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Risk factors for gastric cancer in Latin-America: a meta-analysis

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Abstract

Background—Latin America has among the highest gastric cancer incidence rates in the world, for reasons that are still unknown. In order to identify region-specific risk factors for gastric cancer, we conducted a meta-analysis summarizing published literature.

Methods—Searches of PubMed and regional databases for relevant studies published up to December 2011 yielded a total of 29 independent case-control studies. We calculated summary odds ratios (OR) for risk factors reported in at least five studies, including socioeconomic status (education), lifestyle habits (smoking and alcohol use), dietary factors (consumption of fruits, total vegetables, green vegetables, chili pepper, total meat, processed meat, red meat, fish and salt) and host genetic variants (*IL1B*-511T, *IL1B*-31C, *IL1RN**2, *TNFA*-308A, *TP53* codon 72 Arg and *GSTM1* null). Study-specific ORs were extracted and summarized using random-effects models.

Results—Chili pepper was the only region-specific factor reported in at least five studies. Consistent with multifactorial pathogenesis, smoking, alcohol use, high consumption of red meat or processed meat, excessive salt intake and carriage of *IL1RN*2* were each associated with a moderate increase in gastric cancer risk. Conversely, higher levels of education, fruit consumption, and total vegetable consumption were each associated with a moderately decreased risk. The other exposures were not significantly associated. No prospective study data were identified.

Conclusion—Risk factor associations for gastric cancer in Latin America are based on case-control comparisons that have uncertain reliability, particularly with regard to diet; the specific factors identified and their magnitudes of association are largely similar to those globally recognized. Future studies should emphasize prospective data collection and focus on region-specific exposures that may explain high gastric cancer risk.

Keywords

epidemiology; gastric cancer; Latin-America; meta-analysis; risk factors

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BACKGROUND

Gastric cancer represents the second leading cause of cancer death worldwide [1]. This neoplasia arises primarily as a consequence of chronic *Helicobacter pylori* infection [2] which is typically acquired in childhood and, if untreated, usually lifelong [3]. The great variation in gastric cancer incidence across populations may be related to differences in prevalence of *H. pylori* infection and/or environmental and host cofactors that modify gastric cancer risk [4].

Latin American countries have high prevalence of *H. pylori* infection [5, 6] and some of the highest gastric cancer incidence rates in the world [1]. In order to identify region-specific risk factors that could be amenable to tailored interventions, we summarized the published literature on gastric cancer risk in Latin American populations. We contrasted our findings with global meta-analyses, which generally overlook regional studies included in local databases.

MATERIALS AND METHODS

Search strategy and selection criteria

The literature databases PubMed® (U.S. National Library of Medicine, Bethesda, MD), LILACS® (Latin America and the Caribbean Literature on Health Sciences; http://lilacs.bvsalud.org/en), and SciELO® (Scientific Electronic Library Online; http://scielo.org) were searched for observational studies evaluating gastric cancer risk factors in the 20 countries comprising Latin America as defined by the United Nations Educational Scientific and Cultural Organization [7], published in any language up to December 31, 2011.

To identify studies in PubMed, the following search strategy was used: (gastric cancer *OR* stomach cancer) *AND* (risk *OR* risk factors *OR* risk assessment *OR* epidemiologic factors *OR* diet *OR* food habits *OR* fruit *OR* vegetables *OR* sodium, dietary *OR* salts *OR* table salt *OR* sodium chloride, dietary *OR* nitrites *OR* meat *OR* chili pepper *OR* tobacco use *OR* smoking *OR* alcohol *OR* alcoholic beverages *OR* alcohol drinking *OR* polymorphism, genetic *OR* polymorphism, single nucleotide *OR* SNPs) *AND* (case-control studies *OR* cohort studies *OR* cohort *OR* case-control) *AND* (Latin America *OR* Central America *OR* South America *OR* Argentina *OR* Aruba *OR* Bolivia *OR* Brazil *OR* Colombia *OR* Costa Rica *OR* Cuba *OR* Chile *OR* Dominican Republic *OR* Ecuador *OR* El Salvador *OR* Guatemala *OR* Honduras *OR* Mexico *OR* Nicaragua *OR* Panama *OR* Paraguay *OR* Peru *OR* Uruguay *OR* Venezuela). Analogous strategies were used to search the other two databases.

Two investigators (PB and MCC) independently reviewed titles and abstracts for selection of potentially relevant articles; any disagreement was resolved by consulting a third reviewer (FMG). Full-text articles were retrieved for potential inclusion if at least one risk factor was mentioned. Citations of retrieved articles were reviewed for studies that may have been missed or absent from our searches.

The following information was abstracted from each selected article: year of publication, first author, recruitment period, study location (country), numbers of cases and controls, source of controls, participant age range (or mean), proportion of males, tumor distribution by histologic type and anatomic subsite, risk factors, and odds ratios (OR) for gastric cancer. From each study, we extracted fully adjusted ORs with corresponding 95% confidence intervals (CIs), and the adjustment variables. For studies reporting association with genetic polymorphisms, genotype frequencies in cases and controls were also extracted. In addition, we obtained national incidence rates of gastric cancer from GLOBOCAN 2008 estimates for the countries where these studies were conducted [8].

Risk factors

ORs were summarized for risk factors that were reported in at least five studies, including socioeconomic status (SES; level of education), lifestyle habits (smoking and alcohol use), dietary factors (consumption of total fruits, total vegetables, green vegetables, chili pepper, total meat, processed or salted meat, red meat, fish, and table salt use), and human genetic variants *IL1B*-31C, *IL1B*-511T, *IL1RN*2*, *TNFA*-308A, *TP53* codon 72 Arg and *GSTM1* null.

Other risk factors reported in fewer than five studies and therefore not summarized included sociodemographic and geographic characteristics (occupation, rural *vs*. urban residence, refrigerator use, drinking water source and altitude of residence), personal characteristics (height, weight, body mass index, ethnicity, birth order, family history of gastric cancer and ABO blood group), specific types of alcohol consumed, dietary components (consumption of carbohydrates, fats, oils, legumes, tubers, grains, cereals, dairy products, desserts, salty snacks, beverages, micronutrients, trace elements and specific types of fruits, vegetables or meat), cooking methods, and genetic variants (in *IL6*, *IL8*, *IL10*, *TLR2*, *TLR3*, *TLR4*, *NOS2*, *XRCC1*, *XRCC3*, *hOGG1*, *CYP1A1*, *GSTP1*, *GSTT1*, *MCP1*, *CYP2E1*, *CDH1* and *MTHFR*). Regarding region-specific dietary factors other than chili pepper, four of these studies reported on mate, four on beans (including black, fava or kidney beans), two on sweet potatoes or other root tubers and two on maize preparations.

Statistical analysis

Since the categories of the dietary factors varied across studies, our meta-analysis summarized the ORs for the highest *vs.* the lowest consumption category for each study. For studies only reporting subgroups of vegetable consumption (e.g., yellow, green and other), we summarized type-specific ORs by random effects models to obtain an average effect for total vegetables.

In our primary analysis, smoking and alcohol use were analyzed as binary variables (i.e., ever *vs.* never smokers and ever *vs.* never drinkers). Because some studies reported stratum-specific associations each compared to the same referent (e.g., current or former smokers *vs.* never smokers), we averaged those risk estimates using random effects models to estimate the overall effects. As a secondary analytic approach, the effects of current and former smoking were considered in separate meta-analyses. Also, dose-response was evaluated for lifetime exposure to cigarette smoking.

Host genetic polymorphisms were analyzed as binary variables mainly assuming a dominant genetic model; ORs were calculated if not provided in the original report. Given the almost complete linkage disequilibrium between the two reviewed *IL1B* polymorphisms [9], we performed a meta-analysis combining the study-specific OR for either *IL1B-511* or *IL1B-31*. For studies that reported both associations, we averaged those risk estimates by random effects models.

For each risk factor, a summary OR with corresponding 95% CI was obtained using the random effects method of DerSimonian and Laird [10]. We calculated the standard error for the ln(OR) using the reported 95% CI of the OR [11]. Between-study heterogeneity was assessed for statistical significance using the Q test and quantified with the I^2 statistic as low (<25%), moderate (25%–50%) or high (>50%) [12, 13]. If moderate or high heterogeneity was identified for a given risk factor, meta-regression models were used to examine the extent to which one or more of the following study-related quality or other characteristics might be explanatory: type of controls (gastroenterology patients, non-gastroenterology patients, healthy volunteers or population-based sample), sample size (≤200, 201–400, 401–

600, or >600 subjects), adjustment for SES-related variables such as education and/or income (present *vs.* absent), and national gastric cancer incidence rate (<16 *vs.* ≥16 cases/100,000 population). Galbraith plots were also used to visually identify studies which were major contributors to moderate or high heterogeneity [14]. Data points positioned over or below the 95% CI of the regression line were defined to be outliers. Sensitivity analyses excluding such studies were performed to assess the influence on the summary OR.

For each of the studied risk factors, publication bias was investigated by visual inspection of Begg's funnel plots and formally tested using Egger's regression asymmetry method [15, 16].

Meta-analyses were performed with Stata version 11 (StataCorp, College Station, TX) using a combination of published macros, including metan, metareg, galbr, metafunnel and metabias [17]. A p-value less than 0.05 was considered statistically significant for all tests except the heterogeneity and Egger tests, for which $p<0.10$ was considered significant. All statistical tests were two-sided.

RESULTS

Literature search and description of studies

The literature searches identified a total of 417 articles: 204 from PubMed, 120 from LILACS, and 93 from SciELO (Figure 1). After excluding 354 irrelevant, insufficiently documented or duplicate publications, 63 full text articles were retrieved for further evaluation; 12 additional publications were identified from citations of these articles. Thus, we evaluated 75 articles reporting risk factor associations with gastric cancer.

Twenty-four publications reported exposure factors for which less than five articles were identified. Six articles were excluded [18–23] because the authors had other publications involving the same risk factors in larger, but overlapping samples. Thus, a total of 45 articles (33 written in English and 12 in Spanish) [24–68] published between 1990 and 2011 were included in this meta-analysis (Supplementary Table 1).

These 45 articles represented 29 independent studies assessing different risk factors among overlapping samples. No prospective study data were identified. All 29 studies correspond to case-control comparisons, including three with population-based controls, eight with other healthy controls, and 18 with hospital-based controls. Eight studies were conducted in Brazil, seven in Colombia, four in Mexico, three in Uruguay, two in Costa Rica, two in Venezuela, one in Chile, one in Peru, and one in Honduras. In terms of the total sample size (cases and controls combined), seven studies included less than 200 subjects, eleven studies between 201 and 400, two between 401 and 600 subjects, and nine were based on more than 600 subjects.

Adjustment variables differed among the studies. Twenty-three studies adjusted for age and sex, eleven for sociodemographic characteristics (e.g., SES, urban *vs.* rural residence, or level of education), ten for diet-related variables, seven for both smoking and alcohol use, five for *H. pylori* infection, and four for other personal characteristics (i.e., body mass index, race/ethnicity, country of birth, or family history of gastric cancer).

Regarding characteristics of cases, 12 studies provided information about the anatomic location of the tumor and 18 studies had histological subtype. Among the classified tumors, the proportion localized to noncardia sites ranged from 75 to 100% and the proportion of tumors classified as intestinal type ranged from 35 to 100%. Nine articles presented analyses

stratified by these variables, with less than five studies for any given risk factor [36, 43, 48–51, 53, 56, 59].

Associations with SES

Education—Six studies examined the association between education and gastric cancer [35, 37, 38, 40, 62, 66]. Study-specific OR for the highest level of education as compared to the lowest ranged from 0.24 to 0.84 (Figure 2a). The summary OR indicated a significant inverse association with a 52% decreased risk of gastric cancer (Table 1). High heterogeneity was detected among the studies, but meta-regression analysis of potential explanatory factors failed to explain the variability. The association was attenuated when an outlier study [66] was excluded (38%; 95% CI, 9–57%).

Associations with lifestyle habits

Smoking—Fourteen studies examined the association of smoking and gastric cancer [24, 25, 32–36, 40, 42, 49, 58, 59, 62, 66]. Study-specific ORs for ever smokers *vs.* never smokers ranged from 0.56 to 5.87 (Figure 2b). The summary OR associated smoking with a 47% increased risk of gastric cancer (Table 1). High between-study heterogeneity was detected among the studies, but there were no significant explanatory variables in meta-regression analysis. A Galbraith plot indicated that four outlier studies [24, 34, 35, 40] contributed to heterogeneity; the summary OR estimated after their exclusion was 1.49 (95% CI, 1.29–1.73).

Six of the 14 studies [24, 25, 36, 58, 59, 66] evaluated the association of smoking and gastric cancer separately for current and for former smokers. Study-specific ORs for current smokers *vs*. never smokers ranged from 0.70 to 2.69. The summary OR showed a 60% increased risk of gastric cancer among current smokers (Table 1). Between-study heterogeneity was high, but meta-regression analysis failed to explain the variability. The summary OR was slightly modified (OR, 1.41; 95% CI, 1.05–1.89) after excluding an outlier study [59]. On the other hand, study-specific ORs for former-smokers *vs.* never smokers ranged from 0.60 to 1.90. The summary OR was 1.23 with low heterogeneity across studies (Table 1).

Five studies reported the association between lifetime exposure to cigarette smoking, measured in pack-years, and gastric cancer risk [24, 25, 42, 59, 62]. In a dose response meta-analysis, the increase in gastric cancer risk per 10 pack-years was 12% (95% CI, 6–18%).

Alcohol—Risk estimates for alcohol use were reported in 16 studies [24, 25, 32–35, 37, 40, 41, 49, 52, 56, 58, 59, 62, 66]. For six of these studies [24, 25, 58, 59, 62, 66], dose-specific ORs for ever drinkers were averaged since overall associations were not reported. Study-specific ORs comparing ever drinkers *vs*. never drinkers ranged from 0.68 to 3.97 (Figure 2c). The summary OR showed ever drinkers had a significant 61% increased risk of gastric cancer (Table 1). Between-study heterogeneity was high, but meta-regression analysis failed to explain this variability. In a sensitivity analysis excluding five outlier studies [33, 34, 52, 62, 66], the summary OR was slightly attenuated (OR, 1.45; 95% CI, 1.24–1.70).

Associations with dietary factors

Total fruits—Eleven studies examined the association between fruit consumption and gastric cancer risk [24, 25, 36, 38, 40, 50, 52, 58, 60, 63, 66]. Study-specific OR for the highest consumption as compared to the lowest ranged from 0.30 to 2.27 (Figure 3a). The summary OR indicated a significant inverse association with a 32% decreased risk of gastric cancer (Table 1). High heterogeneity was detected among the studies, but the decrease was

similar (39%; 95% CI, 28–47%) after the exclusion of two outlier studies [58, 66] which reported extreme opposite effects. Meta-regression analysis identified nominal significance of SES adjustment (p=0.03), reflecting such adjustment in one of the outlier studies and not in the other.

Total vegetables—Twelve studies provided results about vegetable consumption and gastric cancer risk [24, 25, 36, 38, 40, 50, 52, 56, 58, 60, 63, 66], with study-specific ORs for highest consumption in comparison to lowest ranging from 0.30 to 2.72 (Figure 3b). For the studies by Hamada *et al*. [24] and Nishimoto *et al*. [25], average ORs derived from results for green, yellow and other vegetables were used in this meta-analysis since only type-specific associations were originally reported. The summary OR for total vegetables indicated a significant 42% risk reduction in gastric cancer risk (Table 1). Between-study heterogeneity was high, but meta-regression analysis did not identify any explanatory factors. With the exclusion of three outlier studies [38, 52, 63], the risk reduction was 53% (95% CI, 43–62%).

Green vegetables—The association of green vegetable consumption with gastric cancer was evaluated in five studies [24, 25, s38, 50, 61]. The study-specific ORs for the highest consumption compared to the lowest ranged from 0.27 to 1.00. The summary OR was 0.87, with low heterogeneity across studies.

Chili peppers—The association of chili pepper consumption was studied in six studies, including five which directly assessed chili peppers as a food item [37, 40, 48, 56, 66], and one which evaluated calculated consumption of the putative active component capsaicin [51]. The study-specific OR for the highest consumption *vs.* the lowest ranged from 0.50 to 2.10, except for a study [48], which had an OR of 28. The summary OR was 2.30 (Table 1). High heterogeneity was detected, but there were no significant explanatory variables in meta-regression analysis. When two outlier studies [48, 66] were excluded, the summary OR was 1.94 (95% CI, 1.40–2.68).

Total meat—Five studies provided information on total meat consumption [38, 50, 58, 65, 66], with study-specific ORs for highest consumption in comparison to lowest ranging from 0.31 to 3.10. The summary OR was 1.14 (Table 1). High heterogeneity was detected, but there were no significant explanatory variables in meta-regression analysis. Two studies [50, 66] were identified as outliers, and the summary OR derived from their exclusion was 1.53 (95% CI, 0.91–2.57).

Processed meat—Risk estimates for highest *vs.* lowest frequency of processed or salted meat consumption were reported in six studies [37, 38, 40, 50, 58, 64], and ranged from 0.82 to 3.19 (Figure 3c). The summary OR for processed meat indicated a significant 64% increased risk of gastric cancer (Table 1). High heterogeneity was detected, but there were no significant explanatory variables in meta-regression analysis. When two outlier studies [50, 64] were excluded, the summary OR was 1.62 (95% CI, 1.25–2.10).

Red meat—For the analysis of red meat consumption, a total of five studies were identified [24, 25, 40, 60, 65]. Study-specific ORs for the highest *vs.* the lowest consumption ranged from 1.11 to 4.01 (Figure 3d). The summary OR showed a significant 73% increased risk of gastric cancer (Table 1). Between-study heterogeneity was high, but meta-regression analysis failed to explain the variability. With the exclusion of an outlier study [24], the summary OR was 1.47 (95% CI, 1.13–1.90).

Fish—The association of fish consumption and gastric cancer was reported in six studies [24, 25, 40, 50, 62, 66]. The study-specific ORs for the highest consumption as compared to the lowest ranged from 0.30 to 4.76, with a summary OR of 0.86 (Table 1). Between-study heterogeneity was high, but meta-regression analysis failed to explain the variability. Two studies [50, 66] were identified as outliers, and the summary OR derived from their exclusion was 0.82 (95% CI, 0.48–1.40).

Salt—Seven studies provided information on use of table salt [34, 36, 38, 40, 49, 56, 66]. Study-specific ORs for the highest *vs.* the lowest intake ranged from 1.13 to 5.58 (Figure 3e). The summary OR found a significant association with a 2.24-fold increased risk of gastric cancer (Table 1). Between-study heterogeneity was high, but meta-regression analysis failed to show any significant source of heterogeneity. With the exclusion of one outlier study [66], the summary OR was 1.98 (95% CI, 1.40–2.82).

Associations with genetic variants

***IL-1B* polymorphisms—**Eleven studies evaluated the associations of gastric cancer risk with either *IL1B-511T* [39, 46, 47, 57, 67], *IL1B-31C* [29, 53, 54] or both [26, 30, 43]. Allele frequency of the putative risk variant (i.e., *IL1B*-511T or *IL1B*-31C) among controls ranged from 45 to 80% across studies. Study-specific ORs for carriers of the risk alleles as compared to non-carriers ranged from 0.44 to 2.99, except for an outlier study [54] which had an OR of 8.0. The summary OR including all studies was 1.07, with moderate heterogeneity (Table 1). The summary OR derived from the exclusion of an outlier study was 1.0 (95% CI, 0.76–1.31).

***IL-1RN* variable number tandem repeat (VNTR) allele 2—**Risk estimates of the association between *IL1RN*2* and gastric cancer were reported in eleven studies [26, 29, 30, 39, 43, 46, 47, 53, 54, 57, 67]. Allele frequency of the *2 VNTR among controls ranged from 17 to 38% across studies. Study-specific ORs for the comparison of *2 carriers (i.e., heterozygous or homozygous) *vs.* *2 non-carriers ranged from 0.65 to 2.77 (Figure 4). The summary OR found a significant 51% increased risk of gastric cancer (Table 1). Although no outliers were identified, there was moderate heterogeneity and no factors were significantly associated with this variability by meta-regression.

***TNFA*-308 polymorphism—**The association of *TNFA*-308A and gastric cancer was reported in six studies [29, 30, 35, 39, 47, 54]. Allele frequency of the A variant among controls ranged from 4 to 14% across studies. Study-specific ORs for carriers of A (i.e., heterozygous or homozygous) as compared to G/G genotype ranged from 0.41 to 1.39. The summary OR was 0.96 (Table 1), with low heterogeneity across studies.

***TP*53 codon 72 polymorphism—**Six studies examined the association of *TP*53 codon 72 polymorphism and gastric cancer [27, 31, 41, 44, 55, 68]. Allele frequency of Pro among controls ranged from 27 to 38% across studies. Study-specific ORs for the comparison of Pro carriers (i.e., Arg/Pro or Pro/Pro) *vs.* Arg/Arg ranged from 0.51 to 1.12. The summary OR was 0.87 (Table 1), with low heterogeneity across studies.

***GSTM1* polymorphism—**Five studies evaluated the associations of gastric cancer risk with *GSTM1* variation [28, 33, 35, 42, 45]. The frequency of null/null genotype among controls ranged from 18 to 60% across studies. Study-specific ORs for the null genotype as compared to non-null genotypes ranged from 0.81 to 5.45. The summary OR was 1.36, with high heterogeneity (Table 1); meta-regression analysis failed to show any significant source of variation. The summary OR derived from the exclusion of an outlier study [35] was 1.14 (95% CI, 0.62–1.60).

Publication bias

The p-values for Egger's test of publication bias were greater than 0.10 for all risk factors with the exception of green vegetable consumption (p=0.10) (Table 1). A funnel plot confirmed moderately asymmetric distribution of the data points for this exposure.

DISCUSSION

Identification of risk factors may provide insight into disease etiology and suggest prevention strategies. Our meta-analysis of Latin-American studies identified increased gastric cancer risks associated with smoking, alcohol use, high consumption of red and processed meat, excessive salt intake and carriage of *IL1RN*2* and decreased risks with high level of education and high consumption of fruits and vegetables. We found no significant associations with *IL1B*, *TP53*, *TNFA*, or *GSTM1* variants, nor with high consumption of green vegetables, chili pepper, total meat, or fish. With the exception of chili pepper consumption, the factors summarized in this meta-analysis represent common exposures worldwide.

Previous meta-analyses of these gastric cancer risk factors have generally utilized international databases. By encompassing both international and regional sources, our meta-analysis aimed to summarize all available epidemiologic data from Latin American studies in order to identify exposures of particular importance in this population. In the following paragraphs we compare our regional findings with those reported by previous global studies.

In agreement with the most recent meta-analyses addressing the association between cigarette smoking and gastric cancer globally [69, 70], we found a 60% increased risk in current smokers compared to never smokers in Latin America, and a weaker association in former smokers. Although the mechanisms by which smoking increases the risk of gastric cancer are not completely understood, tobacco carcinogens may damage the gastric mucosa and smoking may adversely affect *H. pylori* persistence [71] as well as the efficacy of eradication therapy [72]. These effects become particularly important due to the increasing prevalence of smoking in Latin American populations [73].

The potential effect of alcohol on promotion of gastric carcinogenesis is still unclear [74]. A recent global meta-analysis of the association between alcohol drinking and gastric cancer found a significant association with heavy consumption (≥4 drinks per day), but no association with moderate consumption [75]. Our meta-analysis found that the risk of gastric cancer is increased in drinkers compared to never drinkers in Latin America, which may be related to greater alcohol consumption in the Americas as compared to other parts of the world [76].

Regarding diet, high fruit and vegetable consumption have been found to be protective by global case-control studies [77], a conclusion mirrored by our meta-analysis in Latin America. However, weak-to-null associations with fruits and vegetables have been found in prospective studies [78, 79], none of which were conducted in Latin American populations. This paradox is unexplained and whether a true association exists remains to be determined. Our regional findings on consumption of red meat, processed meat and salt do not differ with global studies of both retrospective and prospective design, supporting the hypothesis that excessive consumption of these items increases the risk of gastric cancer [80–82]. Neither our regional data nor prior global meta-analyses [83] support an association between fish consumption and gastric cancer risk.

The studies we summarized provided little or no validation data for their dietary self-report questionnaires, which generally omitted food items specific for this geographic region.

There is a need for higher quality assessment instruments that cover regionally specific dietary components and preparation methods for Latin American populations. Furthermore, food frequency questionnaires may be usefully complemented by biomarker studies as a more objective method to estimate intake of specific nutrients [84].

The inverse association of education level with gastric cancer risk in our meta-analysis is in line with previous findings [85, 86]. Education captures aspects of the construct SES and may be particularly related to *H. pylori* infection, lifestyle habits and/or diet. Nevertheless, previous large prospective studies conducted in Europe and North America have attributed only some of the educational gradient to *H. pylori* infection [87] and smoking [88]. Additional mechanisms underlying the consistent protective relationship between education and gastric cancer remain to be identified.

Candidate gene and genome-wide association studies (GWAS) have implicated polymorphisms in several genes as significantly associated with gastric cancer risk, including *IL1B, IL1RN, IL8, IL10, CDH1, MTHFR, PSCA, PLCE1, PTGER4, PRKAA1*, and *ZBTB20* [89–96]. In particular, global meta-analyses summarizing data on *IL1B* and *IL1RN* variants have suggested race-specific associations [89–92], with increased gastric cancer risk in Caucasians and weak or null associations in Asians. Caucasians have a lower prevalence than Asians of the putative risk alleles *IL1B-31C* and *IL1B-511T*. Therefore, it has been suggested that the effect is difficult to detect due to the high population frequency of the risk allele, or alternatively, that these variants do not influence gastric cancer susceptibility in Asians. Our data indicate that similar to Asians, Latin Americans have a high prevalence of *IL1B* risk alleles and null associations with gastric cancer. On the other hand, our results for the *IL1RN**2 VNTR support its involvement in gastric carcinogenesis.

Although the association of gastric cancer with *TNFA*-308 and *TP*53 codon 72 Arg polymorphisms are not entirely consistent in global data [92, 97–99], neither of these polymorphisms appears to be associated with gastric cancer in Latin American populations. Apart from the six variants summarized by our meta-analysis, the potential of Latin American populations to identify unique risk-associated loci and/or to replicate GWAS findings has not been fully exploited. Association studies in this genetically admixed population (including Amerindian, Caucasian and African variants) offer opportunities for elucidating patterns of linkage disequilibrium, in studies of adequate sample size with proper adjustment for genetic ancestry.

Our findings, based primarily on small, convenience samples representing nine of the 20 Latin American countries, imply that most gastric cancers in this region are noncardia and intestinal-type. However there are no population-based data on subsite- and histology-specific incidence. Unfortunately, cancer registration coverage in Latin America is limited [100] and available data do not generally include these tumor characteristics.

As a meta-analysis of observational studies, our re-analysis is prone to biases inherent in the original studies. All the data for this meta-analysis were extracted from case-control comparisons, mainly using hospital-based controls, which are of uncertain validity and representativeness. Also, variation in the categorization of exposure levels may have contributed to the high heterogeneity. Although we used the reported multivariable adjusted ORs where available, there may have been residual confounding.

Assessment of *H. pylori* in case-control comparisons is problematic. Although essentially all gastric cancer is attributable to chronic *H. pylori* infection, some cases are serologically negative since the infection tends to diminish with progression of carcinogenesis [101]. The majority of studies included in this meta-analysis did not evaluate *H. pylori* serology, and

five adjusted for infection status by multivariable regression without considering potential misclassification. A potentially better approach would be testing controls only, and comparing seropositives to gastric cancer cases regardless of serostatus. Nevertheless, our summary risk estimates should not have been substantially biased, since *H. pylori* infection is highly prevalent in Latin American populations and not believed to be highly correlated with most of the reviewed risk factors.

Future research efforts should be directed toward Latin American-specific exposures that may have etiologic significance, such as yerba mate consumption, locally grown fruits and vegetables, fermented and non-fermented beverages, and indoor use of wood stoves. Additional insights may be derived from the higher gastric cancer mortality in the Andes mountain range compared to adjacent coastal areas with equally high *H. pylori* prevalence [102]. Differences in *H. pylori* genotypes and its ancestral origin (European *vs*. African) [103], parasitic infections [104], dietary patterns, soil composition, or other environmental exposures have all been suggested as potential explanations.

About 9% of gastric carcinomas have Epstein-Barr virus (EBV) in the tumor cells [105]. EBV-positive tumors are characterized by episomal monoclonality [106], distinct clinical and genetic characteristics [107], and high anti-EBV antibody titers [108], which support viral involvement in gastric carcinogenesis. Previous studies in Latin America have found prevalence of tumor EBV positivity in gastric cancer ranging from 3.9% in Peru [109] to 16.8% in Chile [110]. The specific role of viral infection in gastric cancer development in this region, if any, may vary in magnitude across populations.

In conclusion, our meta-analysis identified risk factors for gastric cancer in Latin American countries that are similar to those identified globally. Most of our summarized risk estimates were moderate in magnitude, suggesting that additional risk factors contributing to the high incidence of gastric cancer in Latin America are yet to be recognized. Although there is insufficient evidence for dietary modifications to prevent gastric cancer, our findings further support lifestyle modifications to reduce smoking in this geographic region. In addition, the heavy burden of infection-related cancers in Latin America warrants serious consideration of a prospective epidemiologic study, which could simultaneously assess other common chronic morbidities such as diabetes, obesity, and cardiovascular disease. Solving the conundrum of the high gastric cancer incidence in Latin America would reduce mortality in this region and could improve our understanding of cancer etiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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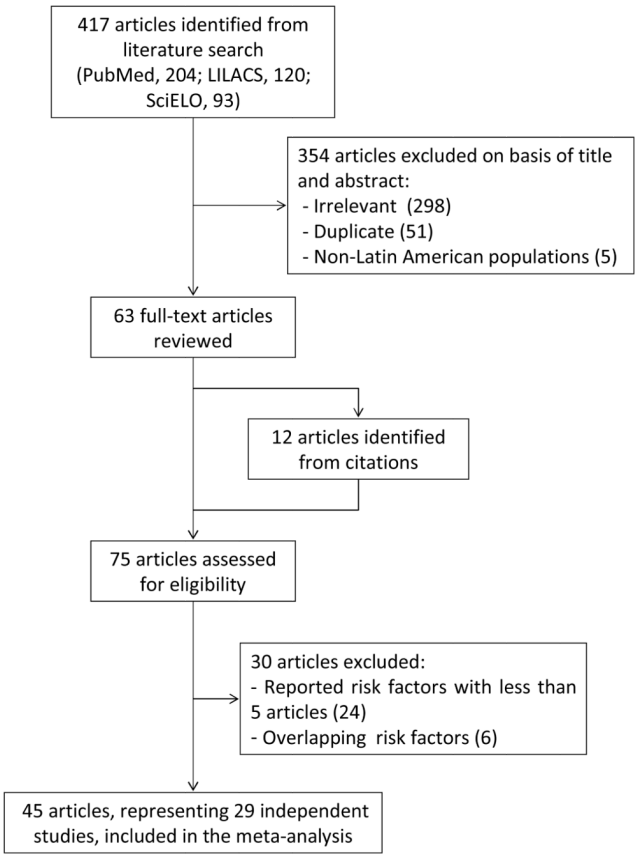
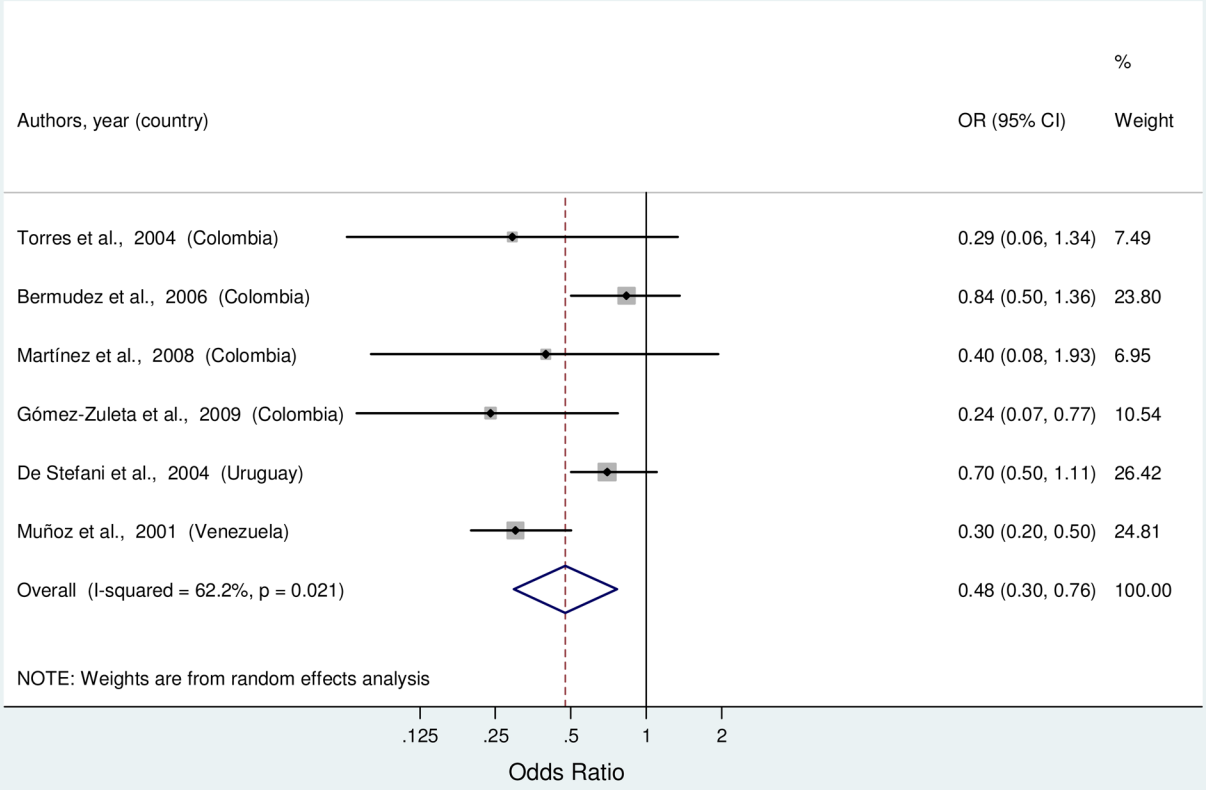
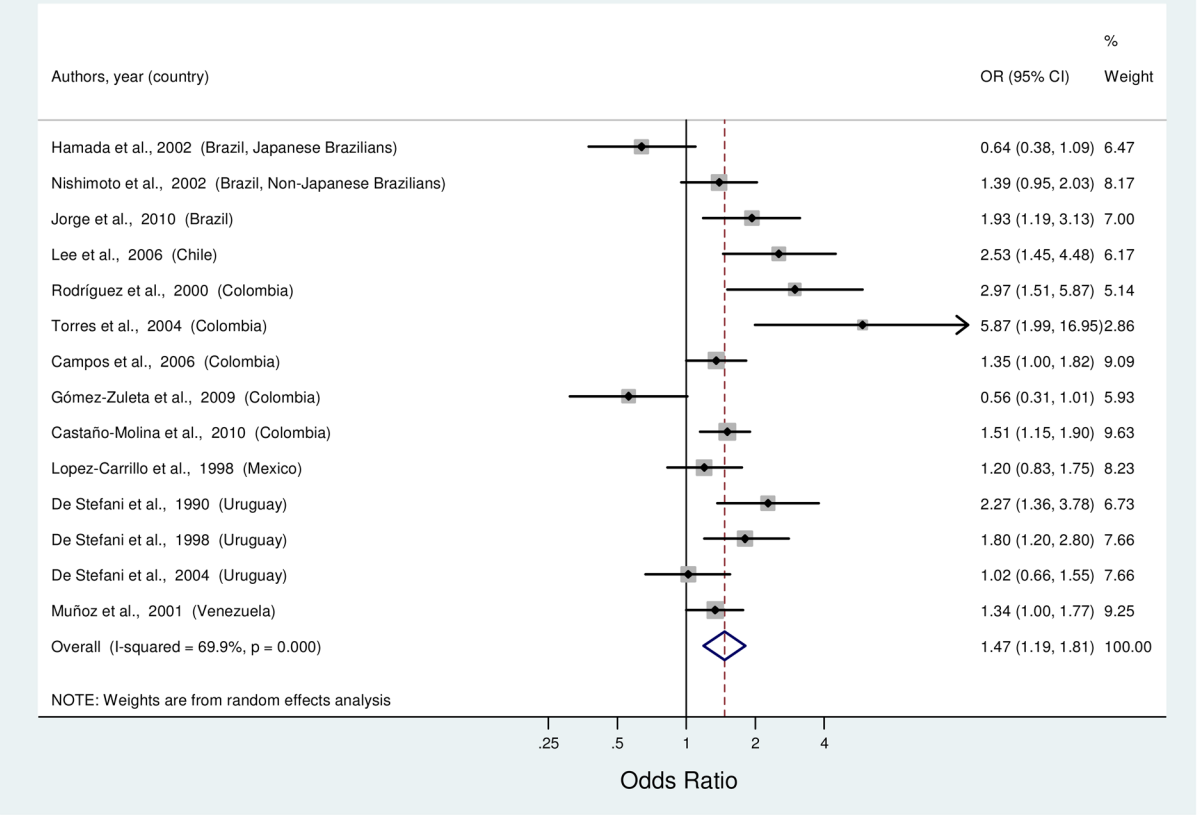


Figure 1.
Flow diagram of the literature search.

2a



2b



2c

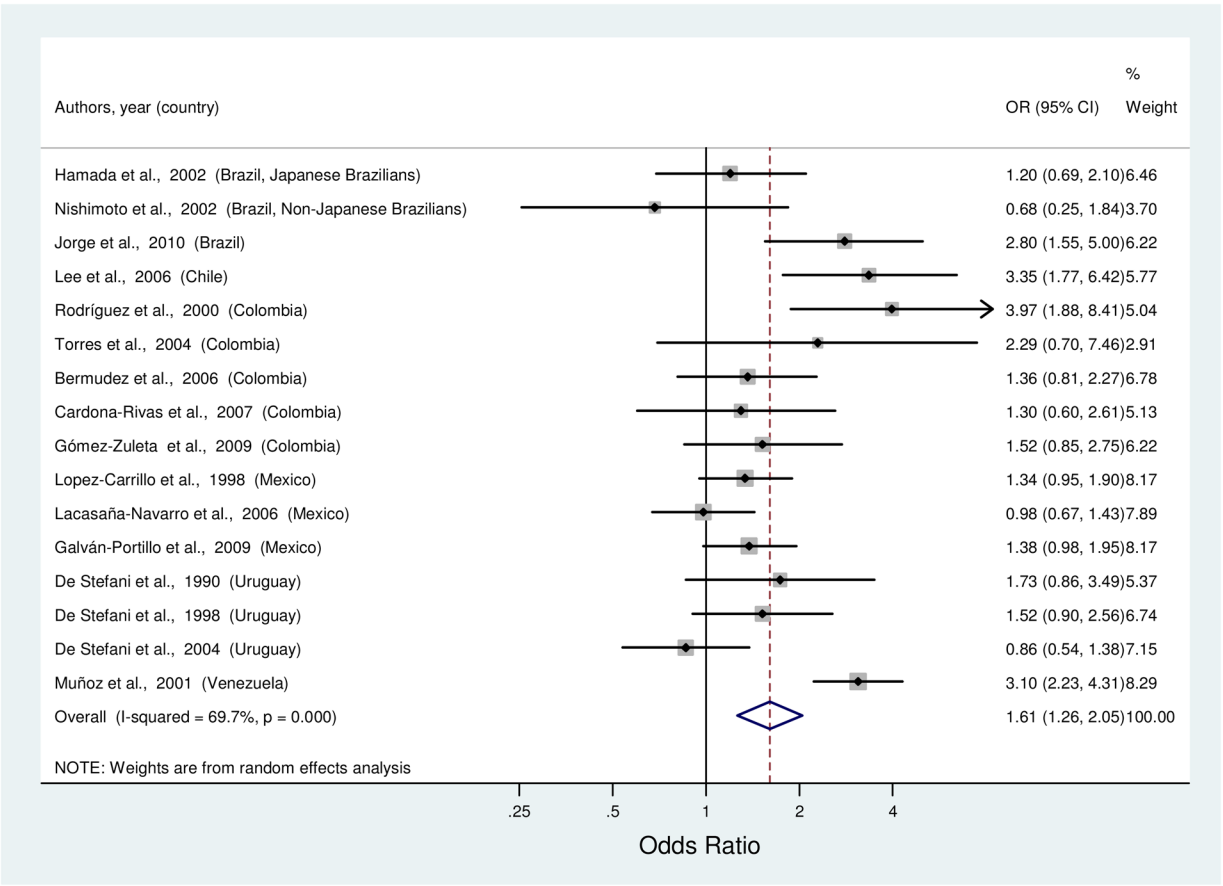
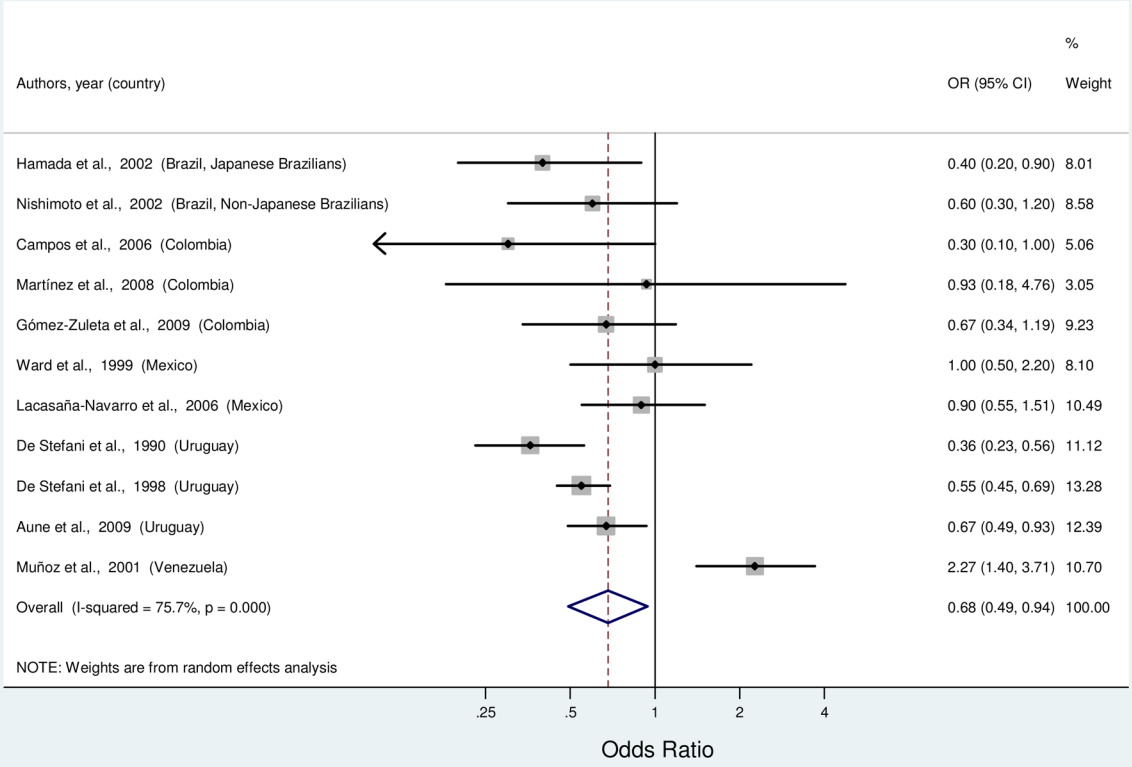


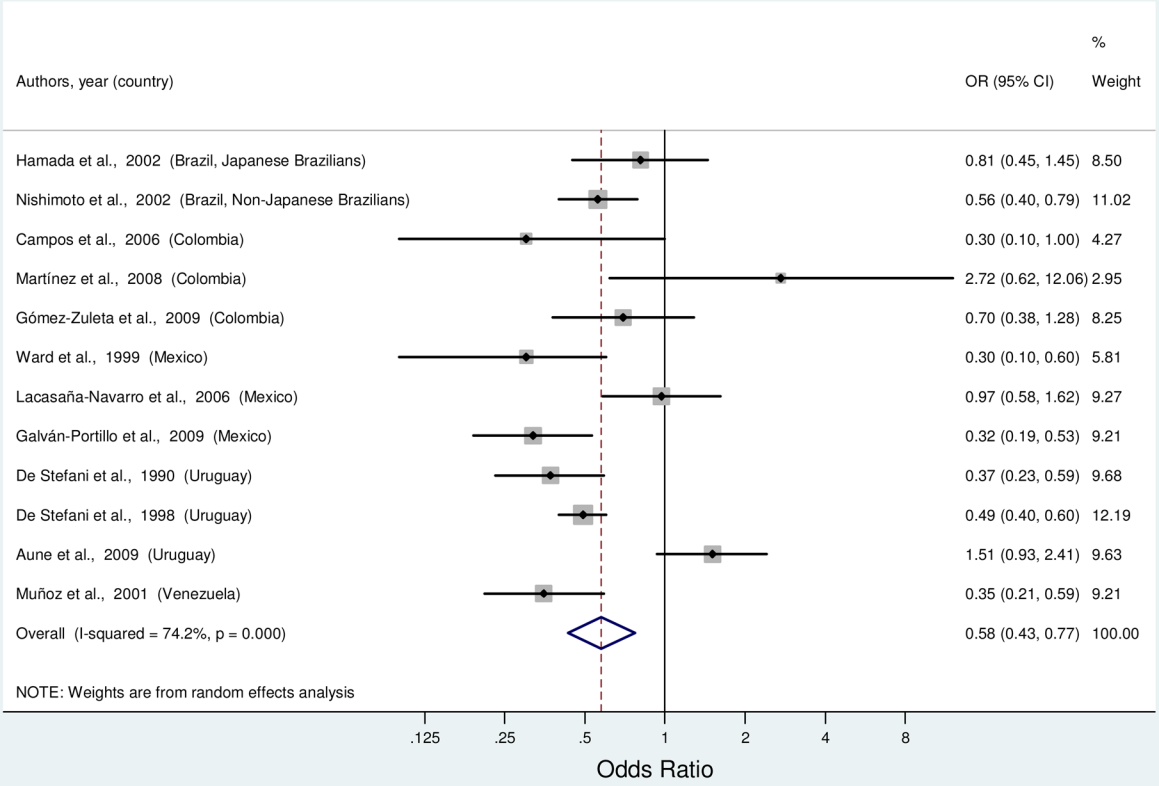
Figure 2.

a to c, random-effects estimates and 95% CIs of gastric cancer odds ratio (OR) associated with (A) education (highest *vs.* lowest level), (B) cigarette smoking (smokers *vs.* nonsmokers) and (C) alcohol use (drinkers *vs.* nondrinkers). Study-specific RRs are shown as squares, with the size of the symbol inversely proportional to the study-specific variance. Summary ORs are shown as diamonds, with the middle corresponding to the point estimate and the width representing the 95% CI.

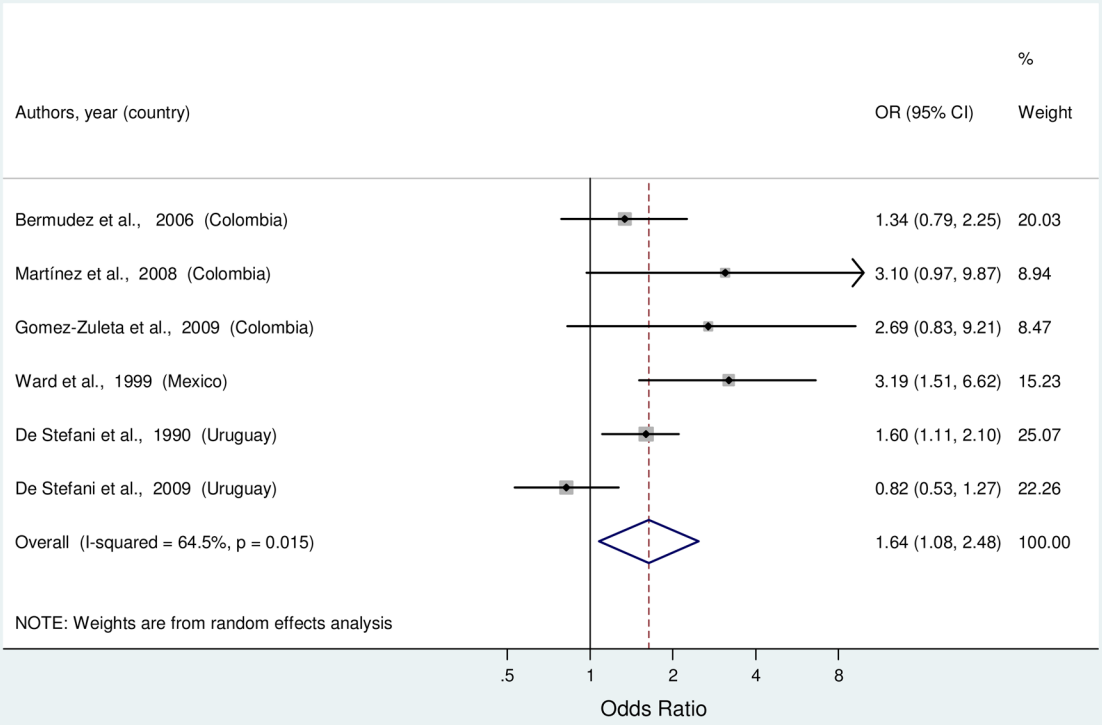
3a



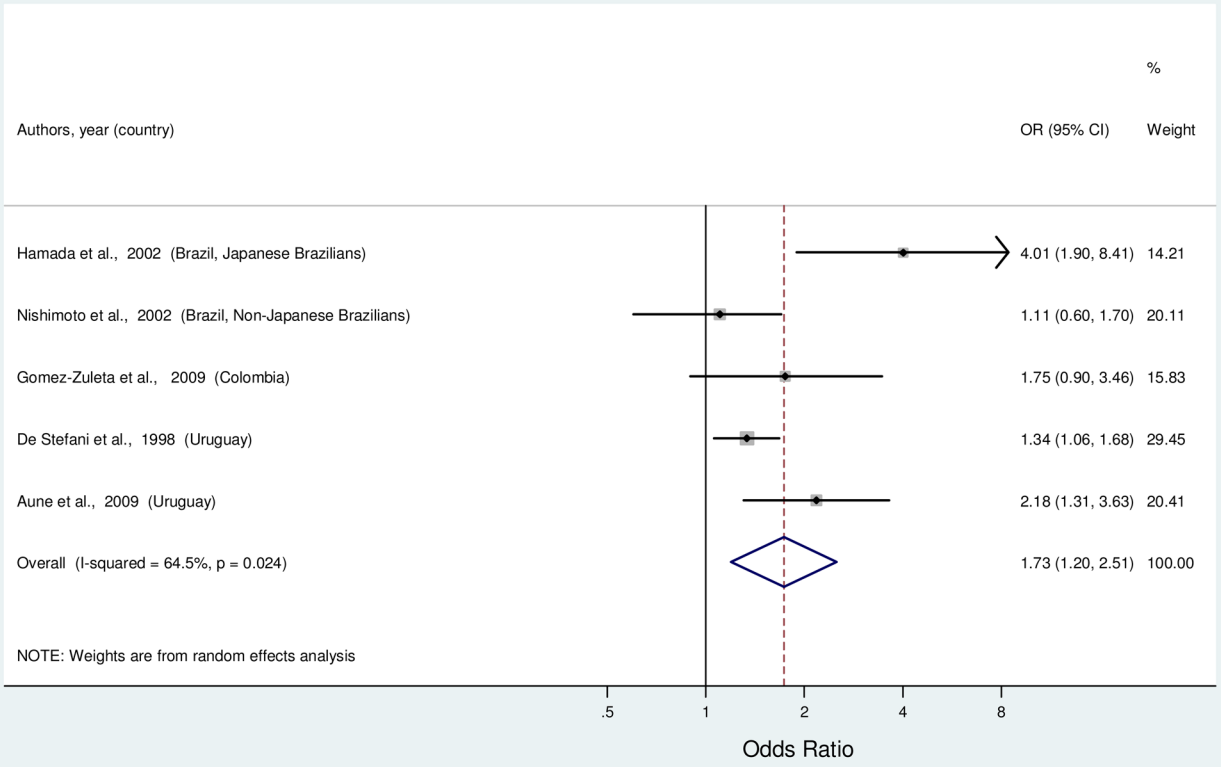
3b



3c



3d



3e

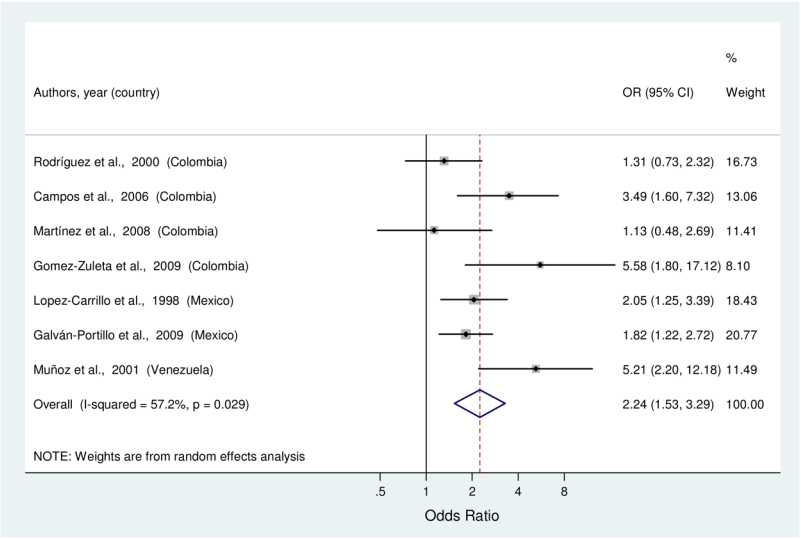


Figure 3.

a to e, random-effects estimates and 95% CIs of gastric cancer odds ratio (OR) associated with (a) total fruit consumption (highest *vs.* lowest category), (b) total vegetable consumption (highest *vs.* lowest category), (c) processed or salted meat consumption

(highest *vs.* lowest category), (d) red meat consumption (highest *vs*. lowest category), and (e) Table salt use (yes *vs.* no). Study-specific RRs are shown as squares, with the size of the symbol inversely proportional to the study-specific variance. Summary ORs are shown as diamonds, with the middle corresponding to the point estimate and the width representing the 95% CI.

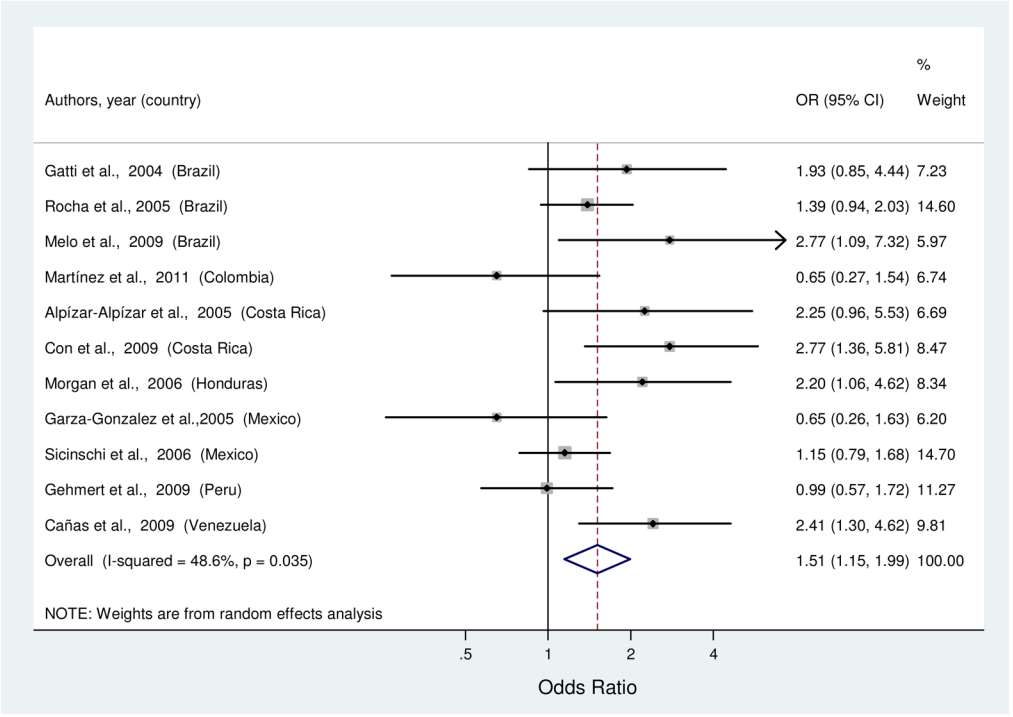


Figure 4.

Random-effects estimates and 95% CIs of gastric cancer odds ratio (OR) associated with IL*1RN* VNTR (*2 carrier *vs.* *2 non-carrier). Study-specific ORs are shown as squares, with the size of the symbol inversely proportional to the study-specific variance. Summary RRs are shown as diamonds, with the middle corresponding to the point estimate and the width representing the 95% CI.

Table 1

Summary of risk factor associations with gastric cancer

Risk Factor	Exposure categories		Number of studies by type of controls			Summary OR for gastric cancer (95% CI)	P_Q for heterogeneity	I^2 for heterogeneity,%	$P_{Egger's}$ for publication bias
	Highest[a] (min to max)	Referent[b] (min to max)	Hospital- based[c]	Healthy volunteers	Population- based				
Education	some to secondary/superior	none to 0–2 years	5	1	0	0.48 (0.30 –0.76)	0.02	62.2	0.47
Smoking	smokers	never smokers	10	3	1	1.47 (1.19 –1.81)	<0.001	69.9	0.38
	current smokers	never smokers	5	1	0	1.60 (1.13 –2.27)	0.01	69.2	0.49
	former-smokers	never smokers	5	1	0	1.23 (0.95 –1.60)	0.25	24.1	0.46
Alcohol use	drinkers	never drinkers	11	3	2	1.61 (1.26 –2.05)	<0.001	69.7	0.84
Total fruit consumption	frequent consumption to daily	infrequent consumption to <2 times/day	9	1	1	0.68 (0.49 –0.94)	<0.001	75.7	0.67
Total vegetable consumption	frequent consumption to daily	infrequent consumption to <3.05 portions/day	9	1	2	0.58 (0.43 –0.77)	<0.001	74.2	0.57
Green vegetable consumption	>4 times/week to daily	< 1 times/week to<5 times/week	3	1	1	0.87 (0.65 –1.16)	0.57	0	0.10
Chili pepper consumption	often to >9 jalapeños/day	never to < 3 jalapeños/day	3	1	2	2.30 (0.94 –5.64)	<0.001	90.1	0.28
Total meat consumption	>5 times/week to >8 times/ week	<3 to <4 times/week	3	1	1	1.14 (0.47 –2.73)	<0.001	89.6	0.85
Processed or salted meat consumption	frequent consumption to >5times/week	no consumption to infrequent	5	0	1	1.64 (1.08 –2.48)	0.02	64.5	0.30
Red meat consumption	frequent consumption to daily	infrequent to less than 2 times/ week	5	0	0	1.73 (1.20 –2.51)	0.02	64.5	0.24
Fish consumption	3–4 times/week to daily	infrequent consumption to <1 times/week	4	1	1	0.86 (0.45 –1.67)	<0.001	80.7	0.72
Table salt use	frequently to always	infrequent	4	1	2	2.24 (1.53 –3.29)	0.03	57.2	0.22
IL1B-511(rs16944) or *IL1B*-31(rs1143627)	T or C carrier, respectively	C/C or T/T, respectively	7	3	1	1.07 (0.78 –1.47)	0.04	47.2	0.26
IL1RN VNTR	*2 carrier (homozygous or heterozygous)	*2 non-carrier	7	3	1	1.51 (1.15 –1.99)	0.04	48.6	0.41
TNFA-308(rs1800629)	A carrier	G/G	3	2	1	0.96 (0.70 –1.31)	0.63	0	0.15
TP53 codon 72(rs1042522)	Pro carrier	Arg/Arg	3	3[d]	0	0.87(0.66 –1.15)	0.52	0	0.99
GSTM1 deletion	null/null genotype	present/null or present/present	3	2	0	1.36 (0.83 –2.23)	0.07	53.2	0.41

Abbreviations: OR, odds ratio; CI, confidence interval; VNTR, variable number tandem repeat.

[a]Range of highest categories of exposure.

[b] Range of lowest categories of exposure.

[c] Includes gastroenterology and other medical services.

[d] Includes one study [27] for which genotype frequencies among controls were estimated from allele frequencies under the assumption of Hardy-Weinberg equilibrium.