Title

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Journal
British Journal of Cancer, 126(12)

ISSN
0007-0920

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Publication Date
2022-06-01

DOI
10.1038/s41416-022-01750-5

Peer reviewed

British Journal of Cancer www.nature.com/bjc

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ARTICLE

Epidemiology

Allium vegetables intake and the risk of gastric cancer in the Stomach cancer Pooling (StoP) Project

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BACKGROUND: The role of allium vegetables on gastric cancer (GC) risk remains unclear.
METHODS: We evaluated whether higher intakes of allium vegetables reduce GC risk using individual participant data from 17 studies participating in the “Stomach cancer Pooling (StoP) Project”, including 6097 GC cases and 13,017 controls. Study-specific odds ratios (ORs) were pooled using a two-stage modelling approach.
RESULTS: Total allium vegetables intake was inversely associated with GC risk. The pooled OR for the highest versus the lowest study-specific tertile of consumption was 0.71 (95% confidence interval, CI, 0.56–0.90), with substantial heterogeneity across studies ($I^2 > 50\%$). Pooled ORs for high versus low consumption were 0.69 (95% CI, 0.55–0.86) for onions and 0.83 (95% CI, 0.75–0.93) for garlic. The inverse association with allium vegetables was evident in Asian (OR 0.50, 95% CI, 0.29–0.86) but not European (OR 0.96, 95% CI, 0.81–1.13) and American (OR 0.66, 95% CI, 0.39–1.11) studies. Results were consistent across all other strata.
CONCLUSIONS: In a worldwide consortium of epidemiological studies, we found an inverse association between allium vegetables and GC, with a stronger association seen in Asian studies. The heterogeneity of results across geographic regions and possible residual confounding suggest caution in results interpretation.

British Journal of Cancer (2022) 126:1755–1764; https://doi.org/10.1038/s41416-022-01750-5

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Received: 27 July 2021 Revised: 21 January 2022 Accepted: 9 February 2022
Published online: 24 February 2022

INTRODUCTION

Despite the decreasing incidence and mortality trends in most areas of the world [1], gastric cancer remains a major public health issue, being the fourth leading cause of cancer mortality worldwide in 2020 [2].

The major established determinant of gastric cancer is *Helicobacter pylori* (HP) infection [3]. Tobacco smoking [4] and selected dietary habits also play a role in the development of gastric cancer [5, 6]. Heavy alcohol intake [7], a high consumption of salt-preserved foods [5] and red and processed meat [8] are positively associated with the disease, while diets rich in fruit [9] and vegetables [10], including healthy dietary patterns such as the Mediterranean diet [11, 12], have been inversely related with the risk.

There has been longstanding interest in the favourable effects of allium vegetables intake on human health; still, details of the associations and their underlying mechanisms are not fully understood [13]. The most widely used allium vegetables include garlic, onions, leeks, chives and scallions, which are rich in flavonoids and organosulfur compounds [14]. Epidemiological studies support a protective role of allium vegetables intake on several cancers [15, 16], particularly those of the gastrointestinal tract [17, 18]. Previous meta-analyses indicated a protective role of allium vegetables intake on gastric cancer [18–20]. In particular, a meta-analysis of 22 case–control and 4 cohort studies updated through 2013, and including over 10,000 cases, reported overall relative risks between 0.55 (onions) and 0.78 (total allium vegetables) for the highest level of consumption; results were, however, inconsistent by study design, with case–control studies reporting a significant inverse association and cohort studies null association. Recently, a pooled analysis of two US cohorts indicated no consistent relation [21].

The "Stomach cancer Pooling (StoP) Project" is a global collaborative consortium of epidemiological investigations on gastric cancer. The StoP project aims to examine and quantify the role of lifestyle and genetic determinants on the aetiology of gastric cancer [22]. To date, the StoP Project includes more than 30 case–control studies (or case–control studies derived from cohort investigations) conducted in areas around the world with different rates of gastric cancer, distribution of risk factors for the disease, dietary patterns and lifestyle habits. The StoP Project includes patient-level data on allium vegetables intake for approximately 6000 gastric cancer cases and 13,000 controls, providing a unique opportunity to finely quantify the association between allium vegetables intake and gastric cancer.

The present investigation within the StoP Project aims to evaluate whether a higher intake of allium vegetables, including onions and garlic, is associated with a reduced risk of gastric cancer.

MATERIALS AND METHODS

Study population

The StoP Project is a consortium of epidemiological investigations on gastric cancer (http://www.stop-project.org/). Studies eligible for participation in the consortium are those with a case–control design, including case–control studies nested within cohort studies, with at least 80 cases of incident, histologically confirmed gastric cancer (both cardia and non-cardia anatomical subsites). Details on the StoP Project methods have been previously reported [22]. Principal investigators of the studies included in the StoP Project agreed to participate in the consortium by providing a signed data transfer agreement and the original dataset to the coordinating centre. One study from Greece computed its own results locally (through standardised analyses) and then provided estimates for the second-stage meta-analysis to the StoP Project consortium [23]. Questionnaires used for data collection and any further information useful for data handling (e.g., codebooks, labels) were also obtained from the participating studies. All data were harmonised according to a pre-specified format at a centralised pooling centre. The participating studies were conducted in accordance with applicable laws, regulations and guidelines for the protection of human subjects, and the StoP Project was approved by the University of Milan Review Board (reference 19/15 on 01/04/2015). Informed consent was not obtained from all studies because some of them were carried out during the 1980s and 1990s.

Of the 34 studies included in the v.3.2 release of the StoP Project, 17 studies—accounting for a total of 6097 gastric cancer cases and 13,017 controls—had information on allium vegetables intakes and were included in the present analysis (Supplementary Fig. S1). These included two studies from Greece [23, 24], two from Italy [25, 26], two from Spain [27, 28], one from Portugal [29], one from Russia [30], two from Iran [31, 32], three from China [33–35], one from Japan [36], two from Mexico [37, 38] and one from Brazil (unpublished data).

One study from the USA [39] was excluded from the analysis because of the high number of missing information on allium vegetables intake, and one study from Canada [40] was excluded because it only collected qualitative information on the frequency of onions and garlic intake (i.e., seldom or never, sometimes, often or always).

Allium vegetable intake

In all studies, dietary intake was assessed by means of food frequency questionnaires, asking participants to report the consumption of foods and beverages at least 1 year before diagnosis (for cases), hospital admission (for controls in hospital-based case–control studies) or recruitment (for controls in population-based case–control studies).

Total allium vegetables intake was obtained by combining the available information on the intake of single allium vegetable items, including onions, garlic, chives, leeks and scallions, in each study. Onion (available from 15 studies) and garlic (8 studies) intakes were also considered separately. Allium vegetables consumption was converted into grams per week, taking into account the serving size and the frequency of consumption indicated in each study-specific food frequency questionnaire. When consumption was not expressed in grams, the amount of allium vegetables reported was converted into grams by considering the following average weight for each vegetable: 150 g for leeks, 40 g for onions and 15 g for garlic or scallions.

Allium vegetables intake was then categorised into study-specific tertiles (based on the study-specific distribution among controls). Onion and garlic intakes were categorised into above and below the study-specific median value as the distribution of intake did not allow meaningful computation of tertiles in some studies.

Statistical analysis

The statistical analysis was based on subjects with complete information on allium vegetables intake (5892 cases and controls 12,493). The association between total allium vegetables, onion and garlic intake, and gastric cancer was assessed through a two-stage modelling approach [41]. First, the odds ratios (ORs) of gastric cancer and the corresponding 95% confidence intervals (CIs) according to study-specific categories of intake were derived for each study using multivariable unconditional logistic regression models. Subjects with missing information on allium vegetables intake (3.4% among cases and 4.0% among controls) were excluded from the analyses. Models included, when available and applicable, terms for age (5-year age groups: <40; 40–44; …; 70–74; ≥75), sex, education/social class (low, intermediate or high, as defined in each original study based on education, income and/or occupation), tobacco smoking (never, former, and current smokers of ≤10 cigarettes/day, >10–20 cigarettes/day and >20 cigarettes/day), alcohol drinking (never, low: ≤12 g of ethanol/day, intermediate: >12–47 g of ethanol/day, high consumption: >47 g of ethanol/day), fruit and vegetable consumption (study-specific tertiles), family history of gastric cancer in first degree relatives, study centre (for multicentric studies) and matching study area/hospital (for matched studies). Missing values on covariates were imputed as the study-specific modal category when the proportion of missing values on that covariate was low (i.e. <5%) in that specific study. Otherwise, they were retained in the model by including them in a separate ad hoc category of the variable. At the second stage, summary ORs were obtained by pooling the study-specific ORs using random-effects models [42]. Heterogeneity across studies was tested with the Cochran's Q test statistic and quantified using the I^2 statistic, which measures the percentage of total variation due to heterogeneity rather than chance (values of 25%, 50% and 75% were considered to represent low, moderate and considerable heterogeneity, respectively) [43].

Table 1. Distribution of gastric cases and controls according to study centre, sex, age and other selected variables in the Stomach cancer Pooling (StoP) Project consortium.

	Cases (*n* = 6097)		Controls (*n* = 13,017)	
	N	%[a]	*N*	%[a]
Study (StoP ID. Country (Reference))				
Europe				
03. Italy 1 [25]	230	3.8	547	4.2
05. Italy 2 [26]	1016	16.7	1159	8.9
06. Greece 1 [24]	110	1.8	100	0.8
09. Russia [30]	450	7.4	611	4.7
17. Portugal [29]	692	11.3	1667	12.8
21. Spain 1 [27]	441	7.2	3440	26.4
23. Spain 2 [28]	401	6.6	455	3.5
33. Greece 2 [23]	82	1.3	410	3.1
Asia				
02. China 1 [35]	266	4.4	533	4.1
08. China 2 [33]	206	3.4	415	3.2
10. Iran 1 [31]	217	3.6	394	3.0
11. Iran 2 [32]	286	4.7	304	2.3
12. China 3 [34]	711	11.7	711	5.5
30. Japan [36]	153	2.5	303	2.3
The Americas				
25. Mexico 1 [37]	248	4.1	478	3.7
26. Mexico 2 [38]	220	3.6	752	5.8
36. Brazil	368	6.0	738	5.7
Sex				
Men	3870	63.5	7423	57.0
Women	2227	36.5	5594	43.0
Age (years)				
<40	288	4.7	671	5.2
40–44	245	4.0	724	5.6
45–49	387	6.3	1008	7.7
50–54	539	8.8	1265	9.7
55–59	761	12.5	1588	12.2
60–64	904	14.8	1947	15.0
65–69	1111	18.2	2155	16.6
70–74	1063	17.4	1888	14.5
≥75	799	13.1	1771	13.6
Socioeconomic status[b]				
Low	3647	60.6	6275	48.6
Intermediate	1764	29.3	4213	32.6
High	603	10.0	2416	18.7
Smoking habits[b]				
Never smoker	2791	46.6	6397	49.9
Former smoker	1478	24.7	3203	25.0
Current smoker, number of cigarettes/day				
≤10	475	7.9	1231	9.6
>10–20	672	11.2	1076	8.4
>20	574	9.6	912	7.1
Alcohol drinking (g/day)[b]				
Never	1488	30.4	3716	33.5
≤12	983	20.1	3353	30.2
>12–47	1657	33.9	2907	26.2
>47	759	15.5	1111	10.0
Family history of gastric cancer[b,c]				
No	2814	79.5	7348	91.4
Yes	726	20.5	692	8.6
Total fruit and vegetables intake[b,d]				
Low	1905	32.4	3485	28.6
Intermediate	1987	33.8	4172	34.2
High	1985	33.8	4545	37.2

[a]Percentages may not add to 100 due to rounding.
[b]Frequencies do not sum up to the total beacuse of missing values.
[c]In first degree relatives.
[d]Based on study-specific tertiles.

The functional form of the relation between allium vegetable intake (grams per week) and gastric cancer risk was modelled using one-order and two-order fractional polynomial models, adjusting for the aforementioned confounders. The best-fitting model, i.e., the one minimising the model deviance, was selected.

A number of sensitivity analyses were conducted: (i) including total energy intake in the models for further adjustment; (ii) estimating the associations between allium vegetables, onion and garlic intake and gastric cancer using a one-stage approach (i.e., generalised linear mixed effect models with a logistic link function and a random intercept for each study, with adjustment factors as previously described); (iii) estimating the ORs for any intake versus no intake based on studies in which the proportion of non-consumers was higher than 10%; (iv) examining whether the number of single allium vegetable items considered in each study and the proportion of onion intake on the total allium vegetable consumption in each study had different effects on gastric cancer risk by using meta-regression models; and (v) assessing the impact of individual studies on the pooled ORs by removing one study at a time from the two-stage procedure.

Stratified analyses were conducted to evaluate whether the effect of total allium vegetables intake on gastric cancer differed across subgroups defined by age, sex, geographic area, socioeconomic status, smoking habits, alcohol drinking, total fruit and vegetable intake, family history of gastric cancer and markers of HP serostatus, and according to the type of controls (hospital-based, population-based), cancer anatomical subsite (cardia, non-cardia) and histological type (intestinal, diffuse and unspecified, according to the Lauren classification). In analyses by cancer anatomical subsite and histological type, multinomial logistic regression models were used to estimate the study-specific ORs for each type of cancer respectively. Heterogeneity across groups was evaluated by Cochran's *Q* test statistic.

Analyses were carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC), Stata version 14 (StataCorp., College Station, Texas, USA) and RStudio version 1.2.5019 (RStudio, Inc., Boston, MA, USA). *P* values <0.05 were considered statistically significant.

RESULTS

Table 1 shows the distribution of sociodemographic characteristics and selected lifestyle factors of the 6097 gastric cancer cases and 13,017 controls considered in the present analysis. About 56% of cases were from Europe, 30% from Asia and 14% from the Americas. The distribution of age was similar among cases and controls. Compared to controls, cases were more often males, heavy smokers and alcohol drinkers, and more frequently reported a low socioeconomic status, a family history of gastric cancer and a low consumption of fruit and vegetables. There was a moderate correlation between onion

Table 2. Two-stage pooled odds ratios (ORs) and 95% confidence intervals (CIs) for gastric cancer according to allium vegetables consumption in the Stomach cancer Pooling (StoP) Project consortium.

	Cases		Controls			
	n	%[a]	*n*	%[a]	OR (95% CI)	I^2 (%)
Allium vegetables[b]						
1st tertile	2278	37.4	4200	32.3	1	
2nd tertile	1827	30.0	3956	30.4	0.80 (0.69–0.93)	59.5%
3rd tertile	1787	29.3	4337	33.3	0.71 (0.56–0.90)	82.2%
Missing	205	3.4	524	4.0		
Onions[c]						
Below the median	3071	53.4	5730	47.5	1	
Above the median	2467	42.9	5817	48.2	0.69 (0.55–0.86)	86.6%
Missing	211	3.7	527	4.4		
Garlic[d]						
Below the median	1729	58.4	3678	54.0	1	
Above the median	1108	37.4	2704	39.7	0.83 (0.75–0.93)	0.0%
Missing	123	4.2	426	6.3		

[a]Percentages may not add to 100 due to rounding.
[b]Included studies: StoP ID #2, #3, #5, #6, #8, #9, #10, #11, #12, #17, #21, #23, #25, #26, #30, #33, #36.
[c]Included studies: StoP ID #3, #5, #6, #8, #9, #10, #11, #12, #17, #21, #23, #25, #26, #30, #36.
[d]Included studies: StoP ID #8, #9, #10, #11, #12, #21, #23, #25.

and garlic consumption (Pearson's $r = 0.23$, consistent among cases and controls).

Table 2 provides the pooled ORs and the corresponding 95% CIs of gastric cancer according to the intakes of total allium vegetables, onions and garlic. The corresponding forest plots with study-specific and pooled ORs for the highest versus the lowest level of intake are provided in Fig. 1 (panel a for total allium vegetables, panel b for onions and panel c for garlic). For total allium vegetables intake, compared with the first tertile of intake, pooled ORs were 0.80 (95% CI, 0.69–0.93) for the second and 0.71 (95% CI, 0.56–0.90) for the third tertile (Table 1), in the presence, respectively, of moderate ($I^2 = 59.5\%$) and substantial ($I^2 = 82.2\%$) heterogeneity across studies. The study-specific ORs for the third versus the first tertile of intake were below unity in 13 out of the 17 studies analysed (Fig. 1a). As for specific allium vegetables, the ORs for high versus low intake were 0.69 (95% CI, 0.55–0.86; $I^2 = 86.6\%$) for onions and 0.83 (95% CI, 0.75–0.93; $I^2 = 0\%$) for garlic. Further adjustment for total energy intake in studies with available information did not affect the results (Supplementary Table S1). No significant changes in the effects emerged when removing one study at a time; ORs varied between 0.70 (95% CI, 0.67–0.92) and 0.84 (95% CI, 0.73–0.96) for the second versus the first tertile, and between 0.67 (95% CI, 0.53–0.85) and 0.78 (95% CI, 0.64–0.96) for the third versus the first tertile of allium vegetables intake.

In sensitivity analyses, results derived using a one-stage modelling approach were similar to those obtained through the two-stage modelling approach, although the magnitude of association with onion intake was slightly decreased (Supplementary Table S2). In another analysis comparing any consumption versus no consumption, the pooled ORs were 0.84 (95% CI, 0.66–1.08) for allium vegetables, 0.88 (95% CI, 0.77–1.01) for onions and 0.92 (95% CI, 0.80–1.06) for garlic (Supplementary Table S3). The number of specific allium vegetable types included in each study or the proportion of onions in the total allium vegetables variable did not influence the association of allium vegetables with gastric cancer (ORs from meta-regression models: 1.03, 95% CI: 0.70–1.51 for the addition of 1 vegetable and 1.00, 95% CI: 0.99–1.01 for 1-point percent increment in the proportion of onions, when considering the highest versus the lowest tertile of consumption). In stratified analyses (Table 3), similar effects of allium vegetables intake (third versus the first tertile) were observed in subgroups of sex, age, socioeconomic status, intake of fruit and vegetables, smoking status, HP serostatus, and cancer anatomical subsite and histological type. The inverse association appeared stronger in never/low alcohol drinkers, subjects with a family history of gastric cancer, and studies using population-based controls. There was significant heterogeneity across geographic areas ($P = 0.04$), with no association in studies from Europe and a strong inverse association in studies from Asia.

Figure 2 provides the exposure-response relationships between intake of allium vegetables (Fig. 2a), onions (Fig. 2b) and garlic (Fig. 2c), and gastric cancer risk. A trend towards decreasing gastric cancer risk with higher consumption of allium vegetables and onions emerged; the favourable effect of garlic intake increased progressively until 50–60 g/day and levelled off thereafter. The analysis in strata of geographic area (Supplementary Fig. S2) indicates a stronger favourable effect in Asian Countries.

DISCUSSION

In this uniquely large database, derived from a worldwide consortium of epidemiological investigations on gastric cancer, we found an inverse association between allium vegetables intake, including garlic and onions, and gastric cancer. The association was evident in studies from Asia and, to a lesser extent, in those from America, but not in studies from Europe. Results were fairly consistent in strata of cancer anatomical subsites (cardia and non-cardia) and histological type (intestinal and diffuse), and across the other subgroups analysed.

The anticancer effects of allium vegetables have been mainly attributed to various organosulfur compounds, mainly allyl derivatives [14]. In experimental animal studies, diallylsulfide, diallyldisulfide, allylmethyldisulfide, allylmercaptan, diallyltrisulfide and allylmethylsulfide inhibited forestomach cancer [44]. Cancer protection by allium vegetables may arise from several mechanisms, including modulation of the activities of metabolising enzymes that activate (cytochrome P450s) or detoxify (glutathione S-transferases) carcinogens, inhibition of DNA adduct formation, and inhibition of cell proliferation and tumour growth by apoptosis and alteration of the cell cycle [14, 44]. In addition,

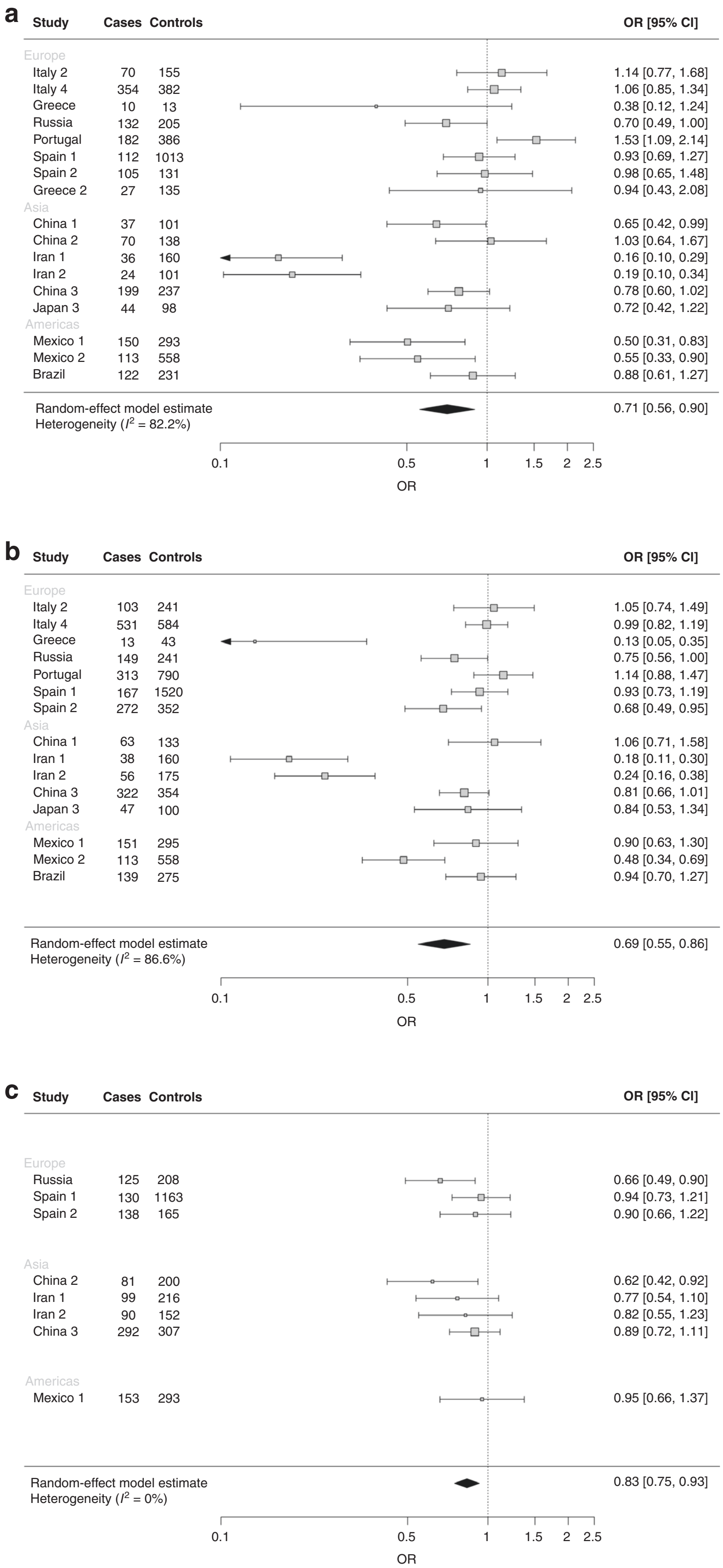

Fig. 1 Forest plot of allium vegetables consumption and gastric cancer risk. Study-specific and pooled odds ratios (ORs) of gastric cancer, and corresponding 95% confidence intervals (CIs), for the highest compared to the lowest category of consumption[1] of allium vegetables (**a**), onions (**b**) and garlic (**c**) in the Stomach cancer Pooling (StoP) Project consortium. Footnote: [1]Comparisons: highest versus lowest study-specific tertile of consumption for allium vegetables, and above versus below the study-specific median consumption for onions and garlic. The numbers of cases and controls reported in the forest plots for each study refer to subjects in the highest category of consumption.

Table 3. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of gastric cancer for the highest compared to the lowest study-specific tertile of allium vegetables intake in strata of selected variables in the Stomach cancer Pooling (StoP) Project consortium.

	Cases/controls (number of included studies)	OR (95% CI)	I^2 (%)
Area			
Europe	3422/8389 (8)	0.96 (0.81–1.13)	38.3
Asia	1839/2660 (6)	0.50 (0.29–0.86)	89.5
The Americas	836/1968 (3)	0.66 (0.39–1.11)	78.7
		p-value heterogeneity = *0.042*	
Sex			
Men	3870/7423 (17)	0.71 (0.56–0.90)	73.9
Women	2227/5594 (17)	0.76 (0.58–1.01)	63.2
		p-value heterogeneity = *0.700*	
Age (years)			
<60	2220/5256 (17)	0.74 (0.57–0.95)	61.0
≥60	3877/7761 (17)	0.70 (0.54–0.91)	77.5
		p-value heterogeneity = *0.79*	
Socioeconomic status			
Low-intermediate	3680/6311 (17)	0.72 (0.54–0.96)	77.9
High	2373/6640 (17)	0.73 (0.58–0.92)	581
		p-value heterogeneity = *0.933*	
Smoking habit			
Never-former	4376/9798 (17)	0.73 (0.59–0.91)	73.1
Smoker	1721/3219 (17)	0.67 (0.48–0.94)	66.3
		p-value heterogeneity = *0.690*	
Alcohol drinking (g/day)			
Never-low (≤12)	2498/7112 (15)	0.74 (0.57–0.96)	71.3
Intermediate (>12–47)–High (>47)	2427/4020 (12)	0.93 (0.80–1.10)	7.4
		p-value heterogeneity = *0.136*	
History of gastric cancer in first degree relatives			
No	2871/7410 (12)	0.71 (0.50–1.00)	84.4
Yes	718/691 (11)	1.01 (0.73–1.40)	0.0
		p-value heterogeneity = *0.138*	
Total fruit and vegetable intake[a]			
Low-Intermediate	3824/7520 (16)	0.73 (0.56–0.95)	76.2
High	2003/4598 (17)	0.68 (0.49–0.94)	75.1
		p-value heterogeneity = *0.701*	
Type of controls			
Hospital-based	1978/3287 (7)	0.82 (0.67–1.00)	36.3
Population-based	4119/9730 (10)	0.64 (0.45–0.91)	88.9
		p-value heterogeneity = *0.237*	
HP infection			
Seronegative	668/1378 (8)	0.66 (0.43–0.99)	43.1
Seropositive	1738/4588 (9)	0.57 (0.32–1.03)	89.8
		p-value heterogeneity = *0.716*	
Histological type[b]	(9)		
Intestinal	1689/9315	0.74 (0.48–1.14)	84.6
Diffuse	989/9315	0.80 (0.56–1.14)	67.0
Unspecified	846/9315	0.60 (0.39–0.94)	72.5
		p-value heterogeneity = *0.628*	
Site[b]	(12)		
Cardia	613/10196	0.73 (0.42–1.27)	77.6
Non-cardia	3158/10196	0.67 (0.47–0.97)	86.4
		p-value heterogeneity = *0.808*	

HP *Helicobacter pylori*.
[a]Study-specific tertiles.
[b]Analysed using multinomial multivariable logistic model.

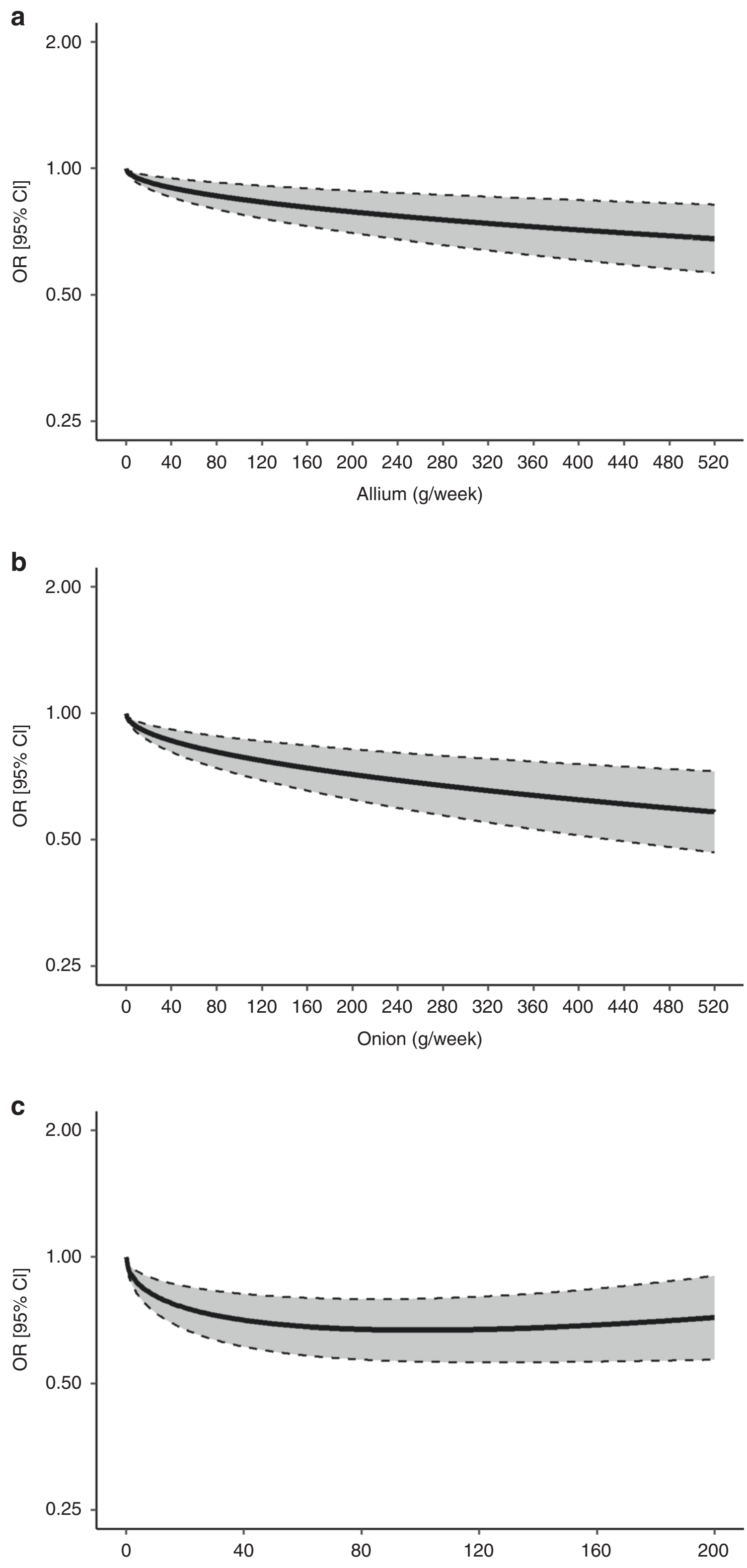

Fig. 2 Exposure-response relation between allium vegetables consumption and gastric cancer. Best-fitting fractional polynomial models describing the relationship (solid line) with its 95% confidence intervals (CIs) (dashed lines) between the intake (g/week) of allium vegetables (**a**), onions (**b**) and garlic (**c**) with gastric cancer risk in the Stomach cancer Pooling (StoP) Project consortium[1,2]. OR odds ratio. Footnotes: [1]Details of the models are given in Supplementary Table S4 (Supplementary materials). [2]Study StoP ID #33 (Greece 2) excluded due to policy reasons on the transfer of original data.

allium vegetables, in particular garlic, showed antibacterial effects against HP infection—a key risk factor for gastric cancer [45]—in in vitro [46] and animal studies [47]. However, evidence from observational and experimental human studies is not consistent [48]. In particular, among trials on HP infected subjects, the Shandong Intervention Trial from China did not find a reduced HP prevalence after long-term administration (7.3 years) of garlic supplements compared to the placebo [49], while one smaller trial from Turkey found a significantly increased HP eradication rate when allicin (a major compound of garlic) was added to the standard eradication regimen [50]. In this study, the association between allium vegetables intake and gastric cancer was similar among subjects with and without HP infection, suggesting independent effects on gastric cancer.

The heterogeneity of results across geographical regions can be explained by the different consumption quantities and patterns of allium vegetables. Preparation or processing methods influence the bioavailability and activity of bioactive compounds of allium vegetables [51, 52]. Cutting, chopping or crushing fresh garlic lead to the formation of organosulfur compounds but heating destroys garlic's active allyl sulfur compound formation [53]; a previous study showed a 30% reduction in the content of quercetin (i.e., the major flavonoid present in onions) when onions are boiled [52]. In Mediterranean countries, onions are consumed both raw (added to salads) and cooked, while garlic is often cooked in combination with other foods or used for dressings, and is unfrequently eaten raw. Studies from this area generally reported null associations, particularly with garlic intake. In Asian countries, an inverse relation between allium vegetables and gastric cancer was found, with, however, substantial heterogeneity among studies. Again, consumption patterns differ widely across countries: in China, onions are consumed almost exclusively cooked, whereas in Iran, where we observed a stronger inverse association with onions intake in two studies, onions are consumed both raw and cooked. Conversely, for garlic, the inverse association was similar among Asian studies where it is consumed mainly as raw (i.e., China) or cooked (i.e., other Asian countries). However, the available information from studies included in the present investigation did not allow us to conduct separate analyses for raw versus cooked allium vegetables, nor according to cooking methods. Differences in the genetic background and possibly in microbiome composition across populations may also partly or largely account for the difference in the results across geographic areas. With reference to familial, and hence likely genetic, related neoplasms, no heterogeneity was observed across strata of family history and the association was, if anything, stronger among subjects without family history of gastric cancer.

Besides the case–control studies included in the StoP Project database, other case–control studies worldwide indicated an inverse association between allium vegetables intake and gastric cancer [54–57]. However, available prospective cohort studies have provided essentially null results. A lack of a significant association was reported by the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS), which focused on garlic [21], the European Prospective Investigation into Cancer and Nutrition (EPIC) study [58], the Shanghai Women's and Men's Health studies (SWHS and SMHS) [59], the Swedish Mammography Cohort and Cohort of Swedish Men [60], and the Netherlands Cohort Study (NCS) [61]. In the double-blind randomised Shandong Intervention Trial, 7.3 years of oral supplementation with garlic extract and oil was associated with a non-statistically significant reduction in gastric cancer incidence (OR 0.80, 95% CI: 0.53–1.20) and mortality (hazard ratio, 0.65, 95% CI: 0.35–1.20) over 14.7 years of follow-up [62]. The only case–control study derived from a cohort study included in the present analysis [23] reported an OR of 0.94 (95% CI, 0.43–2.08) for high versus low total allium intake. Case–control studies are generally more prone to selection and recall bias than cohort studies. In addition, the presence of symptoms of the disease and pre-neoplastic lesions in the stomach may have led to a decrease in the intake of allium vegetables among cases (reverse causation), and this may explain part of the inverse association observed in retrospective studies. Nevertheless, cohort studies might suffer from exposure misclassification because they typically measure diet at one point in time only.

It is possible that, at least in Europe, subjects with high allium vegetables intake also have a diet richer in vegetables and a healthier lifestyle. Fruit and vegetable intake has been associated with decreased risk of gastric cancer [6, 63]. Although we adjusted our models for total fruit and vegetable intake, socioeconomic status, tobacco smoking and alcohol drinking, and, in sensitivity analyses, we found similar ORs after adjusting for total energy intake, some residual confounding cannot be ruled out.

The major strengths of this study are that it is based on a pooled analysis from a worldwide consortium of epidemiological studies and it includes a large number of cases. Individual participant data pooled analyses allowed to overcome some of the limitations of meta-analyses of published data [64, 65], allowing the harmonisation of information and analyses, consistency in adjustment factors and multivariate models, and a thorough investigation of heterogeneity across subgroups [66]. For this study, we obtained the most complete data available on allium vegetables intake and other variables of interest, including possible confounding factors, from the original studies of the StoP Project, and we were able to apply uniform criteria to the variable definition and statistical analysis. The number of studies and participants allowed us to perform stratified analyses considering various factors, including cancer anatomical subsite and histological type, and to address the exposure-response relationships. In addition, we included in the analysis studies that did not specifically assess the association of allium vegetables with gastric cancer in previous reports, and this prevented publication bias.

Among the limitations, this analysis was based almost exclusively on case–control studies. However, all the studies enrolled incident gastric cancer cases and collected dietary data in a period preceding diagnosis (for cases) of at least 1 year. Allium vegetables are typically used in mixed dishes in varying amounts or as garnishes (e.g., shallots and chives); in some countries, they are added as flavouring ingredients and then removed before food consumption. Deriving accurate estimates of their usual intake through food frequency questionnaires is therefore challenging. Notably, allium vegetables intake may have been underestimated in studies collecting information on a few types only. However, based on the meta-regression, the number of specific vegetables included in the total allium vegetables variable did not significantly affect the observed association. Further, information on HER2 expression in gastric cancer cases was not available for most studies and thus we could not assess whether the association with allium vegetables differed by HER2 status.

CONCLUSION

In conclusion, the present investigation within a worldwide consortium of epidemiological studies found an inverse association between allium vegetables consumption, including onions and garlic, and gastric cancer risk. The apparent heterogeneity across geographic areas, likely attributable to different patterns of consumption across populations, and the possibility of residual confounding suggest the need for caution in the interpretation of our findings.

DATA AVAILABILITY

The data that support the findings of our study are available from the StoP Project but restrictions apply to the availability of these data, which were used under license for this study and so are not publicly available. Data are, however, available from the authors upon reasonable request and permission of the Steering Committee of the StoP Project.

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ACKNOWLEDGEMENTS

The authors thank the European Cancer Prevention (ECP) Organization for providing support for the StoP Project meetings and all MCC-Spain study collaborators (CIBERESP, ISCIII, ISGlobal, ICO, University of Huelva, University of Oviedo, University of Cantabria, ibs.Granada, Instituto Salud Pública de Navarra, FISABIO, Murcia Regional Health Authority and cols).

AUTHOR CONTRIBUTIONS

MD performed the statistical analysis, interpreted the data and revised the manuscript; FT drafted the manuscript; MR and GM contributed to the statistical analysis; MR, CP, RB and CG harmonised the data, as part of the Stomach Cancer Pooling (StoP) Project; ZFZ, NL, DP, MF, GPY, SM, RM, LLC, DZ, DM, NA, GFT, VM, JV, MGH, MPC, FJFC, PA, MP, JH, RUHR, MW, FP, LM, ST, AH, PL, AL, AT, AK, PB, MCC, EN and CLV supplied the data as part of the StoP Project; CLV and CP supervised the analysis and interpretation of data, and reviewed the manuscript for important intellectual content; CP defined the study hypotheses and designed the investigation, and had primary responsibility for final content. All authors have read and approved the final manuscript.

FUNDING

This study was supported by the Fondazione AIRC per la Ricerca sul Cancro, Project no. 21378 (Investigator Grant), and by the Italian League for the Fight Against Cancer (LILT), which did not play a role in study design, data collection, data analysis, interpretation of the results or in the writing of this manuscript. The Unidade de Investigação em Epidemiologia—Instituto de Saúde Pública da Universidade do Porto (EPIUnit; UIDB/04750/2020) was funded by the Foundation for Science and Technology—FCT (Portuguese Ministry of Science, Technology and Higher Education). SM was also funded by the project "NEON-PC—Neuro-oncological complications of prostate cancer: a longitudinal study of cognitive decline" (POCI-01–0145-FEDER-032358; ref. PTDC/SAU-EPI/32358/2017), which is funded by FEDER through the Operational Programme Competitiveness and Internationalisation, national funding from FCT, and the EPIUnit – Junior Research – Prog Financing (UIDP/04750/2020). The Brasilian study was funded by Fundação de Amparo à Pesquisa do Estado de São Paulo-FAPESP number 2014/26897-0 SaoPaulo Brasil.

COMPETING INTERESTS

The authors declare no competing interests.

CONSENT TO PUBLISH

Not applicable.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The participating studies were performed in accordance with laws, regulations and guidelines for the protection of human subjects (including consent from the participants) applicable at the time of study conduction, and in accordance with the Declaration of Helsinki. All identifying information was removed before data were pooled at the study coordinating centre located at the University of Milan. The StoP Project received ethical approval from the University of Milan Review Board (reference 19/15 on 01/04/2015).

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41416-022-01750-5.

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