1	460	7.2	1,997	8.2	711	7.3	
High	450	4.4	75	2.2	809	5.7	248	3.9	1,259	5.2	323	3.3	
Missing	7,762	75.4	2,658	77.8	10,645	75.6	4,786	75.4	18,407	75.5	7,444	76.2	
Tobacco smoking													
Never	6,825	66.2	2,488	72.8	4,098	29.1	1,620	25.5	10,923	44.8	4,108	42.0	<0.01
Former	1,596	15.5	363	10.6	5,234	37.2	2,313	36.4	6,830	28.0	2,676	27.4	
Current ≤10 cigarettes/day	790	7.7	210	6.1	1,284	9.1	495	7.8	2,074	8.5	705	7.2	
Current 10–20 cig/day	622	6.0	182	5.3	1,698	12.1	902	14.2	2,320	9.5	1,084	11.1	
Current >20 cig/day	281	2.7	67	2.0	1,468	10.4	803	12.6	1,749	7.2	870	8.9	
Missing	188	1.8	109	3.2	289	2.1	221	3.5	477	2.0	330	3.4	

(Continues)

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

	Women				Men				All				
	Controls (*n* = 10,302)		Cases (*n* = 3,419)		Controls (*n* = 14,071)		Cases (*n* = 6,354)		Controls (*n* = 24,373)		Cases (*n* = 9,773)		
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*p*
Alcohol drinking													
Never	3,849	37.4	1,304	38.1	2,544	18.1	1,067	16.8	6,393	26.2	2,371	24.3	<0.01
≤1 drink/day	3,415	33.1	848	24.8	4,254	30.2	1,470	23.1	7,669	31.5	2,318	23.7	
>1 to <4 drinks/day	1,277	12.4	602	17.6	3,377	24.0	1,631	25.7	4,654	19.1	2,233	22.8	
>4 drinks	171	1.7	62	1.8	1,940	13.8	1,075	16.9	2,111	8.7	1,137	11.6	
Missing	1,590	15.5	603	17.6	1,956	13.9	1,111	17.5	3,546	14.5	1,714	17.6	
Family history of GC													
No	4,516	43.8	1,465	42.8	6,160	43.8	2,765	43.5	10,676	43.8	4,230	43.3	<0.01
Yes	394	3.8	383	11.2	530	3.8	521	8.2	924	3.8	904	9.2	
Missing	5,392	52.3	1,571	46.0	7,381	52.5	3,068	48.3	12,773	52.4	4,639	47.5	
Fruit/vegetables consumption													
Low	2,340	22.7	924	27.0	3,523	25.0	1,783	28.1	5,863	24.1	2,707	27.7	<0.01
Intermediate	3,083	29.9	976	28.5	3,887	27.6	1,860	29.3	6,970	28.6	2,836	29.0	
High	3,580	34.8	1,106	32.3	4,174	29.7	1,856	29.2	7,754	31.8	2,962	30.3	
Missing	1,299	12.6	413	12.1	2,487	17.6	855	13.5	3,786	15.5	1,268	13.0	
H. pylori infection													
No	677	6.6	300	8.8	761	5.4	445	7.0	1,438	5.9	745	7.6	<0.01
Yes	2,203	21.4	729	21.3	2,921	20.8	1,350	21.2	5,124	21.0	2,079	21.3	
Missing	7,422	72.0	2,390	69.8	10,389	73.8	4,559	71.7	17,811	73.0	6,949	71.1	

[1]Geographic area was classified according to the countries grouping of the Statistics Division of the United Nations.
[2]According to the Gross National Income (GNI) *per capita* historical classification computed by the World Bank Atlas method.[35]
[3]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.
[4]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] and Brazil (São Paulo).[31]

GC risk emerged in the highest as compared to the lowest household income category (OR 0.65, 95% CI, 0.48–0.89, Supporting Information Fig. S2). 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, high 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 noncardia cancers (HR 0.66, 95% CI, 0.36–1.22).[6] In a large cohort in the USA (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 with follow-up from 1991 to 2010 found a decreased incidence of cardia (incidence rate ratio [IRR] 0.74, 95% CI, 0.63–0.87) and noncardia 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 noncardia GC), while in women the association emerged only for education, and was limited to noncardia 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 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 disparities in GC risk among socioeconomic classes have been attributed to the uneven distribution of lifestyle risk factors

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

	Cases	Controls	Age and sex adjusted OR (95% CI)	Fully adjusted[1] OR (95% CI)	I^2, *p* for heterogeneity
All gastric cancer					
Low	5,762	10,675	1 (ref)	1 (ref)	
Intermediate	2,818	8,955	0.66 (0.53–0.82)	0.68 (0.55–0.84)	84.5%, <0.01
High	1,027	4,509	0.56 (0.39–0.79)	0.60 (0.44–0.84)	85.5%, <0.01
Relative index of inequality (RII)	9,607	24,139	0.43 (0.28–0.67)	0.45 (0.29–0.69)	90.9%, <0.01
By anatomical subsite					
Cardia gastric cancer					
Low	575	8,572	1 (ref)	1 (ref)	
Intermediate	448	7,966	0.81 (0.58–1.14)	0.80 (0.55–1.15)	42.5%, 0.05
High	265	4,374	0.66 (0.42–1.04)	0.65 (0.41–1.03)	47.6%, 0.05
Relative index of inequality (RII)	1,288	20,912	0.49 (0.23–1.06)	0.47 (0.22–0.99)	78.2%, <0.01
Noncardia gastric cancer					
Low	2,945	8,572	1 (ref)	1 (ref)	
Intermediate	921	7,966	0.63 (0.47–0.83)	0.62 (0.46–0.83)	77.6%, <0.01
High	329	4,374	0.53 (0.34–0.83)	0.50 (0.32–0.78)	82.4%, <0.01
Relative index of inequality (RII)	4,195	20,912	0.38 (0.21–0.69)	0.39 (0.22–0.70)	86.6%, <0.01
By histological subtype					
Diffuse-type					
Low	1,020	6,907	1 (ref)	1 (ref)	
Intermediate	332	5,904	0.72 (0.51–1.00)	0.73 (0.53–1.00)	65.0%, <0.01
High	131	3,320	0.59 (0.34–1.04)	0.62 (0.35–1.11)	76.5%, <0.01
Relative index of inequality (RII)	1,483	16,131	0.44 (0.21–0.96)	0.46 (0.22–0.98)	83.0%, <0.01
Intestinal-type					
Low	1,790	6,907	1 (ref)	1 (ref)	
Intermediate	361	5,904	0.59 (0.41–0.86)	0.62 (0.43–0.90)	75.9%, <0.01
High	149	3,320	0.49 (0.29–0.82)	0.54 (0.32–0.91)	75.4%, <0.01
Relative index of inequality (RII)	2,300	16,131	0.32 (0.16–0.67)	0.35 (0.17–0.70)	83.6%, <0.01

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.
[1]Adjusted for age, sex, alcohol drinking, tobacco smoking, race/ethnicity, fruit and vegetable consumption and study center (for multicenter studies).

for GC that favors 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 risk of noncardia GC, 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, in studies using population-based compared to those using 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 study conduction. Low and middle-income countries account for substantial inequalities as wealth remains

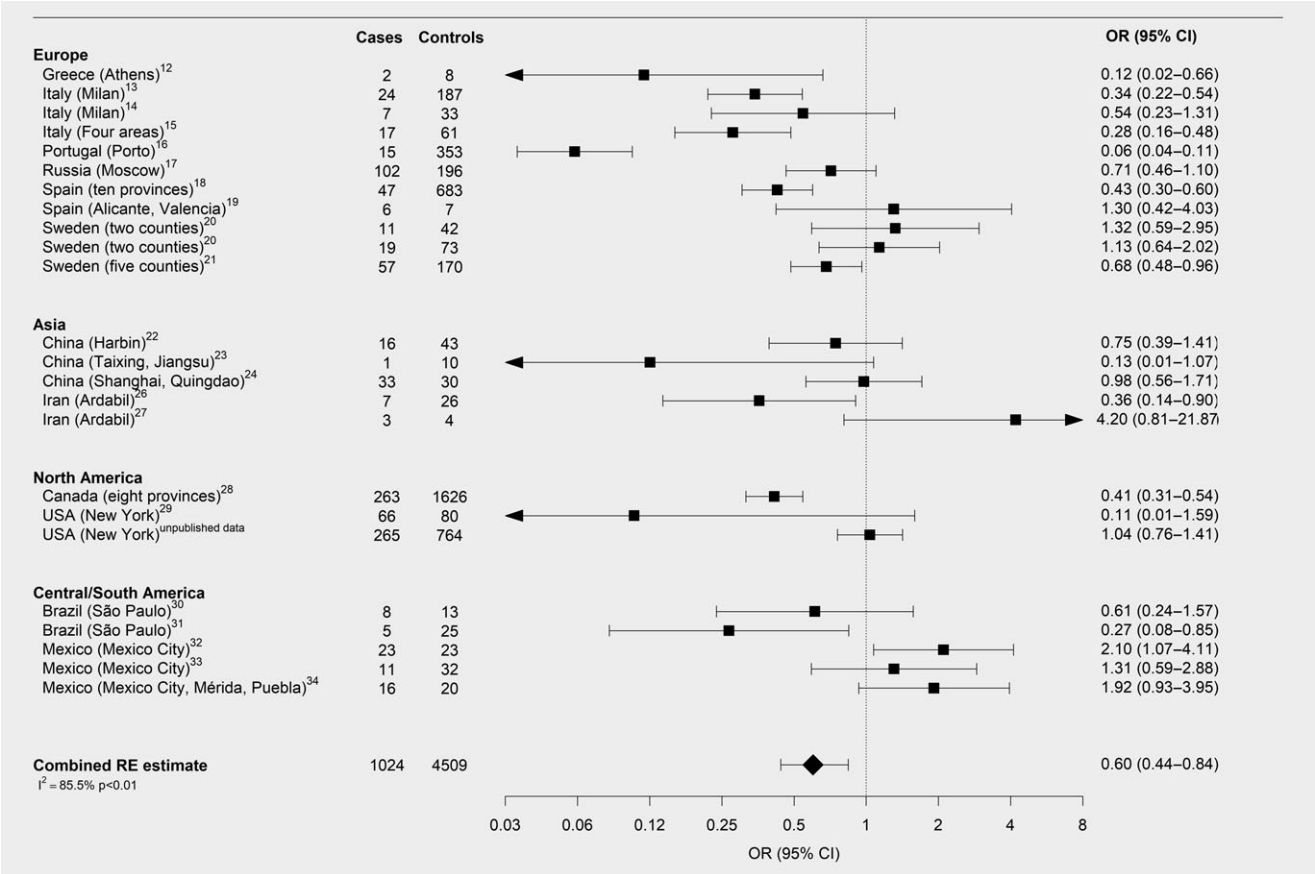

Figure 1. Study-specific and pooled ORs and corresponding 95% CIs of gastric cancer risk for high (ISCED 5–6) as compared to low (ISCED 0–1) educational level in the Stomach cancer Pooling (StoP) Project consortium. Geographic area was classified according to the countries grouping of the Statistics Division of the United Nations. Abbreviations: CI, confidence interval; OR, odds ratio; RE, random effect.

concentrated in the hands of the rich, while the vast majority of the population remains poor, with limited access to education, and thus to better living conditions. 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 remarkably 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 the Portuguese study[16] did not reduce the heterogeneity. In the StoP consortium, a huge effort has been done to harmonize data according to a prespecified 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 to 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 similar 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 could not have a uniform definition of occupational position among the included studies. 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.

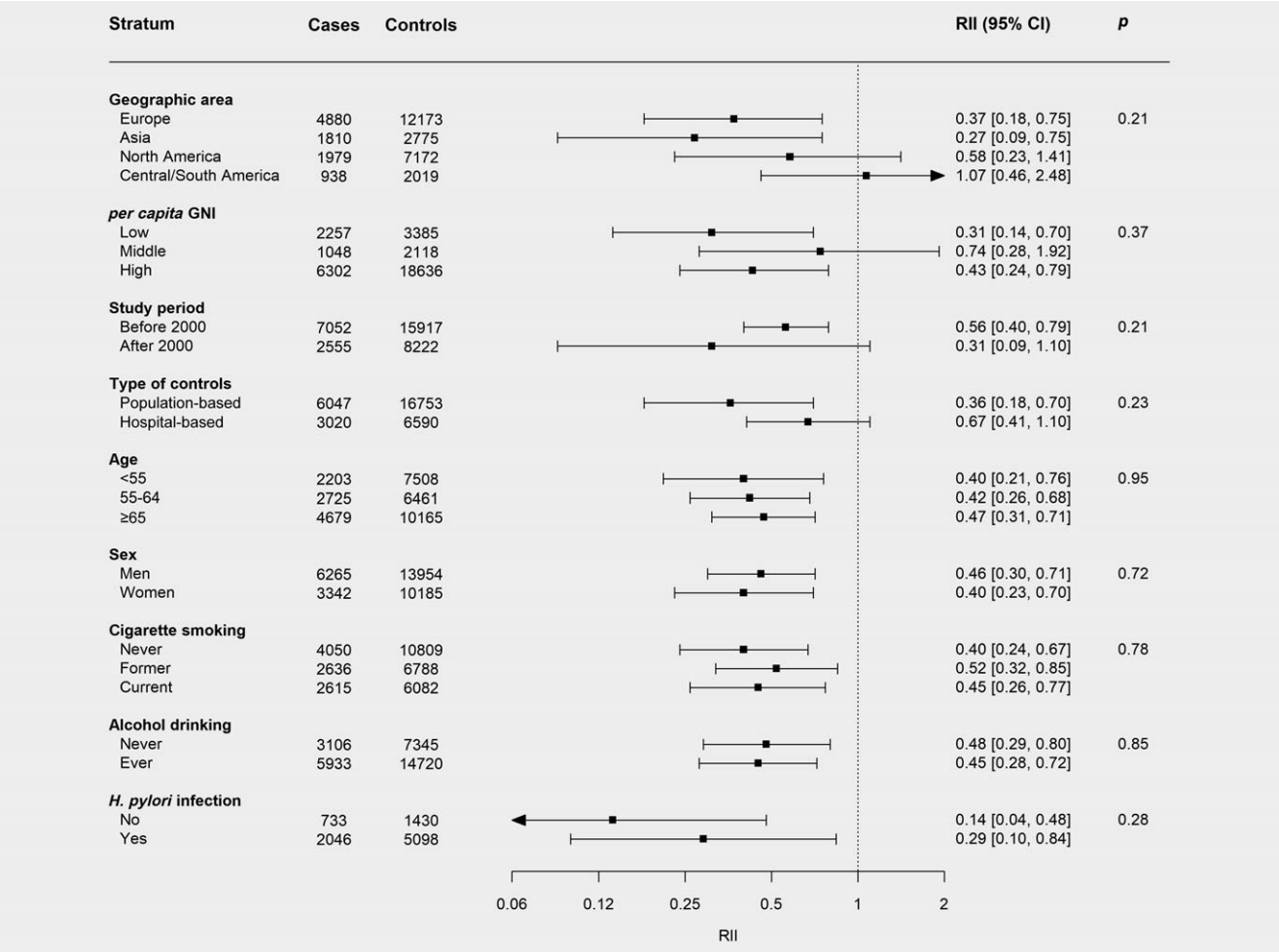

Figure 2. Pooled education-based RIIs and 95% CIs for gastric cancer risk in strata of geographic area, *per capita* GNI of the country where the study was conducted, study period, type of controls, age, sex, cigarette smoking, alcohol drinking and *H. pylori* infection in the Stomach cancer Pooling (StoP) Project consortium. Geographic area was classified according to the countries grouping of the Statistics Division of the United Nations. Abbreviations: CI, confidence interval; GNI, gross national income; RII, relative index of inequality.

In fact, in 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 advantage of the availability of detailed and uniform information on important covariates as compared to 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 and 1999.[50] In these studies, the RII ranged between 1.96 in Spanish men and 3.24 in Italian men, that is, people in the highest rank of the socioeconomic hierarchy had a 30–50% 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] that 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 socioeconomic inequalities at local,

national and international level are needed to reduce GC risk among the more vulnerable groups of the population. Being GC strongly related to low SEP, these interventions will reduce the burden of the disease in the whole population.

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