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The protective effect of dietary folate intake on gastric cancer is modified by alcohol consumption: A pooled analysis of the StoP Consortium

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Abstract

Dietary folate intake has been identified as a potentially modifiable factor of gastric cancer (GC) risk, although the evidence is still inconsistent. We evaluate the association between dietary folate intake and the risk of GC as well as the potential modification effect of alcohol consumption. We pooled data for 2829 histologically confirmed GC cases and 8141 controls from 11 case–control studies from the international Stomach Cancer Pooling Consortium. Dietary folate intake was estimated using food frequency questionnaires. We used linear mixed models with random intercepts for each study to calculate adjusted odds ratios (OR) and 95% confidence interval (CI). Higher folate intake was associated with a lower risk of GC, although this association was not observed among participants who consumed >2.0 alcoholic drinks/day. The OR for the highest quartile of folate intake, compared with the lowest quartile, was 0.78 (95% CI, 0.67–0.90, *P*-trend = 0.0002). The OR per each quartile increment was 0.92 (95% CI, 0.87–0.96) and, per every 100 μg/day of folate

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intake, was 0.89 (95% CI, 0.84–0.95). There was a significant interaction between folate intake and alcohol consumption (*P*-interaction = 0.02). The lower risk of GC associated with higher folate intake was not observed in participants who consumed >2.0 drinks per day, $OR_{Q4v\ Q1} = 1.15$ (95% CI, 0.85–1.56), and the $OR_{100\ \mu g/day} = 1.02$ (95% CI, 0.92–1.15). Our study supports a beneficial effect of folate intake on GC risk, although the consumption of >2.0 alcoholic drinks/day counteracts this beneficial effect.

KEYWORDS
alcohol consumption, dietary folate, gastric cancer, interaction

What's new?

Getting adequate amounts of the B vitamin folate may help reduce the risk of gastric cancer (GC), although study results have been inconsistent so far. Here, the authors analyzed data from the Stomach Cancer Pooling Consortium to assess not only the association between folate intake and GC but also how alcohol consumption affects the association. They found that higher folate intake, as determined by food questionnaires, was associated with a lower GC risk. However, this association was not observed among those reporting alcohol consumption of more than 2 drinks per day.

1 | INTRODUCTION

Gastric cancer (GC) is the fourth cause of cancer death and the fifth most frequently diagnosed cancer worldwide.[1] Among factors identified in the etiology of GC, chronic *Helicobacter pylori* infection plays a key role,[2] although additional modifiable factors have been related to GC, including tobacco smoking,[3] heavy alcohol consumption[4] and diet.[2,5] Regarding diet, different dietary factors have been associated with higher GC risk such as low consumption of fruits and vegetables,[6–8] high consumption of red and processed meat,[9] salt and salt-preserved foods,[10] inadequate intake of several antioxidant minerals and vitamins,[5] and low adherence to the Mediterranean diet.[11]

Several studies have pointed out that higher dietary folate intake is associated with a reduced risk of oropharyngeal, laryngeal, oesophageal, gastric, pancreatic and colorectal cancers, among others.[12–15] In relation to GC, some studies have reported inverse relationships.[16–19] A systematic review and meta-analysis based on 21 studies[15] showed a significant association between increased folate intake and decreased risk of GC (OR = 0.76, 95%CI = 0.65–0.88) and a reduction of 1.5% per every 100 μg/day increments in dietary folate intake. Nevertheless, other meta-analysis studies[20,21] found inconsistent results for the association between dietary folate intake and GC.

Folate is present in many common foods such as vegetables, legumes or nuts; however, folate deficiency is very prevalent worldwide.[22] The most common causes of folate inadequacy are low dietary intake[22] and poor stability of dietary folates after cooking.[23] Moreover, there are other common factors that could lead to folate deficiency such as increased requirements (e.g., pregnancy or malabsorptive diseases), certain drugs, and chronic alcohol consumption.[24] However, alcohol consumption deserves special consideration as it can interact with dietary folate in different physiological pathways resulting in limiting folate intake and absorption, altering its metabolism and increasing renal excretion of folate.[25] In this line, several studies have reported significant interactions between dietary folate intake and alcohol consumption for some cancer types.[13,26,27] However, other studies found no interaction.[28–31]

The Stomach Cancer Pooling (StoP) Project is an international Consortium of epidemiological studies on GC, which provides the opportunity to investigate the role of different risk factors with detailed information for a large number of individuals. Our study aimed to evaluate the effect of dietary folate intake on GC risk in the StoP Consortium, and to explore if alcohol consumption modified this association.

2 | MATERIALS AND METHODS

2.1 | Study design and population

The present study is based on 11 studies included in the StoP Consortium (http://www.stop-project.org/), whose design and methods have been described previously.[32] The StoP project Consortium includes 34 case–control or nested-within-cohort studies from 15 countries, and a total of 13,121 cases of GC and 31,420 controls. The principal aim of the StoP Consortium is to evaluate the role of main factors in the aetiology of GC through pooled analyses of individual-level data. Under a transfer agreement among collaborating centers, the original study-specific databases were harmonized according to a pre-specified format, and all variables were checked for consistency and completeness. All these processes and analyses were performed at the University of Milan, using a two-stage approach whenever required.

TABLE 1 Main characteristics of StoP Consortium studies including information on dietary folate intake.

Study area(s)	Reference	Period	Controls	Cases
Milan, Italy	Lucenteforte et al., 2008[32]	1997–2007	537	224
Ardabil, Iran	Pakseresht et al., 2011[33]	2005–2007	301	271
Porto, Portugal	Lunet et al., 2007[34]	1999–2006	1459	601
10 provinces, Spain	Castaño-Vinyals et al., 2015[38]	2008–2012	2699	316
Valencia, Spain	Santibañez et al., 2012[39]	1995–1999	455	397
Mexico City 1, Mexico	Hernández-Ramírez et al., 2009[40]	2004–2005	464	245
Mexico City 2, Mexico	López-Carrillo et al., 1994[41]	1989–1990	664	166
3 areas, Mexico	López-Carrillo et al., 2003[42]	1994–1996	457	223
Nagano, Japan	Machida-Montani et al., 2004[36]	1998–2002	295	147
Nebraska, USA	Ward et al., 1997[37]	1988–1993	405	157
Greece	Psaltopoulou et al., 2008[35]	1994–1999	405	82

Table 1 shows the main characteristics of the 11 studies with complete information for dietary folate intake which were included in the pooled analyses: one study from Italy,[33] Iran,[34] Portugal,[35] Greece,[36] Japan[37] and the United States,[38] two studies from Spain[39,40] and three studies from Mexico.[41–43] The study from Greece[36] computed its own results locally (through standardized analyses) and provided estimates to the StoP Consortium. The final analysis included 2829 histologically confirmed GC cases, ICD-O-3 codes (C16.0-C16.9), and 8141 controls. Regarding the case–control design, six studies were population-based,[34,35,38,39,41,42] four hospital-based[33,37,40,43] and one was a nested case–control study.[36] Controls were individually matched by age, sex, and residence to cases in two hospital-based studies.[37,43] Frequency matching by age, sex and residence was used in five studies.[35,38–41]

2.2 | Dietary folate intake

Dietary assessment was evaluated for each participant using country-specific food frequency questionnaires that included standard portion sizes for most frequently eaten foods. Usual mean daily folate intake (in micrograms, μg/day) was calculated by multiplying the reported food frequency for each food by their nutrient content according to country-specific food composition tables. Estimates of daily folate intake from each study were pooled in the same database and were energy-adjusted using the residual method.[44] In our study, dietary folate intake only included natural folate from foods and did not include any other source of folate (synthetic, fortification or supplemental folate). We excluded participants with implausible energy intake, <500 kcal/day or >4500 kcal/day.[44]

2.3 | Covariates

Additional information was collected and harmonized according to a pre-specified format in the StoP Consortium: age (<49, 50–59, 60–69, ≥70 years), sex (male, female), social class basically based on educational level (low, less than high school; intermediate, high school; high, more than high school),[45] smoking (never, former, current), *H. pylori* infection (seronegative, seropositive, missing), anatomical site (cardia, non-cardia, unspecified) and histological type of GC (diffuse, intestinal, other types and unspecified), total energy intake (in kcals/day) and alcohol consumption (0 drinks/day, 0.1–2.0 drinks/day, and >2.0 drinks/day).

2.4 | Statistical analyses

Main characteristics of participants were described according to control or case status. We reported the mean and standard deviation (SD) for continuous variables, number (*n*) and percentages (%) for categorical variables.

We conducted a one-stage pooled analysis for the associations between energy-adjusted dietary folate intake and GC. We ran linear mixed effect models with random intercept for study to estimate the odds ratio (OR) and 95% confidence intervals (CIs) of GC across study-specific quartiles of dietary folate intake. ORs and corresponding 95% CI were also estimated for quartiles as an ordinal variable (per each quartile increment) and per 100 μg/day of dietary folate intake. We presented three models: (a) Model 1 adjusted for sex and age; (b) Model 2 like model 1 plus social class, smoking, alcohol consumption and energy intake; (c) Model 3, variables of model 2 plus *H. pylori* infection.

We used likelihood ratio tests to explore the multiplicative interaction between quartiles of energy-adjusted dietary folate intake and alcohol consumption (three categories). We also performed stratified analyses according to categories of alcohol consumption (0 drinks/day, 0.1–2.0 drinks/day, and >2.0 drinks/day) and sex (male; female), adjusting for the same variables as in model 2. Multinomial logistic regression analyses were also performed to explore the association between dietary folate intake with anatomical site (cardia, non-cardia, unspecified) and histological type of GC (diffuse, intestinal, other types and unspecified).

All the statistical analyses were performed with the STATA software (version 16.1, StataCorp, United States of America, http://www.stata.com). *P*-values <.05 were considered statistically significant.

3 | RESULTS

The main sociodemographic and lifestyle characteristics according to control or case status are shown in Table 2. The final analyses included 8141 controls and 2829 cases of GC. Cases showed lower social class (54.4%), lower fruit and vegetable consumption (34.7%) and lower seroprevalence of *H. pylori* infection (35.1%) than controls (45.2%, 28.4%, and 42.5%, respectively). In addition, the percentage of controls included in the >2.0 drinks/day category of alcohol consumption was 20.7 whereas the percentage of cases was 28.6. Smoking habits were similar in both controls and cases. The mean (SD) daily folate intake was 291.4 (123.9) μg/day in cases and 305.1 (122.7) μg/day in controls.

TABLE 2 Distribution of 2829 cases and 8141 controls according to sociodemographic and lifestyle characteristics in the StoP Consortium.

	Controls ($n = 8141$)	Cases ($n = 2829$)
Sex, *n* (%)		
Male	4477 (55.0)	1799 (63.6)
Female	3664 (45.0)	1030 (36.4)
Age in years, *n* (%)		
<49	1555 (19.1)	476 (16.8)
50–59	1644 (20.2)	556 (19.7)
60–69	2423 (29.8)	820 (29.0)
≥70	2519 (30.9)	977 (34.5)
Social class, *n* (%)		
Low	3680 (45.2)	1540 (54.4)
Intermediate	2583 (31.7)	861 (30.4)
High	1878 (23.1)	428 (15.1)
Smoking, *n* (%)		
Never	4043 (49.7)	1379 (48.8)
Former	2245 (27.6)	773 (27.3)
Current	1853 (22.8)	677 (23.9)
Helicobacter pylori infection, *n* (%)		
Seronegative	675 (8.3)	230 (8.1)
Seropositive	3457 (42.5)	994 (35.1)
Missing	4009 (49.2)	1605 (56.7)
Alcohol consumption (drinks[a]/day), *n* (%)		
0 (non-drinkers)	2552 (31.4)	997 (35.2)
0.1–2.0	3906 (48.0)	1024 (36.2)
>2.0	1683 (20.7)	808 (28.6)
Fruit and vegetables consumption, *n* (%)		
Low	2314 (28.4)	982 (34.7)
Intermediate	2664 (32.7)	863 (30.5)
High	2706 (33.2)	761 (26.9)
Missing	457 (5.6)	223 (7.9)
Energy intake (kcals/day), mean (SD)	2075 (665)	2212 (703)
Energy-adjusted folate intake (μg/day), mean (SD)	292.2 (93.8)	264.7 (88.7)
Quartile 1 (70.7–219.5)	186.4 (25.7)	181.8 (28.1)
Quartile 2 (219.6–273.2)	246.9 (15.6)	245.1 (15.6)
Quartile 3 (273.3–337.5)	303.0 (18.0)	301.6 (18.0)
Quartile 4 (337.6–1105.2)	412.5 (77.9)	409.7 (71.9)

Abbreviation: SD, standard deviation.
[a]One drink is equivalent to 12 g of alcohol.

Table 3 shows pooled OR and 95% CI of the association between energy-adjusted folate intake and GC. As shown in model 2, compared with the lowest quartile, the highest quartile of energy-adjusted folate intake showed an inverse association with GC, OR = 0.78 (0.67–0.90, *P*-trend = 0.0002). A monotonic inverse association was observed for quartiles of folate intake, OR = 0.92 (0.87–0.96, *P*-trend <0.0001) and per each increment of 100 μg/day of energy-adjusted folate intake, OR = 0.89 (0.84–0.95, *P*-trend = 0.0001). Similar results were found for the other models shown in Table 3.

We observed a significant interaction between quartiles of energy-adjusted folate intake and the three categories of alcohol consumption (*P*-interaction = 0.02). Table 4 shows the OR for the association between energy-adjusted folate intake and GC, stratifying by the three categories of alcohol consumption. The ORs observed for participants classified in 0 and 0.1–2.0 drinks/day categories were similar to those observed in the overall pooled analyses, although no association was observed for participants who consumed >2.0 drinks of alcohol per day (Figure 1). In the highest category of alcohol consumption (>2.0 drinks/day), the OR for participants in the highest quartile of folate intake was 1.15 (0.85–1.56), compared to participants in the lowest quartile. The OR per each quartile increase of folate intake was 1.04 (0.95–1.14), and the OR per 100 μg/day of folate intake was 1.02 (0.92–1.15), in the same category of alcohol consumption. (Table 4).

Supplementary Table 1 shows sociodemographic and lifestyle characteristics according to categories of alcohol consumption. Participants who consume >2.0 drinks/day of alcohol were mainly men (88.5%) and from a lower social class (51.4%), had higher mean (SD) of energy intake [2363 (655) kcals/day] and lower dietary folate intake [256.9 (83.3) μg/day] than non-alcohol drinkers. Supplementary Table 2 shows the association between folate intake in quartiles and GC risk for men and women. The results according to sex did not differ substantially from those shown in Table 3 for the overall GC. Supplementary Table 3 shows the ORs estimated by multinomial logistic regression for the association between folate intake and GC risk by anatomical sub-sites of GC (299 cardia, 2292 non-cardia, and 247 unspecified). The ORs for cardia and non-cardia sub-sites were of similar magnitude to those observed for the overall GC analysis shown in Table 3, although they were significant for non-cardia sub-site only. No association was observed for the unspecified GC sub-site. Supplementary Table 4 shows the ORs estimated for the association between folate intake and GC risk by histological type (diffuse, intestinal, other types, unspecified). The ORs for diffuse, intestinal, and unspecified histological sub-types of GC were similar to those observed for the

TABLE 3 Odds ratios and 95% confidence intervals of energy-adjusted folate intake (quartiles, Q) and gastric cancer in the StoP Consortium.

	Q1 (70.7–219.5)[a]	Q2 (219.6–273.2)[a]	Q3 (273.3–337.5)[a]	Q4 (337.6–1105.2)[a]	Per 1 quartile increase	Per 100 μg/day of increment
Controls	1817	2023	2132	2169		
Cases	978	744	601	506		
Model 1	1	0.84 (0.74–0.94)	0.76 (0.67–0.87)	0.75 (0.65–0.86)	0.90 (0.86–0.95)	0.88 (0.83–0.93)
Model 2	1	0.84 (0.75–0.95)	0.78 (0.69–0.90)	0.78 (0.67–0.90)	0.92 (0.87–0.96)	0.89 (0.84–0.95)
Model 3	1	0.85 (0.75–0.95)	0.79 (0.69–0.90)	0.79 (0.68–0.91)	0.92 (0.88–0.96)	0.90 (0.85–0.95)

Note: Model 1: adjusted for sex (male; female), age (<49; 50–59; 60–69; ≥70 years). Model 2: model 1 variables and social class (low; intermediate; high), smoking (never; former; current), alcohol consumption (0; 0.1–2.0, >2.0 drinks/day) and energy intake (kcal/day). Model 3: model 2 variables and *Helicobacter pylori* infection (seronegative, seropositive, missing).
[a]Folate intake range in μg/day.

TABLE 4 Odds ratios (ORs) and 95% confidence intervals (CIs) of energy-adjusted folate intake (quartiles, Q) and gastric cancer by alcohol consumption in the StoP Consortium.

	Controls	Cases	OR (95% CI)
0 drinks/day			
Q1 (70.7–219.5)[a]	546	384	1
Q2 (219.6–273.2)[a]	594	238	0.68 (0.55–0.84)
Q3 (273.3–337.5)[a]	637	197	0.60 (0.48–0.75)
Q4 (337.5–1105.2)[a]	775	178	0.54 (0.42–0.70)
Per each 1 quartile increase			0.81 (0.75–0.88)
Per each 100 μg/day of increment			0.78 (0.70–0.86)
0.1–2.0 drinks/day			
Q1 (70.7–219.5)[a]	680	270	1
Q2 (219.6–273.2)[a]	935	265	0.83 (0.67–1.02)
Q3 (273.3–337.5)[a]	1136	259	0.75 (0.60–0.93)
Q4 (337.5–1105.2)[a]	1155	230	0.77 (0.60–0.97)
Per each 1 quartile increase			0.91 (0.85–0.99)
Per each 100 μg/day of increment			0.91 (0.83–0.99)
>2.0 drinks/day			
Q1 (70.7–219.5)[a]	591	324	1
Q2 (219.6–273.2)[a]	494	241	1.10 (0.89–1.38)
Q3 (273.3–337.5)[a]	359	145	1.07 (0.82–1.39)
Q4 (337.5–1105.2)[a]	239	98	1.15 (0.85–1.56)
Per each 1 quartile increase			1.04 (0.95–1.14)
Per each 100 μg/day of increment			1.02 (0.92–1.15)
Interaction test[b]			*p*-value .02

Note: All analyses were adjusted for sex (male; female), age (<49; 50–59; 60–69; ≥70 years), social class (low; intermediate; high), smoking (never; former; current) and energy intake (kcal/day).
[a]Folate intake range in μg/day.
[b]Interaction *p*-value was calculated using likelihood ratio test between energy-adjusted folate intake in quartiles and alcohol consumption (0; 0.1–2.0, >2.0 drinks/day).

overall GC analysis shown in Table 3, although the associations were significant only for diffuse and unspecified sub-types.

4 | DISCUSSION

Dietary folate intake shows a protective association with the risk of GC in this pooled analysis of 11 studies from the StoP Consortium, with a significant inverse dose–response trend by quartiles and for every 100 μg/day of dietary folate intake. We also found a significant interaction between dietary folate intake and alcohol consumption; the protective association of folate intake was lost among drinkers of >2.0 alcoholic drinks/day.

Higher dietary intake of folate was associated with lower GC risk in all analyses with different covariate adjustments. Compared with the first quartile of energy-adjusted folate intake, participants in the

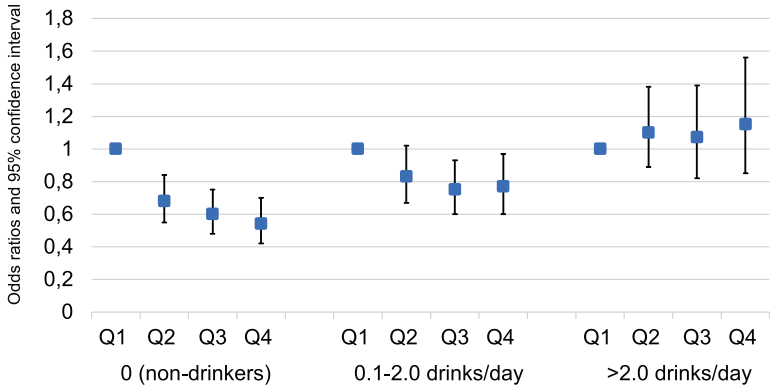

FIGURE 1 Odds ratios and 95% confidence intervals of the association between energy-adjusted folate intake (quartiles) and gastric cancer by alcohol consumption (model 3) in the StoP Consortium ($n = 10{,}970$). *P*-interaction = 0.02. The analyses were adjusted for sex (male; female), age (<49; 50–59; 60–69; ≥70 years), social class (low; intermediate; high), smoking (never; former; current) and energy intake (kcal/day).

second, third and fourth quartile showed a 16%, 22%, and 22% lower risk of GC, respectively (model 2). Previous studies, not included in this pooled analysis, have reported similar trends.[16–19] González et al[16] reported a reduction in GC risk of 28%, 48%, and 50% for the top three quartiles of dietary folate intake, compared with the lowest one. In the same line, a study including 723 cases and 2024 controls reported an inverse trend between dietary folate intake and risk of GC.[19] Compared with the lowest quintile, the top four quintiles of folate intake showed an 18%, 29%, 41%, and 42% risk reduction of GC.[19] In our study, the risk of GC was reduced by 11% per each 100 μg/day folate increment. These results are in line with those from another study that showed a 36% less risk of GC per each additional 100 μg/day of dietary folate intake.[13]

We found a significant interaction between alcohol consumption and dietary folate intake. In stratified analyses by categories of alcohol consumption, the protective association of folate intake on GC risk was significant in the two lowest categories of alcohol consumption (0 and 0.1–2.0 drinks/day), whereas no significant effect was observed in the highest category of alcohol consumption (>2.0 drinks/day). As far as we know, only one study based on 156 incident cases from the Swedish Mammography Cohort analyzed the interaction between dietary folate intake and alcohol consumption on the risk of GC.[28] This study found no interaction (*P*-interaction = 0.17) potentially due to the limited number of cases. Significant interactions between alcohol consumption and dietary folate intake have been reported for other types of cancer. In the French-EPIC cohort study which included 66,481 women and 2812 incident breast cancer cases,[27] a positive association between alcohol consumption and breast cancer risk was observed only in the lowest category of folate intake, hazard ratio = 1.35 (95% CI, 1.10–1.67). In a prospective study with 435 incident cases of hepatocellular carcinoma, folate intake modified the association (*p*-interaction = 0.03), and the increased risk of hepatocellular carcinoma due to alcohol drinking was only observed among those of the two lowest tertiles of folate intake.[26] However, other studies did not find an interaction between folate intake and alcohol consumption on the risk of ovarian,[29] breast,[30] and pancreatic cancer.[31]

Folate is a water-soluble vitamin mainly present in plant-based foods such as green-leaves vegetables, pulses and fruits, but also in eggs, yeast and animal liver.[22] This vitamin plays an important role in maintaining DNA stability[46] and folate deficiency can induce DNA damage that potentially predispose to cancer due to hypomethylation of DNA, leading to inappropriate expression of genes, affecting DNA repair and inducing breaks in chromosomes.[46] Moreover, some polymorphisms in the methylenetetrahydrofolate reductase (MTHFR), a key enzyme in the metabolism of folate, may have a role in the development of cancer.[47,48] Of the several polymorphisms evaluated, two meta-analyses have reported that *MTHFR C677T* polymorphism carriers with low folate levels have an increased risk of GC.[47] The *MTHFR C677T* polymorphism might induce depletion in MTHFR enzymes and favor DNA hypomethylation when folate intake is insufficient.[48] However, those mechanisms can be altered by the consumption of alcohol.[25] The detrimental role of alcohol on the development of GC has been widely reported.[4] However, the minimum carcinogenic dose of alcohol has not been assessed, and most of the studies agree on the association of increased risk of GC with higher alcohol consumption.[49] This is consistent with the interaction we observed in our analysis of a beneficial effect of folate intake in the two lowest categories of alcohol consumption that was not observed in the highest category of alcohol consumption (>2.0 drinks/day). It has been pointed out that alcohol can reduce the effectiveness of the folate functions by several pathways[22,25] such as poorer diet, intestinal malabsorption,[22,24,25] modification of hepatobiliary metabolism or an increased renal folate excretion.[25]

Other dietary variables may be associated with folate intake and GC risk such as the consumption of citrus fruits, meat, salt, fruits and vegetables and other specific nutrients, some of them have been investigated in the context of the StoP Consortium.[6,7,9,10] Instead of including too many dietary variables in the multivariable models and cause potential overadjustment, we have used energy-adjusted folate intake in the analyses, also including total energy intake in the models, to better disentangle the independent effect of folate intake. Regarding the main food source of dietary folate intake, the consumption of fruit and vegetables, we explored the possibility to include it as a covariable in the multivariable models. However, the correlation between folate intake and fruit and vegetable consumption was very high (Pearson's coefficient, $r = 0.69$), and when we included both variables in the multivariable models there was evidence of some collinearity, although the association for folate intake was slightly attenuated (based on 9 studies).[33–35,37,39–43]

Our study has some limitations and strengths. We pooled information from studies performed in different countries, across various timeframes, and using diverse study protocols. However, original databases

were centrally collected and harmonized according to a pre-specified format, and the dietary folate intake was energy-adjusted after pooling all information. Another concern is the high proportion of missing data for some relevant variables. An example is *H. pylori* infection with 51.2% of missing values, although we created a categorical variable assigning a category for missing values, and the results of multivariable analyses remained very similar when adjusted for this variable (model 3). Furthermore, the low proportion of infections among the cases should be referred to reverse causation, which is in fact often observed especially in case–control studies, when the cases are recruited at the moment of diagnosis: the prevalence of a risk factor (*H. pylori*) is modified by the presence of the outcome (GC).[50,51] Nevertheless, this would not have influenced the results on dietary folate intake.[43] In the same line, all participants from the Iranian study[34] showed missing values for alcohol consumption and we assumed "no consumption" based on cultural reasons. In fact, we checked alcohol consumption in the original study in more detail,[34] and the vast majority of the sample reported no alcohol consumption [only 15 participants (0.14%) reported some alcohol consumption]. Considering that information, we assigned 0 g/day of alcohol for all Iranian participants, with the assumption that any misclassification would be negligible. Another limitation is the lack of information on supplement use, which was not collected in any of the studies included in our pooled analysis. Regarding fortification, although a small number of countries have fortification policies (e.g., Mexico, USA, Iran), they were mostly implemented after the studies were performed. Finally, findings from case–control studies should be interpreted with caution as these designs are more susceptible to bias, that may be a source of reverse causation (e.g. stomach cancer may have modified participants' diet, leading them to eat less than normal). However, in our pooled analysis, cases were incident, and dietary information referred to at least 1 year prior to GC diagnosis.

The StoP Consortium[32] brings an invaluable opportunity to evaluate the etiology of GC in a large number of histologically diagnosed cases from different countries around the world. Moreover, our main finding are consistent with the results observed in previous studies, as well as the biological mechanisms proposed for this association. In sensitivity analyses, this overall protective association of folate intake was also consistent by sex, anatomical sub-sites, and histological types. In addition, this study provides novel evidence regarding a possible effect modification by alcohol consumption, since the protective association of folate intake was not observed among participants with >2.0 drinks/day of alcohol (significant interaction).

In conclusion, this study provides further evidence about the protective association of dietary folate intake on GC risk, particularly when the alcohol consumption is less than two alcoholic drinks a day. However, the consumption of more than two alcoholic drinks per day seems to counteract the beneficial effect of folate intake on GC. These results should be interpreted with caution given the observational nature of studies included in the pooled analysis, and they should be confirmed by further studies, ideally prospective cohort studies. Meanwhile, it could be recommended to reduce alcohol consumption to less than two alcoholic drinks per day in order to benefit from the protective effect of folate intake against GC risk.

AUTHOR CONTRIBUTIONS

Conceptualization, S.G.-P. and J.V.; methodology, S.G.-P. and J.V.; formal analysis, S.G-P., G.C., M.R., and J.V.; investigation, E.N., C.P., L.L.-C., N.L., M.H.W., V.M., R.M., M.P., R.U.H-R., M.L-C., C.S.R, S.T., A.H., A.T., M.C.C, M.P.C., Z-F Z., C.LV. P.B., and J.V.; writing–original draft preparation, S.G.-P. and J.V.; writing–review and editing, all authors. All authors have read and agreed to the published version of the manuscript. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Request to use datasets should be made to the StoP Consortium Steering Committee (http://stop-project.org; stop.project@unimi.it). Further information is available from the corresponding author upon request.

ETHICS STATEMENT

All studies included in the Consortium followed ethical principles for medical research involving human subjects according to the Declaration of Helsinki and all participants signed an informed consent. The StoP Consortium received ethical approval from the University of Milan Review Board (reference 19/15 on April 1, 2015).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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