Coffee consumption and gastric cancer: a pooled analysis from the Stomach cancer Pooling Project consortium

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Objective **This study aimed to evaluate and quantify the relationship between coffee and gastric cancer using a uniquely large dataset from an international consortium of observational studies on gastric cancer, including data from 18 studies, for a total of 8198 cases and 21 419 controls.**

Methods **A two-stage approach was used to obtain the pooled odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) for coffee drinkers versus never or rare drinkers. A one-stage logistic mixed-effects model with a random intercept for each study was used to estimate the dose–response relationship. Estimates were adjusted for sex, age and the main recognized risk factors for gastric cancer.**

Results **Compared to never or rare coffee drinkers, the estimated pooled OR for coffee drinkers was 1.03 (95% CI, 0.94–1.13). When the amount of coffee intake was considered, the pooled ORs were 0.91 (95% CI, 0.81–1.03) for drinkers of 1–2 cups per day, 0.95 (95% CI, 0.82–1.10) for 3–4 cups, and 0.95 (95% CI, 0.79–1.15) for five or more cups. An OR of 1.20 (95% CI, 0.91–1.58) was found for heavy coffee drinkers (seven or more cups of caffeinated coffee per day). A positive association emerged for high coffee intake (five or more cups per day) for gastric cardia cancer only.**

Conclusions **These findings better quantify the previously available evidence of the absence of a relevant association between coffee consumption and gastric cancer.** ***European Journal of Cancer Prevention*** **XXX: 000–000**

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Keywords: cardia cancer, case-control study, coffee, gastric cancer, pooled analysis

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Introduction

Gastric cancer is the fifth most common cause of cancer death in the world, and there were about one million (1 089 103) new cases of gastric cancer diagnosed in 2020 (Ferlay *et al*., 2020). Coffee is one of the most popular beverages worldwide, with an annual overall consumption of 1.27 kg per capita, which increased by 18.7% between 2014 and 2017 (Food and Agriculture Organization of the United Nations). Coffee is a complex mixture that includes many substances and chemicals that can play different roles in the etiology of gastric cancer. Some substances, mainly antioxidants (such as phenolic compounds, diterpenes, melanoidins and vitamin precursors), can have anticancer properties, while others can stimulate the carcinogenic process (including very small amounts of aromatic hydrocarbons and heterocyclic amines formed during the processing for the beans) (Borrelli *et al*., 2002; Gallus *et al*., 2009; Shen *et al*., 2015; Alicandro *et al*., 2017; Yu *et al*., 2019).

In 2018, the World Cancer Research Fund/American Institute for Research reported limited evidence for an association between the consumption of coffee and gastric cancer (World Cancer Research Fund/American Institute for Research, 2018). However, the results of available studies were inconsistent. Therefore, to better evaluate and quantify the association between coffee consumption and gastric cancer, we carried out an individual participant pooled data analysis of gastric cancer studies included in an international consortium, the Stomach cancer Pooling (StoP) Project.

Methods

Study population

Data from the v.3.1 dataset release of the StoP Project (http://stop-project.org/) was used. This includes 34 case-control or cohort (participating through a nested case-control approach) studies for a total of about 13 500 gastric cancer cases and 32 000 controls. Detailed information on the aims and methods of the StoP Project is given elsewhere (Pelucchi *et al*., 2015). 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 center, or by computing their own results locally (through standardized analyses) and then providing estimates for the second-stage meta-analysis to the StoP Project consortium [Finland (Cook *et al*., 2012) and Greece 2 (Benetou *et al*., 2008)]. All centralized data were harmonized according to a prespecified format. Ethical approval for the StoP Project was received by the University of Milan Review Board (reference 19/15 on 4 January 2015).

Overall, 21 studies collected data on coffee consumption. Three studies (López-Carrillo *et al*., 2003; Boccia *et al*., 2007; Pourfarzi *et al*., 2009) were excluded from the present analysis due to a high proportion (i.e. >60%) of missing values on coffee consumption. As such, 18 studies with data on coffee drinking conducted in Greece (Lagiou *et al*., 2004; Benetou *et al*., 2008) (two studies), Italy (Buiatti *et al*., 1989; La Vecchia *et al*., 1995; Lucenteforte *et al*., 2008) (three studies), Canada (Mao *et al*., 2002), Russia (Zaridze *et al*., 2000), USA (Zhang *et al*., 1999; Schatzkin *et al*., 2001; Ward *et al*., 2008) (three studies), Portugal (Lunet *et al*., 2007), Spain (Santibañez *et al*., 2012; Castaño-Vinyals *et al*., 2015) (two studies), Mexico (López-Carrillo *et al*., 1994; Hernández-Ramírez *et al*., 2009) (two studies), Brazil (Hamada *et al*., 2002; Nishimoto *et al*., 2002) (two studies) and Japan (Machida-Montani *et al*., 2004) were included. Out of the 18 studies, only two were cohort studies, one from the USA (Schatzkin *et al*., 2001) and one from Greece (Benetou *et al*., 2008), and seven had information on decaffeinated coffee consumption: two from Italy (La Vecchia *et al*., 1995; Lucenteforte *et al*., 2008), one from Russia (Zaridze *et al*., 2000), two from Spain (Santibañez *et al*., 2012; Castaño-Vinyals *et al*., 2015) and two from the USA (Zhang *et al*., 1999; Schatzkin *et al*., 2001).

Coffee intake

Coffee intake was assessed through food frequency questionnaires (FFQs) that asked participants to report the amount of coffee consumed overall or according to specific types of coffee (e.g. caffeinated or decaffeinated coffee) before the gastric cancer diagnosis (for cases) or study recruitment (for controls). Coffee intake was collected either by face-to-face interview (in 12 studies) or by self-administered FFQs (in six studies).

Coffee consumption was expressed in standard unit of cups per day by taking into account the number of coffee cups or times coffee was consumed or the frequency of consumption specified in each study. When coffee consumption was indicated in categories of consumption, the amount of coffee intake was converted into cups per day by considering the average number of coffee cups or times coffee was consumed reported in each category and divided by the number of days considered. For the present analyses, the following three coffee consumption variables were considered: caffeinated coffee, decaffeinated coffee and their combined intake as total coffee. When the FFQ did not contain a specific variable for caffeinated coffee, the various types of caffeinated coffee reported separately were grouped together for the

Table 1 Distribution of gastric cancer cases and controls[a] according to study center, sex, age and other selected covariates in the Stomach cancer Pooling (StoP) Project consortium

	Cases		Controls	
	N	%	*N*	%
Total	8198	100.0	21 419	100.0
Study center (reference)				
Europe	4191	51.0	10 470	48.9
Greece 1 (Lagiou *et al.*, 2004)	110	1.3	100	0.5
Greece 2 (Benetou *et al.*, 2008)	82	1.0	410	1.9
Italy 1 (La Vecchia *et al.*, 1995)	769	9.4	2081	9.7
Italy 2 (Lucenteforte *et al.*, 2008)	230	2.8	547	2.6
Italy 4 (Buiatti *et al.*, 1989)	1016	12.4	1159	5.4
Portugal (Lunet *et al.*, 2007)	692	8.4	1667	7.8
Russia (Zaridze *et al.*, 2000)	450	5.5	611	2.9
Spain 1 (Castaño-Vinyals *et al.*, 2015)	441	5.4	3440	16.1
Spain 2 (Santibañez *et al.*, 2012)	401	4.8	455	2.1
Asia				
Japan 3 (Machida-Montani *et al.*, 2004)	153	1.9	303	1.4
America	3854	47.0	10 646	49.7
Brazil 1 (Nishimoto *et al.*, 2002)	226	2.8	226	1.1
Brazil 2 (Hamada *et al.*, 2002)	93	1.1	186	0.9
Canada (Mao *et al.*, 2002)	1182	14.4	5039	23.5
Mexico 1 (Hernández-Ramírez *et al.*, 2009)	248	3.0	478	2.2
Mexico 2 (López-Carrillo *et al.*, 1994)	220	2.7	752	3.5
USA 1 (Zhang *et al.*, 1999)	132	1.6	132	0.6
USA 3 (Ward *et al.*, 2008)	170	2.1	502	2.3
USA 4 (Schatzkin *et al.*, 2001)	1583	19.3	3331	15.6
Sex				
Men	5385	65.7	12 304	57.4
Women	2813	34.3	9115	42.6
Age				
Missing	41	0.5	18	0.1
<40	240	2.9	1462	6.8
40–44	256	3.1	1144	5.3
45–49	458	5.6	1549	7.2
50–54	615	7.5	1774	8.3
55–59	885	10.8	2161	10.3
60–64	1167	14.2	2943	13.7
65–69	1626	19.8	3779	17.6
70–74	1698	20.7	3672	17.1
≥75	1212	14.8	2917	13.6
Socioeconomic status(study-specific)				
Missing	184	2.2	309	1.5
Low	3873	47.2	7946	37.1
Intermediate	2759	33.7	7638	35.6
High	1382	16.9	5526	25.8
Tobacco smoking				
Missing	384	4.7	563	2.6
Never	3092	37.7	9094	42.5
Former	2843	34.7	7098	33.1
Current				
Low	512	6.2	1603	7.5
Intermediate	745	9.1	1790	8.4
High	622	7.6	1271	5.9
Alcohol drinking				
Missing	366	4.5	1513	7.1
Never	2107	25.7	5582	26.1
Low (≤12 g/day)	2165	26.4	7237	33.8
Intermediate (>12 and ≤ 47 g/day)	2388	29.1	5010	23.4
High (>47 g/day)	1172	14.3	2077	9.7
History of gastric cancer in first-degree relatives[b]				
Missing	828	17.0	1714	15.0
No	3296	67.5	8922	78.2
Yes	759	15.5	773	6.8
Fruit and vegetable intake (study-specific tertiles)				
Missing	179	2.2	745	3.5
Low	2616	31.9	6244	29.2
Intermediate	2620	32.0	7034	32.8
High	2783	33.9	7396	34.5
Salt intake (study-specific tertiles)[c]				
Missing	159	2.3	997	5.0
Low	2794	40.0	7501	38.0
Intermediate	2221	31.8	6192	31.4
High	1816	26.0	5060	25.6

[a]Percentages may not add to 100% due to rounding.
[b]The studies Canada (Mao *et al.*, 2002), Greece 2 (Benetou *et al.*, 2008), Mexico 1 (Hernández-Ramírez *et al.*, 2009), Mexico 2 (López-Carrillo *et al.*, 1994) and USA 4 (Schatzkin *et al.*, 2001) were not included as they did not collect data on family history of gastric cancer.
[c]The studies Greece 1 (Lagiou *et al.*, 2004), Greece 2 (Benetou *et al.*, 2008) and Italy 4 (Buiatti *et al.*, 1989) were not included as they did not collect data on salt intake.

purposes of the present study. For example, espresso and cappuccino intake were considered as caffeinated coffee consumption in the Italy 2 study (Lucenteforte *et al.*, 2008), while for the Russian study (Zaridze *et al.*, 2000), black-instant coffee, coffee with milk and instant coffee with milk consumption were grouped together.

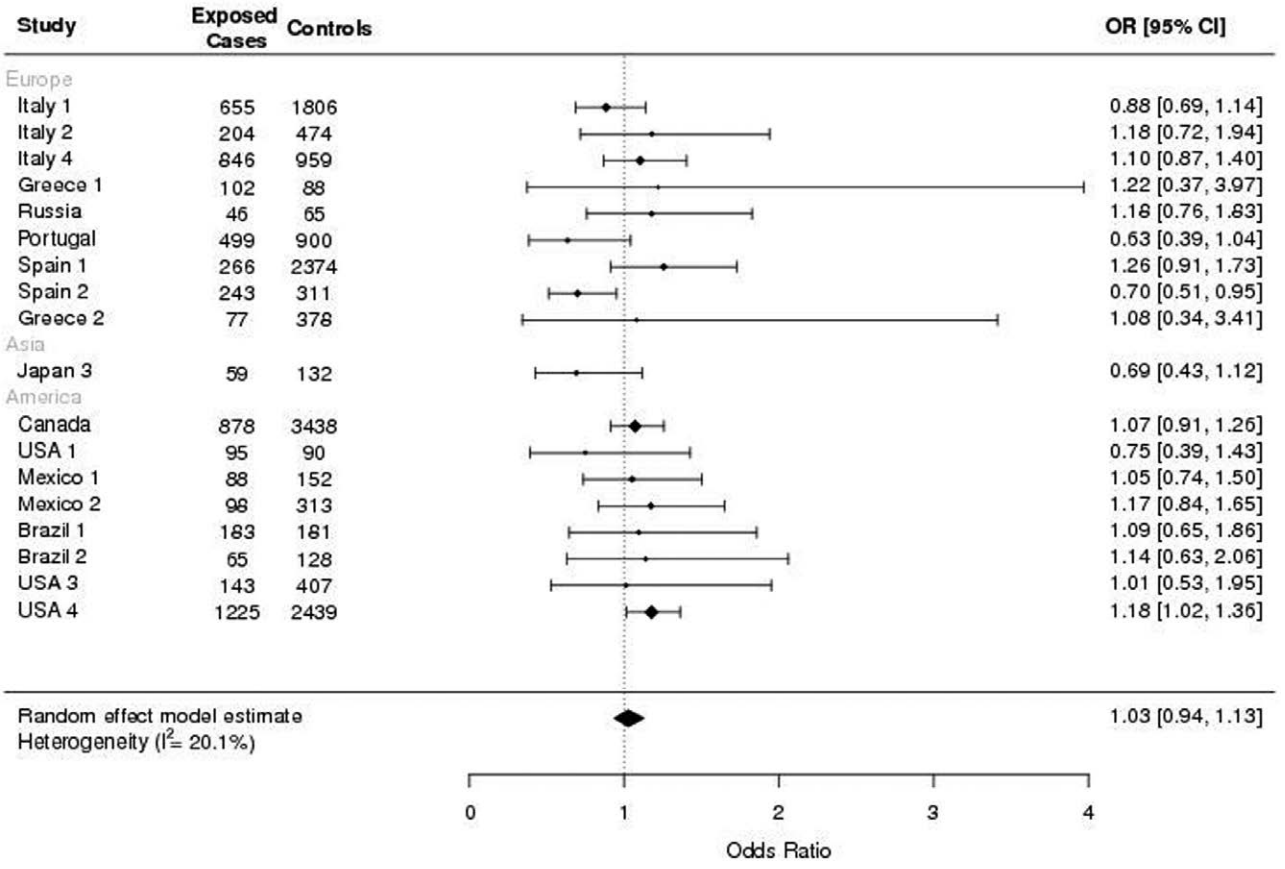
For total coffee consumption, never or rare coffee drinkers were defined as those who reported that they did not consume coffee at all or reported an amount of <1 cup/day while ever coffee drinkers reported that they consumed coffee or reported an amount of ≥1 cup/day. Furthermore, for the 16 studies for which information on the amount of coffee consumed was available [i.e. all except the two studies from Greece (Lagiou *et al.*, 2004; Benetou *et al.*, 2008)], the consumption of caffeinated coffee and total coffee intake were categorized into the following eight categories: <1 cup/day: never or rare drinkers, ≥1 to <2 cups/day, ≥2 to <3 cups/day, ≥3 to <4 cups/day, ≥4 to <5 cups/day, ≥5 to <6 cups/day, ≥6 to <7 cups/day and ≥7 cups/day, that were also classified in four categories of drinking: <1 cup/day: never or rare drinkers, ≥1 to < 3 cups/day, ≥3 to <5 cups/day and ≥5 cups/day. For decaffeinated coffee consumption, the four following categories of drinking were defined: <1 cup/day: never or rare drinkers, ≥1 to <2 cups/day, ≥2 to < 3 cups/day and ≥3 cups/day, since decaffeinated coffee consumption was not reported as often as caffeinated coffee.

Statistical analysis

A two-stage modeling approach was adopted to estimate the pooled odds ratios (ORs) for ever coffee drinkers versus never or rare drinkers, including both the studies that provided original individual data and those that provided locally computed estimates.

First, the study-specific ORs and corresponding 95% confidence intervals (CIs) were estimated for the association between total coffee consumption (ever coffee drinkers versus never or rare drinkers) and gastric cancer, through multivariable conditional or unconditional logistic regression models, as appropriate. In the second stage, the

Fig. 1



Study-specific and two-stage pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of gastric cancer for total coffee drinkers compared with never or rare drinkers in the Stomach cancer Pooling (StoP) Project consortium.

summary (pooled) effect estimates were obtained using a random-effects model (DerSimonian and Laird, 1986).

A one-stage approach was used to evaluate the dose–response relationship between coffee consumption and gastric cancer and for stratified analyses (Burke *et al.*, 2017) excluding two studies [Greece 1 (Lagiou *et al.*, 2004) as the amount of coffee consumed was not reported and Greece 2 (Benetou *et al.*, 2008) that provided locally computed estimates for the two-stage analysis only]. One-stage ORs and the corresponding 95% CIs of gastric cancer were estimated across the categories of coffee consumption using generalized linear mixed-effect models with a logistic link function and a random intercept for each study.

In both one-stage and two-stage approaches, never or rare coffee drinkers were used as the reference category. All models were adjusted for sex, 5-year age groups (<40, 40–44, …, 70–74, ≥75), study-specific socioeconomic status (low, intermediate, high), smoking status (never, former, current low, current intermediate, current high), alcohol drinking (never, <1 drink/day, 1–3 drinks/day, ≥4 drinks/day), study-specific salt intake (low, intermediate, high), study-specific total fruit and vegetable intake (low, intermediate, high) and family history of gastric cancer. Missing values in the study-specific confounders were accounted for by either being included in the models as a separate category of each respective variable or by being included in the lower levels of the categories when there was a low proportion missing (i.e. <1%).

For the stratified analyses, the effect of coffee drinking was explored across strata of sex, age (<65 and ≥65 years), geographical area (Europe, Asia, America), socioeconomic status (low, intermediate, high), smoking status (never smokers, former smokers, current smokers), alcohol drinking (<1 drink/day, 1–3 drinks/day, ≥4 drinks/day), total fruit and vegetable intake (low, intermediate, high), salt intake (low, intermediate, high), family history of gastric cancer (no, yes), *Helicobacter pylori* infection (no, yes), type of controls (hospital-based, population-based), cancer anatomical subsite (cardia, non-cardia) and histological type (intestinal, diffuse). For the strata of *H. pylori* infection, the Spain 2 (Santibañez *et al.*, 2012) study was

Table 2 Distribution of gastric cancer cases and controls[a] according to coffee consumption (in cups/day) categories, and one-stage pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for gastric cancer in the Stomach cancer Pooling (StoP) Project consortium.

	Cases		Controls		
	N	%	*N*	%	OR (CI 95%)[b]
Caffeinated coffee	8006		20 909		
Never/rarely	2726	34.0	6753	32.3	1
1	1441	18.0	3752	17.9	0.84 (0.73–0.95)
2	1874	23.4	5125	24.5	0.91 (0.80–1.04)
3	582	7.3	1345	6.4	0.87 (0.74–1.03)
4	608	7.6	1590	7.6	0.87 (0.71–1.07)
5	111	1.4	281	1.3	0.95 (0.72–1.25)
6	215	2.7	513	2.5	0.94 (0.68–1.31)
≥7	172	2.1	318	1.5	1.20 (0.91–1.58)
Missing	277	3.5	1232	5.9	
Decaffeinated coffee[c]	4006		10 597		
Never/rarely	3274	81.7	8227	77.6	1
1	262	6.5	989	9.3	0.85 (0.69–1.05)
2	252	6.3	717	6.8	1.19 (0.89–1.60)
≥3	101	2.5	258	2.4	1.19 (0.76–1.85)
Missing	117	2.9	406	3.8	
Total coffee	8006		20 909		
Never/rarely	2128	26.6	5462	26.1	1
1	1615	20.2	3901	18.7	0.88 (0.77–1.01)
2	2112	26.4	5673	27.1	0.94 (0.82–1.08)
3	629	7.9	1433	6.9	0.96 (0.81–1.13)
4	698	8.7	1811	8.7	0.93 (0.76–1.14)
5	121	1.5	353	1.7	0.96 (0.74–1.25)
6	223	2.8	568	2.7	0.88 (0.64–1.20)
≥7	195	2.4	430	2.1	1.01 (0.78–1.31)
Missing	285	3.6	1278	6.1	

[a]Percentages may not add to 100% due to rounding.
[b]One-stage pooled ORs were estimated using mixed-effects models adjusted for sex, age category, social class, smoking status, salt intake, fruit intake and vegetable, alcohol intake and family history of gastric cancer.
[c]Information on decaffeinated coffee consumption was available for the studies Italy 1 (La Vecchia *et al.*, 1995), Italy 2 (Lucenteforte *et al.*, 2008), Russia (Zaridze *et al.*, 2000), Spain 1 (Castaño-Vinyals *et al.*, 2015), Spain 2 (Santibañez *et al.*, 2012), USA 1 (Zhang *et al.*, 1999) and USA 4 (Schatzkin *et al.*, 2001).

not included since the information was only available for the cases. For the stratifying variables of cancer anatomical subsite (cardia and non-cardia) and histological type (intestinal and diffuse by Lauren classification), multinomial mixed-effects models were used to estimate the ORs for each type of cancer separately. Heterogeneity between groups was assessed using the Q statistic.

The dose–response relationship was modeled using a one-stage linear random-effects model with natural cubic splines and four knots at fixed percentiles of caffeinated coffee consumption (25th, 50th, 75th and 90th) (Desquilbet and Mariotti, 2010).

Results

Table 1 shows the main characteristics of the 8198 cases of gastric cancer and 21 419 controls included in the present analysis. About 50% of cases and controls were from European studies. Compared to controls, cases were more frequently males (65.7 versus 57.4%), older (55.3 versus 48.3% ≥65 years old) and reported a low socioeconomic status more frequently (47.2 versus 37.1%). Cases were also more frequently high current smokers (7.6 versus 5.9%), heavy alcohol drinkers (14.3 versus 9.7%), and were more likely to have a first-degree relative with a history of gastric cancer in (15.5 versus 6.8%) compared to controls.

The study-specific and summary (pooled) ORs for gastric cancer, from the two-stage approach, according to total coffee drinking (drinkers versus never or rare drinkers) are presented in Fig. 1. No association between total coffee consumption and gastric cancer risk was observed (OR = 1.03, 95% CI, 0.94–1.13).

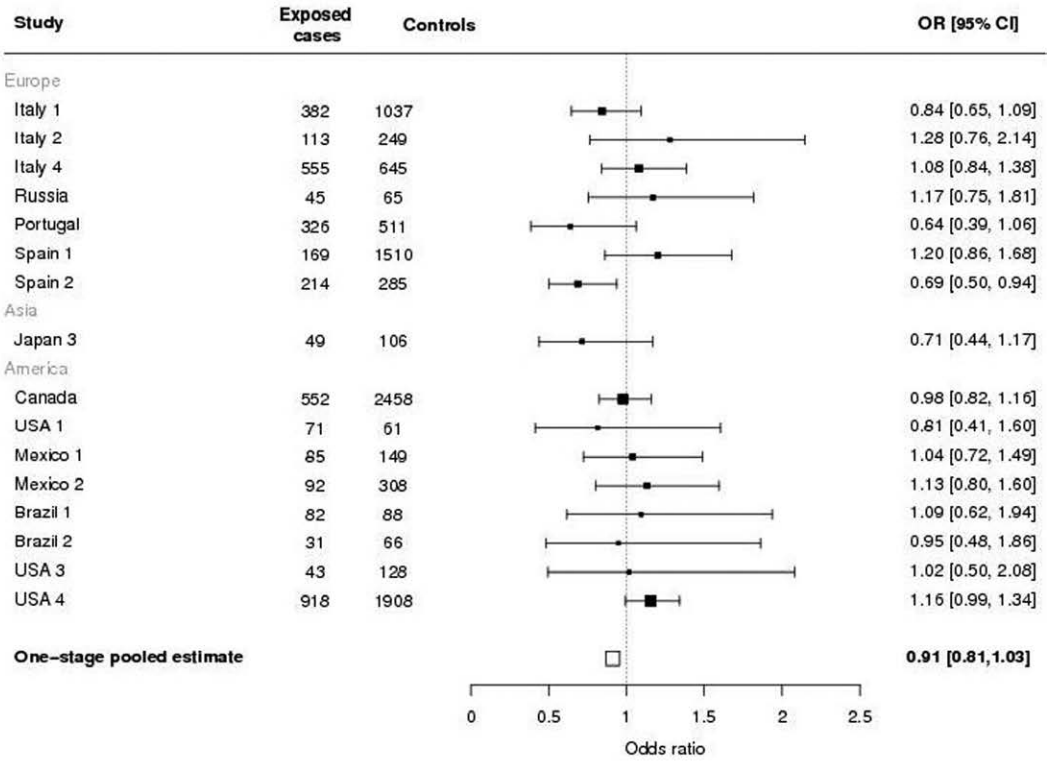
The distribution of cases and controls according to the reported amounts for caffeinated, decaffeinated and total coffee consumption are presented in Table 2. About 63% of cases and 62% of controls reported consumption of ≥1 cup per day of caffeinated coffee, and about 70% of cases and 68% of controls reported consumption of ≥1 cup per day of total coffee. Compared with never or rare drinkers, the one-staged pooled ORs were 1.20 (95% CI, 0.91–1.58) and 1.01 (95% CI, 0.78–1.31) for ≥7 cups per day of caffeinated and total coffee, respectively. Data on decaffeinated coffee consumption were available for a total of seven studies, and approximately 15% of gastric cancer cases and 19% of controls reported drinking decaffeinated coffee. The pooled OR was 1.19 (95% CI, 0.76–1.85) for decaffeinated coffee consumers of ≥3 cups per day, compared to never or rare drinkers.

Figure 2 shows the forest plots of one-stage adjusted pooled ORs for gastric cancer according to the levels of total coffee drinking. There was no consistent association between levels of total coffee consumption and gastric cancer compared with never or rare coffee drinkers. Compared to never or rare coffee drinkers (the reference category), the pooled OR estimates were 0.91 (95% CI, 0.81–1.03) for light coffee drinkers (1–2 cups/day, Panel a), 0.95 (95% CI, 0.82–1.10) for moderate coffee drinkers (3–4 cups/day, Panel b) and 0.95 (95% CI, 0.79–1.15) for high coffee drinkers (≥5 cups/day, Panel c). Figure 3 shows the dose–response relationship, fitted by natural cubic splines, between consumption of caffeinated coffee and gastric cancer.

The results from the one-stage stratified analysis, according to levels of total coffee consumption, are presented in Table 3 and Fig. 4. Subgroup analyses by sex, age, socioeconomic status, alcohol drinking, salt intake, family history of gastric cancer, *H. pylori* infection, type of controls and histotype showed no heterogeneity. Heterogeneity was evident across categories of geographic area of the studies ($Q = 7.00$, $P < 0.01$), smoking status ($Q = 4.83$, $P = 0.03$), fruit and vegetable intake ($Q = 5.58$, $P = 0.02$) and subsite of gastric cancer ($Q = 12.60$, $P < 0.001$). A positive association emerged for gastric cardia cancer (OR = 1.61, 95% CI, 1.27–2.05) with high consumption of total coffee (≥5 cups/day), while no association was found for non-cardia gastric cancer (OR = 0.93, 95% CI, 0.77–1.12).

Fig. 2

(a)



(b)

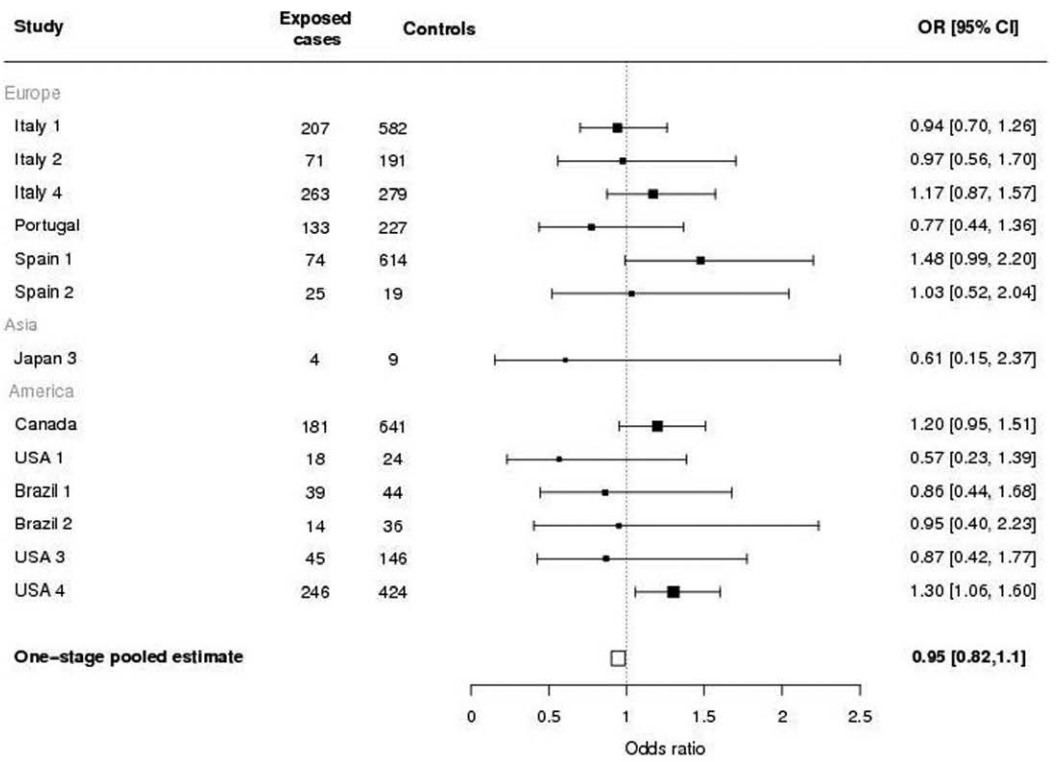


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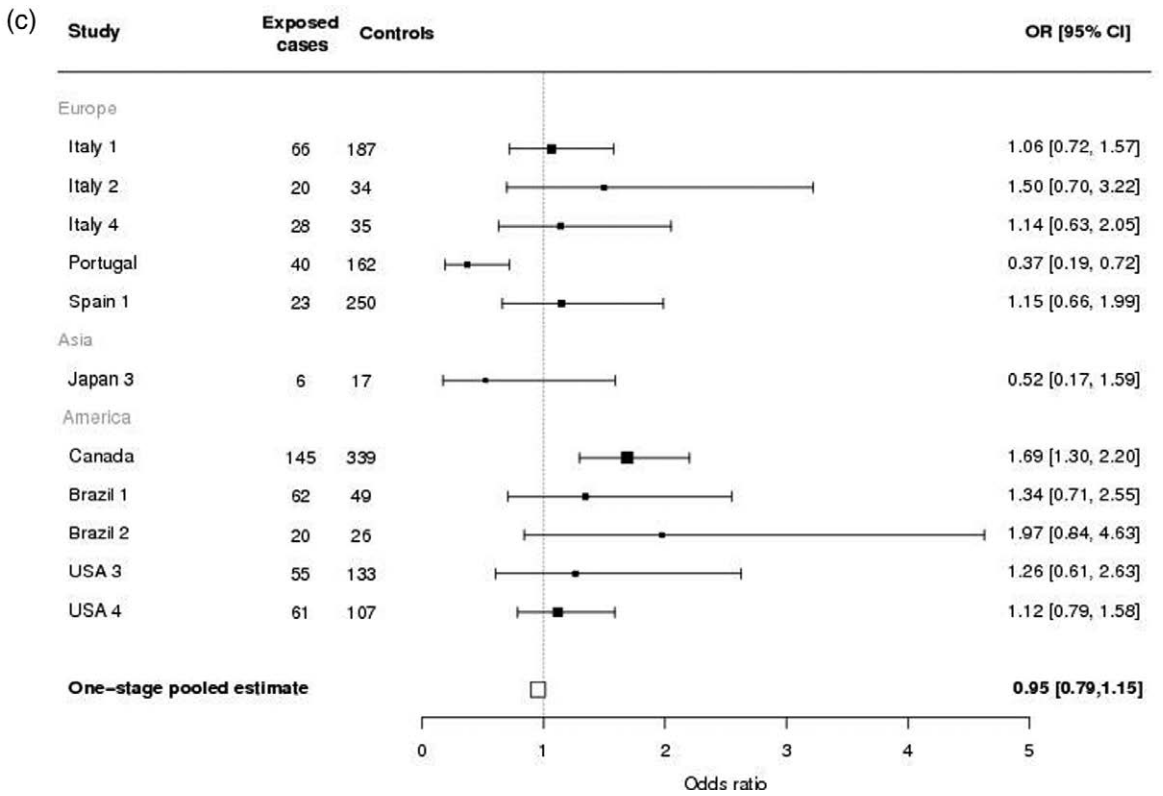
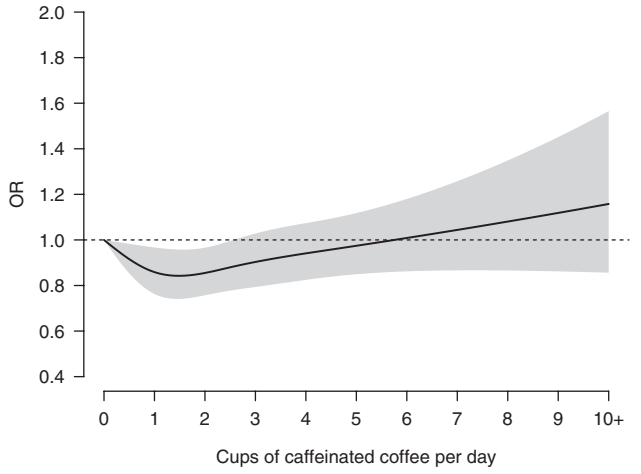
Fig. 2 (*Continued*)



Study-specific and one-stage pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of gastric cancer for total coffee drinkers of 1–2 cups per day (a), 3–4 cups per day (b) and ≥5 cups per day (c) compared with never or rare drinkers in the Stomach cancer Pooling (StoP) Project consortium. Studies with more than five subjects in exposed cases or controls are shown in figures (b) and (c).

Fig. 3



Dose–response relationship between caffeinated coffee consumption and gastric cancer [odds ratios (ORs) and corresponding 95% confidence intervals (CIs)] fitted by natural cubic splines in one-stage linear random-effects model in the Stomach cancer Pooling (StoP) Project consortium.

Discussion

The present analysis, based on 16 case-control studies and two cohort studies from the international StoP Project consortium, including 8198 gastric cancer cases and 21 419 controls, found no material associations between caffeinated, decaffeinated and total coffee consumption and gastric cancer. There was limited evidence of an inverse association for low to moderate consumption, whereas a nonsignificant 20% excess risk was observed for the highest level of consumption. A significant excess risk for high coffee intake emerged for gastric cardia cancer only.

Our findings are in broad agreement with previous reports. A meta-analysis (Poorolajal *et al.*, 2020) reported an OR of 0.99 (95% CI, 0.88–1.11, based on 14 case-control studies) for ever drinkers versus nondrinkers. Results were similar when only cohort studies were considered (Fang *et al.*, 2015; Li *et al.*, 2015; Liu *et al.*, 2015; Zeng *et al.*, 2015). No significant relative risks (RR) for the highest compared with the lowest level of coffee consumption were reported, ranging from 1.13 to 1.18 (Li *et al.*, 2015; Zeng *et al.*, 2015), as

Table 3. One-stage pooled odds ratios (ORs) and 95% confidence intervals (CIs) of gastric cancer according to caffeinated coffee consumption in strata of sex, age, socioeconomic status, geographic area, smoking status, alcohol drinking, fruit and vegetable intake, salt intake, family history of gastric cancer, *Helicobacter pylori* infection, control recruitment, cancer subsite and histotype in the Stomach cancer Pooling (StoP) Project consortium.

		1–2 cups/day			3–4 cups/day			≥5 cups/day		
	Never/rare Ca; Co	Ca; Co	OR[a] (95% CI)	Q (*P*)[b]	Ca; Co	OR[a] (95% CI)	Q (*P*)[b]	Ca; Co	OR[a] (95% CI)	Q (*P*)[b]
Overall	2726; 6753	3315; 8877			1190; 2935			498; 1112		
Sex				1.60 (0.21)			3.5 (0.06)			0.54 (0.46)
Men	1273; 2993	2492; 5567	0.97 (0.83–1.14)		964; 1972	1.04 (0.86–1.26)		406; 890	1.00 (0.79–1.25)	
Women	855; 2469	1235; 4007	0.83 (0.69–1.00)		363; 1272	0.77 (0.60–0.98)		133; 461	0.86 (0.62–1.20)	
Age				0.62 (0.43)			1.29 (0.26)			0.01 (0.91)
<65 years	945; 2856	1479; 4536	0.96 (0.81–1.13)		719; 1930	0.99 (0.81–1.21)		326; 871	0.93 (0.74–1.19)	
≥65 years	1183; 2605	2248; 5032	0.87 (0.73–1.03)		608; 1313	0.83 (0.66–1.04)		213; 478	0.91 (0.67–1.23)	
Socioeconomic status				4.44 (0.04)			0.58 (0.44)			2.59 (0.11)
Low	820; 1724	1844; 3564	0.83 (0.71–0.98)		644; 1166	0.91 (0.74–1.12)		206; 443	0.81 (0.61–1.07)	
Intermediate	875; 2188	1165; 3427	0.92 (0.74–1.13)		443; 1141	0.96 (0.74–1.25)		222; 526	1.05 (0.78–1.43)	
High	376; 1147	636; 2454	1.25 (0.88–1.79)		225; 908	1.08 (0.73–1.61)		107; 366	1.20 (0.75–1.92)	
Geographic area				1.70 (0.19)			0.72 (0.40)			7.00 (<0.01)
Europe	990; 1908	1804; 4302	0.89 (0.77–1.02)		774; 1912	0.97 (0.82–1.15)		181; 675	0.81 (0.64–1.03)	
Asia	91; 168	49; 106	0.72 (0.44–1.18)		4;9	0.66 (0.17–2.59)		6; 17	0.44 (0.15–1.32)	
America	1047; 3386	1874; 5166	1.04 (0.77–1.40)		549; 1323	0.85 (0.60–1.21)		352; 659	1.32 (0.93–1.89)	
Smoking status				1.66 (0.20)			1.81 (0.18)			4.83 (0.03)
Never smokers	1012; 2931	1423; 4029	0.85 (0.73–1.01)		323; 942	0.85 (0.68–1.06)		91; 302	0.73 (0.53–1.02)	
Former smokers	649; 1507	1410; 3513	1.03 (0.80–1.31)		487; 1180	1.09 (0.81–1.45)		201; 465	1.21 (0.86–1.71)	
Current smokers	385; 891	729; 1794	0.92 (0.70–1.21)		457; 1043	0.98 (0.72–1.33)		200; 546	1.05 (0.74–1.48)	
Alcohol drinking				0.83 (0.36)			5.57 (0.02)			2.10 (0.15)
<1 drink/day	1276; 3803	1933; 5755	0.89 (0.76–1.05)		593; 1759	0.87 (0.71–1.06)		296; 745	0.99 (0.77–1.27)	
1–3 drinks/day	453; 890	1222; 2564	0.87 (0.68–1.11)		478; 939	0.85 (0.63–1.15)		126; 307	0.76 (0.51–1.13)	
≥4 drinks/day	336; 497	477; 853	1.02 (0.77–1.35)		222; 392	1.36 (0.97–1.90)		86; 218	1.15 (0.76–1.74)	
Fruit and vegetable intake				1.19 (0.27)			0.17 (0.68)			5.58 (0.02)
Low	624; 1615	1231; 2830	0.82 (0.65–1.04)		460; 955	0.90 (0.68–1.19)		159; 448	0.69 (0.47–0.99)	
Intermediate	667; 1172	1265; 3270	0.90 (0.73–1.11)		433; 1129	0.92 (0.71–1.20)		163; 427	0.94 (0.67–1.31)	
High	833; 2028	1203; 3342	0.97 (0.80–1.18)		430; 1108	0.97 (0.76–1.25)		217; 448	1.22 (0.92–1.63)	
Salt intake[c]				0.46 (0.50)			1.29 (0.26)			1.05 (0.31)
Low	792; 2220	1318; 3420	0.94 (0.79–1.13)		395; 1117	0.86 (0.69–1.08)		202; 530	0.96 (0.73–1.26)	
Intermediate	712; 1752	992; 2996	0.87 (0.71–1.08)		353; 1010	0.93 (0.72–1.21)		136; 382	1.04 (0.75–1.46)	
High	450; 1278	860; 2500	0.86 (0.66–1.12)		316; 831	1.08 (0.78–1.49)		170; 398	0.79 (0.52–1.21)	
Family history of gastric cancer[d]				0.08 (0.78)			0.17 (0.68)			0.76 (0.38)
No	849; 1914	1349; 3746	0.94 (0.83–1.07)		576; 1744	0.95 (0.81–1.12)		259; 726	1.00 (0.82–1.23)	
Yes	191; 196	320; 325	0.89 (0.62–1.27)		151; 158	1.05 (0.67–1.64)		44; 41	1.32 (0.73–2.42)	
Helicobacter pylori infection[e]				0.07 (0.79)			0.69 (0.41)			0.08 (0.77)
No	263; 434	129; 302	0.92 (0.66–1.29)		27; 103	0.69 (0.38–1.24)		28; 61	0.84 (0.46–1.55)	
Yes	469; 980	515; 1546	0.97 (0.80–1.17)		174; 556	0.91 (0.70–1.19)		108; 307	0.76 (0.56–1.03)	
Type of controls				0.68 (0.41)			0.93 (0.33)			1.64 (0.20)
Hospital-based	885; 1341	987; 1957	0.90 (0.78–1.04)		379; 905	0.92 (0.76–1.10)		184; 325	1.14 (0.90–1.44)	
Population-based	1243; 4121	2740; 7617	1.01 (0.80–1.28)		948; 2339	1.08 (0.83–1.42)		355; 1026	0.88 (0.64–1.22)	
Subsite[f]				0.93 (0.34)			4.33 (0.04)			
Cardia	365; 5462	721; 9574	1.09 (0.94–1.26)		260; 3244	1.38 (1.15–1.67)		124; 1351	1.61 (1.27–2.05)	12.6 (<0.001)
Non-cardia	1035; 5462	1859; 9574	1.00 (0.91–1.10)		650; 3244	1.09 (0.96–1.25)		217; 1351	0.93 (0.77–1.12)	
Histotype[g]				0.03 (0.87)			0.34 (0.56)			0.00 (1.00)
Intestinal	474; 5462	832; 9574	0.93 (0.79–1.10)		302; 3244	1.04 (0.84–1.28)		92; 1351	0.83 (0.62–1.12)	
Diffuse	362; 5462	447; 9574	0.91 (0.74–1.12)		157; 3244	0.94 (0.72–1.21)		67; 1351	0.83 (0.59–1.18)	

Ca: cases; Co: control; ORs, odds ratios.

[a]One-stage pooled ORs were estimated using mixed-effect models adjusted, where available and feasible, for sex, age category, social class, smoking status, salt intake, fruit and vegetable intake, alcohol intake and family history of gastric cancer.

[b]*P* values for test of OR heterogeneity across strata.

[c]The study Italy 4 (Buiatti *et al*., 1989) was not included as it did not collect data on salt intake.

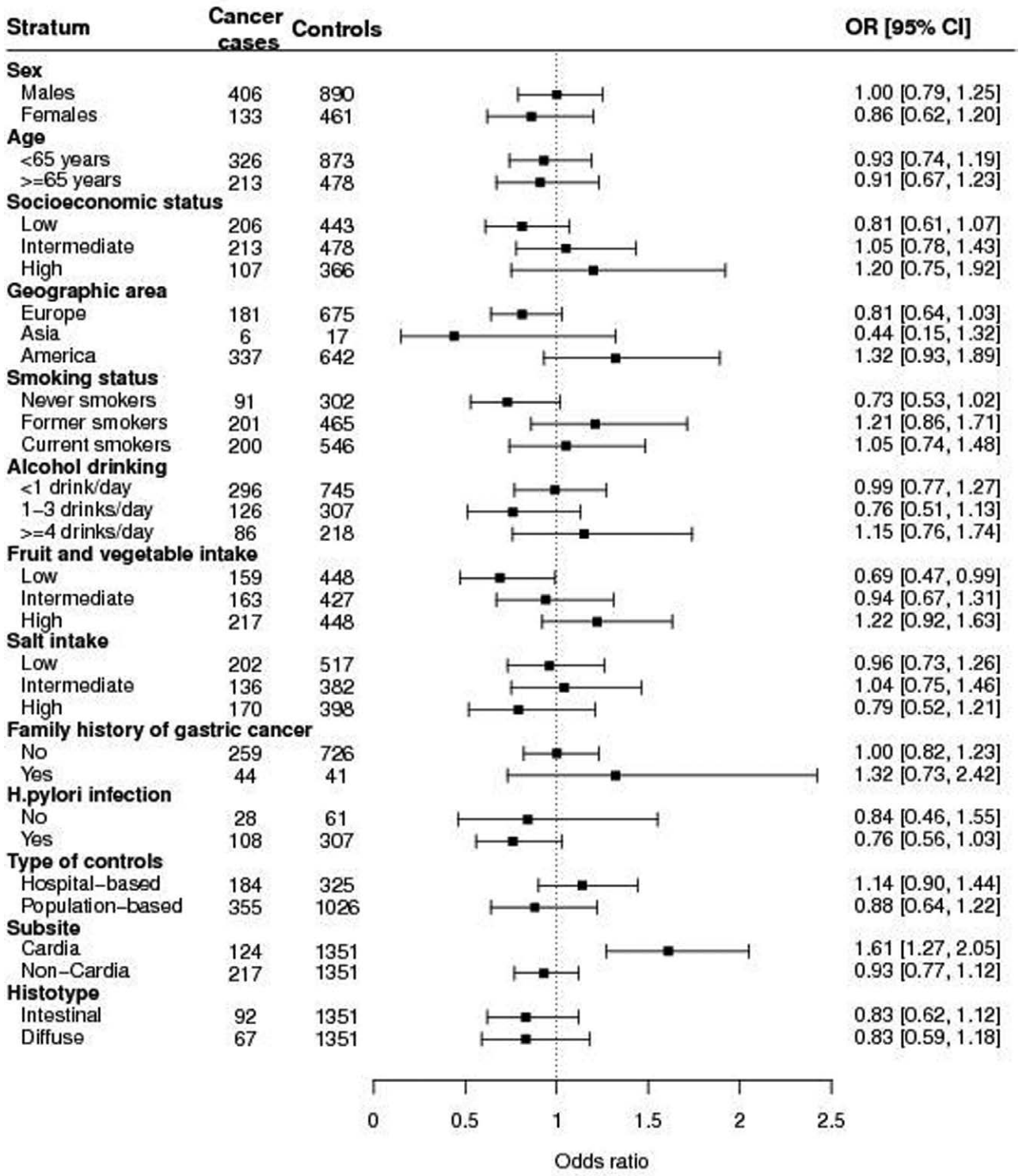
[d]The studies Canada (Mao *et al*., 2002), Mexico 1 (Hernández-Ramírez *et al*., 2009), Mexico 2 (López-Carrillo *et al*., 1994) and USA 4 (Schatzkin *et al*., 2001) were not included as they did not collect data on family history of gastric cancer.

[e]The studies Italy 1 (La Vecchia *et al*., 1995), Italy 2 (Lucenteforte *et al*., 2008), Italy 4 (Buiatti *et al*., 1989), Canada (Mao *et al*., 2002), USA 1 (Zhang *et al*., 1999), Mexico 2 (López-Carrillo *et al*., 1994), USA 3 (Ward *et al*., 2008) and USA 4 (Schatzkin *et al*., 2001) were not included as they did not collect data on *H. pylori* infection. The study Spain 2 (Santibañez *et al*., 2012) was not included because no information on *H. pylori* infection was available for controls.

[f]The studies Mexico 2 (López-Carrillo *et al*., 1994) and USA 3 (Ward *et al*., 2008) were not included as they did not collect data on cancer site.

[g]The studies Italy 1 (La Vecchia *et al*., 1995), Mexico 2 (López-Carrillo *et al*., 1994), Japan 3 (Machida-Montani *et al*., 2004) and USA 3 (Ward *et al*., 2008) were not included as they did not collect data on histological type.

Fig. 4



One-stage pooled odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of gastric cancer for total coffee consumption of ≥5 cups per day compared to never or rare coffee consumption, according to strata of selected variables in the Stomach cancer Pooling (StoP) Project consortium.

well as for regular versus seldom coffee drinkers (RR, 1.05) (Liu *et al.*, 2015). A few meta-analyses, which compared the highest levels of consumption with the lowest ones, found an increased risk, ranging from 1.16 to 1.24, although the highest levels of consumption varied substantially across the studies included (from two to more

than seven cups per day) (Shen *et al.*, 2015; Deng *et al.*, 2016).

Only a few studies have investigated the relationship between coffee drinking and gastric cancer by the anatomic site (cardia or non-cardia gastric cancer). These have suggested a modest excess of cardia risk of 23–50% for high coffee intake (Liu *et al.*, 2015; Deng *et al.*, 2016). Caffeine is a stimulant of gastric acid secretion (Schubert, 2010; Liszt *et al.*, 2017), and coffee intake has been shown to be associated with an increased risk of gastroesophageal reflux symptoms, including heartburn and regurgitation (Mehta *et al.*, 2020), two risk factors for cardia cancer (Derakhshan *et al.*, 2008).

When we explored the effects of coffee consumption on gastric cancer according to geographical region, a nonsignificant excess risk emerged among studies from America [one of which was a prospective study (Schatzkin *et al.*, 2001)], while an inverse association emerged among studies from Europe. This may be related to the amount and type of coffee consumed in America compared to Europe (Li *et al.*, 2015), though chance or residual confounding may account for this apparent association. Coffee consumption varies among the geographic areas according to types of coffee, caffeine content, preparation as well as brewing methods. However, we were unable to consider these differences among the studies included due to lack of information for most. Moreover, the methods used to measure coffee consumption, such as the number of cups of coffee or times coffee was consumed per day as well as the cup size, varied among the studies included.

Individuals with gastric cancer had gastritis or other gastric diseases more frequently, and patients with these conditions are often recommended to avoid or reduce their consumption of coffee. Therefore, subjects at high risk of gastric cancer may have reduced their consumption of coffee before cancer onset, thus inducing reverse causation. This could partially explain the slight inverse association of low/moderate consumption since case-control studies collect data concerning a short period before the diagnosis. In fact, the only cohort study included in the analysis on the amount of coffee consumed (Schatzkin *et al.*, 2001) showed, if any, an increased rather than a decreased risk at low/moderate consumption levels. Nevertheless, the consistency of results between the type of controls (population and hospital) strengthens the reliability of our findings.

The main strength of this study is the uniquely large sample size as well as the availability of information on several covariates, including potential confounders, such as alcohol drinking, smoking, salt intake, fruit and vegetable intake, and family history of gastric cancer. Residual confounding by tobacco smoking is, however, possible since tobacco is related to gastric cancer, and heavy coffee drinkers tend to be smokers more frequently (Praud *et al.*, 2018).

In conclusion, using a unique pool of data of studies from different geographical areas, we provided evidence on the absence of a relevant association between coffee consumption and gastric cancer.

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Conflicts of interest

There are no conflicts of interest.

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