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Alcohol consumption and gastric cancer risk—A pooled analysis within the StoP project consortium

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An association between heavy alcohol drinking and gastric cancer risk has been recently reported, but the issue is still open to discussion and quantification. We investigated the role of alcohol drinking on gastric cancer risk in the "Stomach cancer Pooling (StoP) Project," a consortium of epidemiological studies. A total of 9,669 cases and 25,336 controls from 20 studies from Europe, Asia and North America were included. We estimated summary odds-ratios (ORs) and the corresponding 95% confidence intervals (CIs) by pooling study-specific ORs using random-effects meta-regression models. Compared with abstainers, drinkers of up to 4 drinks/day of alcohol had no increase in gastric cancer risk, while the ORs were 1.26 (95% CI, 1.08–1.48) for heavy (>4 to 6 drinks/day) and 1.48 (95% CI 1.29–1.70) for very heavy (>6 drinks/day) drinkers. The risk for drinkers of >4 drinks/day was higher in never smokers (OR 1.87, 95% CI 1.35–2.58) as compared with current smokers (OR 1.14, 95% CI 0.93–1.40). Somewhat stronger associations emerged with heavy drinking in cardia (OR 1.61, 95% CI 1.11–2.34) than in non-cardia (OR 1.28, 95% CI 1.13–1.45) gastric cancers, and in intestinal-type (OR 1.54, 95% CI 1.20–1.97) than in diffuse-type (OR 1.29, 95% CI 1.05–1.58) cancers. The association was similar in strata of *H. pylori* infected (OR = 1.52, 95% CI 1.16–2.00) and noninfected subjects (OR = 1.69, 95% CI 0.95–3.01). Our collaborative pooled-analysis provides definite, more precise quantitative evidence than previously available of an association between heavy alcohol drinking and gastric cancer risk.

What's new?

How strong is the association between alcohol and gastric cancer risk? These authors pooled data from 20 epidemiological studies worldwide to quantify the connection. People who drank up to four alcoholic drinks a day, they found, had similar risk to those who abstained. Those who took more than four drinks per day saw their risk rise by 20%, while those who imbibed most heavily—6 or more drinks per day—boosted their risk by 50%, or for non-smokers, nearly doubled their risk. Furthermore, they saw the same association with or without *H. pylori* infection.

The World Health Organization's global survey on alcohol and health conducted in 2012[1] reported that around the world almost 40% of people regularly drink alcohol, one of the major avoidable risk factors for cancer.[2] Worldwide, in 2012, 5.5% of all cancer cases were attributed to alcohol drinking,[3] with an increase of ~1.5% in the decade 2002–2012, largely due to the global increase in drinking prevalence and amount of alcohol consumed in several areas of the world.

Despite a steady fall in incidence over the last several decades,[4,5] there are still about one million new diagnoses of gastric cancer per year worldwide, and gastric cancer remains the third leading cause of cancer mortality.[6] Gastric cancer is a multi-factorial disease, involving genetic and environmental factors, and *Helicobacter pylori* (*H. pylori*) infection has been recognized as the major aetiological factor.[7]

In 2009, a working group of the International Agency for Research on Cancer (IARC) concluded that there was inadequate evidence for a role of alcohol in gastric cancer carcinogenesis.[8] Recent data, however, suggested that heavy alcohol drinking is associated with an increased risk of gastric cancer.[9,10] A recent study showed that an increased risk was only observed in the absence of *H. pylori* infection,[11] while in *H. Pylori* infected people moderate alcohol consumption may act as an antimicrobial, favoring suppression and eventual elimination of *H. pylori* infection.[11,12] In April 2016, the World Cancer Research Fund International concluded for a probable increased gastric cancer risk for alcohol intakes of about three drinks or more per day.[13]

Most individual studies are, however, underpowered to accurately investigate the dose-response relationship between alcohol drinking and gastric cancer risk, and the differences in risk according to subsite or histological subtype, or in strata of effect modifiers.

The "Stomach cancer Pooling (StoP) Project,"[14] a recently established consortium of epidemiological studies on risk factors for gastric cancer, represents a unique opportunity to better define and quantify the association between alcohol drinking and gastric cancer risk, using subject-level information.

Material and Methods

All participating studies previously received ethical approval from their local Institutional Review Boards (IRBs). For the collaborative re-analysis, *ad hoc* approval was obtained from the University of Milan IRB.

Studies identification and data standardization

The first release of the StoP Project dataset included 23 case-control studies for a total of 10,290 gastric cancer cases (6,804 men, 3,486 women) and 26,153 controls (15,604 men, 10,549 women).[15] Out of 23 studies, 20 had data on alcohol consumption (Supporting Information Table S1): one from Greece,[16] four from Italy,[17–20] one from Portugal,[21] one from

Table 1. Distribution of 9,669 cases of stomach cancer and 25,336 controls according to study center, sex, age and other selected covariates

	Cases		Controls	
	N	%	*N*	%
Total	9,669		25,336	
Study center (Reference)				
Europe	5,079	52.5	12,664	50.0
Greece (Lagiou *et al*., 2004)[16]	110	1.1	100	0.4
Italy 1 (La Vecchia *et al*., 1995)[19]	769	8.0	2,081	8.2
Italy 2 (Lucenteforte *et al*., 2008)[20]	230	2.4	547	2.2
Italy 3 (De Feo *et al*., 2012)[18]	160	1.7	444	1.8
Italy 4 (Buiatti *et al*., 1989)[17]	1,016	10.5	1,159	4.6
Portugal (Lunet *et al*., 2007)[21]	692	7.2	1,667	6.6
Russia (Zaridze *et al*., 2000)[22]	450	4.7	611	2.4
Spain 1 (Castano-Vinyals *et al*., 2015)[23]	441	4.6	3,440	13.6
Spain 2 (Santibanez *et al*., 2012)[24]	401	4.1	455	1.8
Sweden 1 (Harris *et al*., 2013)[25]	88	0.9	352	1.4
Sweden 2 (Harris *et al*., 2013)[25]	161	1.7	644	2.5
Sweden 3 (Ye *et al*., 1999)[26]	561	5.8	1,164	4.6
Asia	2,576	26.6	5,419	21.4
China 1 (Deandrea *et al*., 2010)[27]	266	2.8	533	2.1
China 2 (Mu *et al*., 2005)[28]	206	2.1	415	1.6
China 3 (Setiawan *et al*., 2005)[29]	711	7.4	711	2.8
China 4 (Setiawan *et al*., 2000)[30]	133	1.4	433	1.7
Japan (Matsuo *et al*., 2013)[31]	1,260	13.0	3,327	13.1
North America	2,014	20.8	7,253	28.6
Canada (Mao *et al*., 2002)[32]	1,182	12.2	5,039	19.9
USA (Zhang *et al*., 1999)[33]	132	1.4	132	0.5
USA (unpublished data, J. Muscat)	700	7.2	2,082	8.2
Sex				
Male	6,357	65.7	15,036	59.3
Female	3,312	34.3	10,300	40.7
Age				
<40	341	3.5	1,901	7.5
40–45	350	3.6	1,521	6.0
45–50	594	6.1	1,976	7.8
50–54	954	9.9	2,624	10.4
55–59	1,271	13.1	3,044	12.0
60–64	1,519	15.7	3,914	15.4
65–69	1,747	18.1	4,125	16.3
70–75	1,740	18.0	3,701	14.6
≥75	1,153	11.9	2,522	10.0
Missing	0	0.0	8	0.0
Social class				
Low	5,135	53.1	10,270	40.5
Intermediate	2,516	26.0	7,606	30.0
High	1,201	12.4	5,335	21.1
Missing	817	8.4	2,125	8.4

Table 1. Distribution of 9,669 cases of stomach cancer and 25,336 controls according to study center, sex, age and other selected covariates (Continued)

	Cases		Controls	
	N	%	*N*	%
History of stomach cancer in first degree relatives[1]				
No	4,694	48.5	12,439	49.1
Yes	827	8.6	1,244	4.9
Missing	4,148	42.9	11,653	45.9
Vegetables and fruit intake[2]				
Low	2,875	29.7	6,721	26.5
Intermediate	2,929	30.3	7,419	29.3
High	2,826	29.2	7,854	31.0
Missing	1,039	10.7	3,342	13.2
Tobacco smoking				
Never	3,869	40.0	11,151	44.0
Former	2,733	28.3	7,405	29.2
Current (cigarettes equivalent/day)	2,708	28.5	6,265	24.9
≤10	623	6.4	1,758	6.9
10–20	1,206	12.5	2,600	10.3
>20	924	9.6	1,959	7.7
Missing	314	3.2	463	1.8

[1]No information available for studies China 1 (Deandrea *et al.*, 2010),[27] Canada (Mao *et al.*, 2002),[32] China 3 (Setiawan *et al.*, 2005),[29] USA (unpublished data, J. Muscat), Sweden 1 (Harris *et al.* 2013)[25] and Sweden 2 (Harris *et al.*, 2013).[25]
[2]No information available for studies USA (unpublished data, J. Muscat) and China 4 (Setiawan *et al.*, 2000).[30]
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Russia,[22] two from Spain,[23,24] three from Sweden (two of which were nested in cohort studies),[25,26] four from China,[27–30] one from Japan,[31] one from Canada[32] and two from the USA (one of which with unpublished data, J. Muscat),[33] including a total of 9,669 cases and 25,336 controls. For two cohort studies included in the StoP Project consortium, the Swedish Mammography Cohort and the Cohort of Swedish Men,[25] a nested case-control design was used by selecting four controls for each case, matched on age.

All data were collected and harmonized according to a prespecified format at the pooling center. Questionnaires on alcohol were comparable across studies. Subjects were asked about their lifetime alcohol drinking habits (drinkers or not), and, if not abstainers, about current status (ex or current drinker), frequency and [in eight studies[19–22,24,27,30] and USA 2 (unpublished data, J. Muscat)] duration of drinking, amount of alcohol consumed overall and according to specific beverages, *i.e.*, beer, wine and hard liquor, and (in six studies[18,21,22,24,27,31]) time since quitting alcohol drinking. When information on red and white wine consumption was collected separately,[17,23] we considered the combined intake, while nonalcoholic beer was not considered. The Russian study[22] collected information on vodka drinking, that was considered a hard liquor. Two studies[29,30] provided information on lifetime alcohol drinking status (*i.e.*, never/ever) only. Each variable was checked for illogical or missing values, and any inconsistency was resolved by contacting study investigators.

The average lifetime daily number of ethanol-standardized drinks (*i.e.*, 1 drink = 12 grams of pure ethanol) was computed applying estimates of the beverage-specific volume percentage of pure ethanol (5% for beer, 12% for wine, 40% for liquor), and categorized across studies as ≤1, >1 to 4, >4 to 6, >6 to 8 and >8 drinks/day, in order to investigate the effect of high levels of alcohol drinking on gastric cancer risk, while minimizing the occurrence of sparse data within the upper category. The amount of pure ethanol per day was also analyzed as a continuous variable using flexible regression modeling to overcome problems related to variable categorization. Moreover, for specific beverages, we identified mutually exclusive subgroups of beer, wine or hard liquor only drinkers, with never drinkers as a common reference group. Categories were defined to avoid sparse data. For wine, numbers allowed to define three levels of drinking (≤1, >1 to 3 and >3 drinks/day), since European populations consumed larger quantities of wine than American and Asian ones.

Duration of drinking was categorized as never drinkers, ≤20, >20 to 40 and >40 years, while time since quitting drinking alcohol as ≤5, >5 to 10 and >10 years, using current drinkers as reference category.

Table 2. Pooled ORs and 95% CIs for gastric cancer according to average lifetime alcohol drinking

	Cases		Controls			
	N	%	*N*	%	OR (CI 95%)[1]	I^2 (*p* for heterogeneity)
Alcohol drinking status	9,669		25,336			
Never alcohol drinker	2,613	27.0	6,862	27.1	1	–
Ever alcohol drinker	6,759	69.9	17,266	68.1	1.10 (0.99–1.21)	47.5% (0.01)
Missing	297	3.1	1,208	4.8		
Alcohol drinking intensity[2]	8,825		24,192			
Never alcohol drinker	2,096	23.8	6,117	25.3	1	–
≤ 1 drink/day	2,239	25.4	7,816	32.3	1.00 (0.86–1.16)	62.1% (<0.01)
>1 to 4 drinks day	2,632	29.8	5,812	24.0	1.11 (1.01–1.23)	17.5% (0.25)
>4 to 6 drinks/day	521	5.9	1,075	4.4	1.26 (1.08–1.48)	11.9% (0.32)
>6 drinks/day	650	7.3	1,023	4.2	1.48 (1.29–1.70)	0% (0.63)
>6 to 8 drinks/day	275	3.1	455	1.9	1.46 (1.18–1.80)	17.1% (0.28)
>8 drinks/day	375	4.2	568	2.3	1.50 (1.26–1.78)	0% (0.99)
Missing	687	7.8	2,349	9.7		
p Value for trend					<0.01	
Never drinkers + Wine only drinkers[3]	3,135		8,369			
Never alcohol drinker	1,619	51.6	4,866	58.1	1	–
>0 to 1	882	28.1	2,147	25.7	1.03 (0.80–1.31)	65.6% (<0.01)
>1 to 3	410	13.1	895	10.7	1.22 (1.02–1.45)	0% (0.82)
>3	216	6.9	437	5.2	1.44 (0.98–2.11)	25.4% (0.23)
Missing	8	0.3	24	0.3		
p Value for trend					0.18	
Never drinkers + beer only drinkers[3]	1,920		5,854			
Never alcohol drinker	1,619	84.2	4,866	83.1	1	–
>0 to 1	215	11.0	728	12.4	1.33 (0.97–1.83)	41.4% (0.04)
>1	65	3.6	188	3.2	1.27 (0.89–1.82)	0% (0.60)
Missing	21	1.2	72	1.2		
p Value for trend					0.21	
Never drinkers+spirits only[3]	2,094		5,828			
Never alcohol drinker	1,619	77.3	4,866	83.5	1	–
>0 to 1	253	12.1	686	11.8	0.94 (0.70–1.27)	35.9% (0.09)
>1	208	9.9	249	4.3	1.66 (1.23–2.22)	4.4% (0.39)
Missing	14	0.7	27	0.5		
p Value for trend					0.06	
Alcohol drinking duration (years)[4]	3,641		8,409			
Never drinker	894	24.6	2,427	28.9	1	–
>0 to 20	276	7.6	952	11.3	1.02 (0.84–1.23)	1.4% (0.42)
>20 to 40	1,044	28.7	2,097	24.9	1.28 (1.08–1.51)	24.3% (0.24)
>40	802	22.0	1,202	14.3	1.13 (0.97–1.33)	0% (0.94)
Missing	625	17.2	1,731	20.6		
p Value for trend					<0.01	
Years since quitting alcohol drinking[5]	2,307		4,745			
Current drinker	1,887	81.8	4,119	86.8	1	–
>0 to 5	269	11.7	267	5.6	1.93 (1.39–2.68)	52.4% (0.06)

Table 2. Pooled ORs and 95% CIs for gastric cancer according to average lifetime alcohol drinking (Continued)

	Cases		Controls			
	N	%	*N*	%	OR (CI 95%)[1]	I^2 (*p* for heterogeneity)
>5 to 10	41	1.8	86	1.8	1.00 (0.66–1.53)	0% (0.64)
>10	49	2.1	87	1.8	0.84 (0.56–1.25)	0% (0.58)
Missing	61	2.6	186	3.9		
p Value for trend					0.43	

[1]Pooled ORs were computed using random-effects models. Study-specific ORs were adjusted, when available, for sex, age, race/ethnicity, social class, tobacco smoking, fruit and vegetable consumption and study center for multicentric studies.
[2]Information was not available for studies China 3 (Setiawan *et al.*, 2005)[29] and China 4 (Setiawan *et al.*, 2000).[30]
[3]Information was not available for studies China 3 (Setiawan *et al.*, 2005)[29] and Japan (Matsuo *et al.*, 2013).[31]
[4]Considered studies: Italy 1 (La Vecchia *et al.*, 1995),[19] Italy 2 (Lucenteforte *et al.*, 2008),[20] Portugal (Lunet *et al.*, 2007),[21] Russia (Zaridze *et al.*, 2000),[22] Spain 2 (Santibanez *et al.*, 2012),[24] China 1 (Deandrea *et al.*, 2010),[27] China 4 (Setiawan *et al.*, 2000)[30] and USA (unpublished data, J. Muscat).
[5]Considered studies: Italy 3 (De Feo *et al.*, 2012),[18] Portugal (Lunet *et al.*, 2007),[21] Russia (Zaridze *et al.*, 2000),[22] Spain 2 (Santibanez *et al.*, 2012),[24] China 1 (Deandrea *et al.*, 2010)[27] and Japan (Matsuo *et al.*, 2013).[31]
StoP Project consortium

We also collected information on a list of additional variables to be introduced as confounders and to define stratified analyses, including *H. pylori* infection data, whenever available (Supporting Information Table S1).

Statistical analysis

We used a two-stage modeling approach.[34] At the first stage, we assessed the association between alcohol drinking and gastric cancer by estimating for each study the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) using multivariable unconditional logistic regression models. We fitted polytomous unconditional logistic regression model when analyzing the association by cancer subsite and histological type. These models included, when available (*i.e.*, <30% of missing values ahead of multiple imputation) and appropriate (see Supporting Information Table S1), terms for age (<40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74 and ≥75 years), sex, education/social class (study-specific low, intermediate, high), race/ethnicity (White, Hispanic/Latino, Black/African American, other), tobacco smoking (never, former, current ≤10 cigarettes/day, >10 to 20 cigarettes/day and >20 cigarettes/day), fruit and vegetable consumption (study-specific tertiles) and study center (for multicentric studies). To account for sporadically missing values in study-specific confounders, we applied multiple imputation using full chained equations.[35] Briefly, assuming that data were missing at random, five imputed datasets were generated for each study, and missing entries filled in with a set of plausible values drawn from the posterior predictive distribution of the missing data conditional on the observed data. The imputation models were congenial with the analysis models and included the same set of covariates plus the disease status. A logistic (polytomous for cancer subsite and histological type), regression model was then fitted in each of the five imputed dataset, and the resulting sets of model estimates were combined through the Rubin's rule to obtain study specific regression coefficients and their standard errors. In the second stage, summary (pooled) effects estimates were computed using a random-effect model.[36]

Heterogeneity between studies was evaluated using the Q test statistics and quantified using I^2, *i.e.*, the proportion of total variation contributed by between-study variance.[37]

The decision to adopt a two-stage analytical approach in the consortium was taken *a priori*.[14] As a sensitivity analysis, we carried out a one-stage analysis through a multivariable unconditional logistic regression model, adjusted for study and the aforementioned covariates.

We carried out several stratified analyses to investigate the effect of alcohol drinking across strata of selected covariates: age (≤ 55, >55 to 65, >65), sex, cigarette smoking (never, former, current), socioeconomic status (low, intermediate, high), geographic area (Europe, Asia, America), cancer subsite (cardia, non cardia), histological type (intestinal, diffuse and undifferentiated), *H. pylori* infection status (positive and negative) and type of controls (hospital-based, population-based; controls from 2 nested case-control studies were considered together with the latter). For *H. pylori* infection, we also carried out a restricted analysis by comparing *H. pylori* positive controls with all cases, under the assumption that *H. pylori* infection is a necessary cause for gastric cancer.[14] In all the strata, alcohol drinking was categorized as never drinkers, ≤1, >1 to 4 and >4 drinks/day, to avoid sparse data in the highest category, being never drinkers the reference category. A *p* values for heterogeneity within levels of each potential effect modifier was computed, and the interaction was tested through a meta-regression model considering the variable as ordinal.

We tested for the significance of linear trends across levels of alcohol drinking by estimating study-specific trends (*i.e.*, considering the variable as ordinal in the logistic model), and using the Wald test *p* values deriving from the summary random-effects estimate.[34]

Further, we modeled the functional form of the relation between grams of alcohol per day (continuously) and gastric cancer risk using one-order and two-order fractional polynomial models. The method was based on a two-stage procedure. In a first step, we fitted first-order and second-order

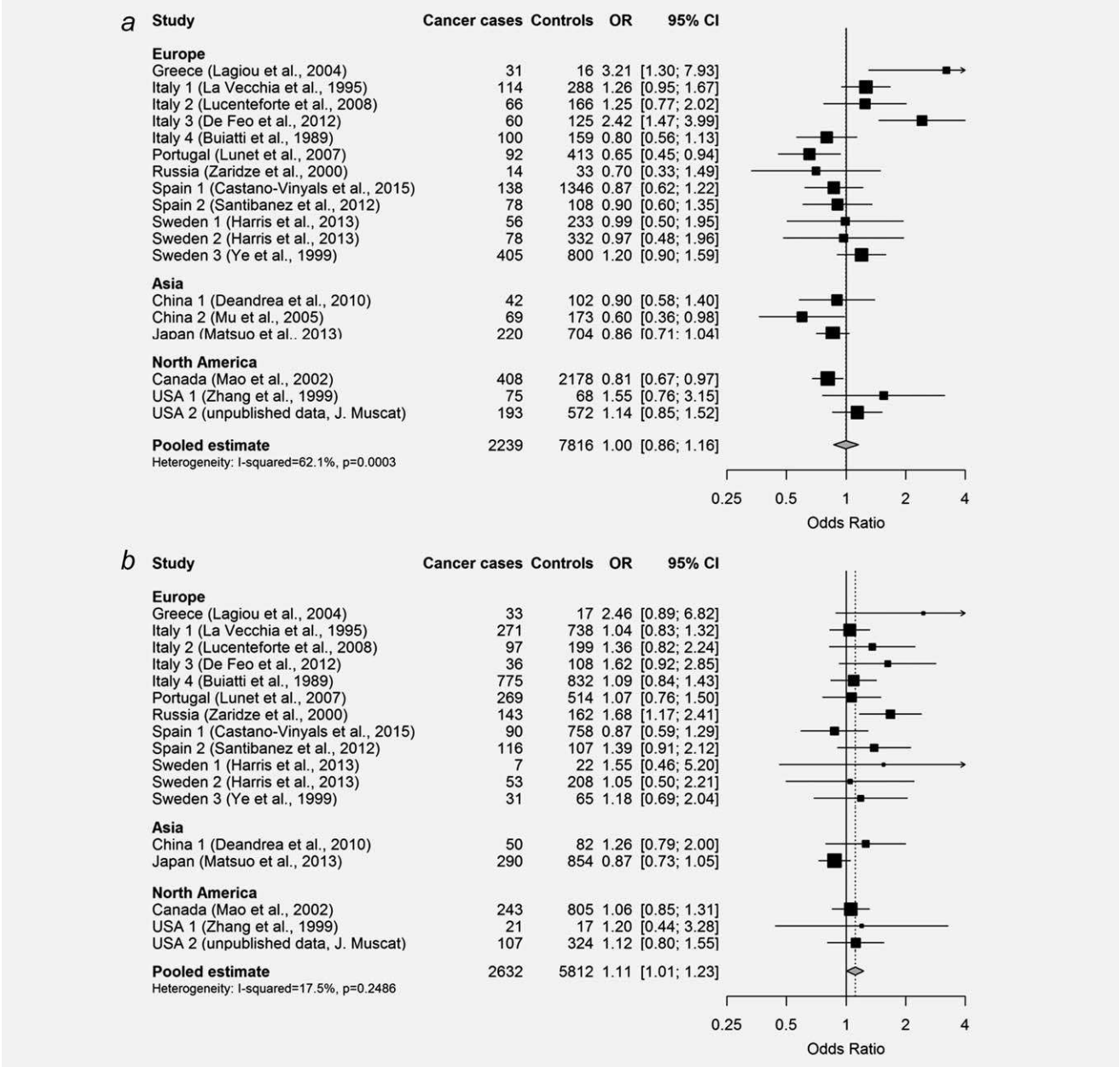

Figure 1. Study-specific and pooled ORs and corresponding 95% CIs of gastric cancer risk for light (≤1 drink/day) (*a*), moderate (>1 to 4 drinks) (*b*), heavy (>4 to 6 drinks) (*c*) and very heavy (>6 drinks/day) (*d*) average lifetime alcohol drinking compared with never drinkers.

fractional polynomial models to each study adjusting for the aforementioned confounders. This family of models includes the linear one. In the second step, the pooled dose-risk relation was estimated through a bivariate random effects model.[38] The best fitting model, *i.e.*, the one minimizing the model deviance, was selected when the best fitting model was non linear.[39]

The first step of the analysis was carried out through *ad-hoc* developed macros in SAS 9.4 using PROC MI and PROC MIANALIZE procedures for the multiple imputation task. The "meta" package[40] of R version 3.1.2 was used to perform the (second stage) random-effects meta-regression model.

Results

The main characteristics of the 9,669 gastric cancer cases and 25,336 controls included in the present analysis are reported in Table 1. Approximately half of the cases and controls were from European studies. About two-thirds of gastric cancer cases (65.7%) were men, and cases were somewhat older (median age 64 years) than controls (median age 62), and more frequently of lower social classes (53.1 *vs.* 40.5%). They also had more frequently than controls a history of stomach cancer in first degree relatives (8.6 *vs.* 4.9%), and were more frequently current smokers (28.5 *vs.* 24.9%).

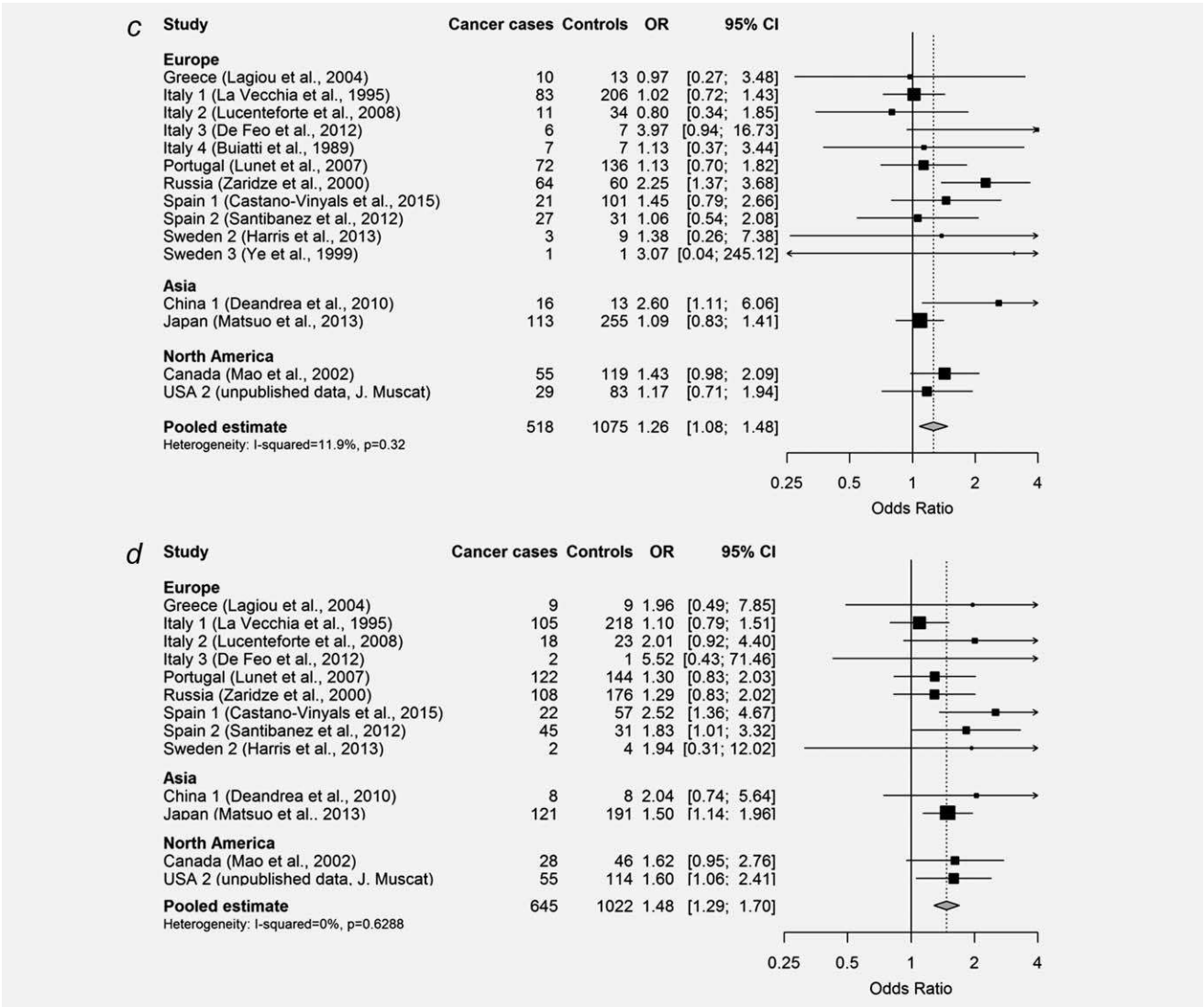

Figure 1. (Continued)

The pooled ORs of gastric cancer according to alcohol drinking are given in Table 2. Approximately 70% of cases and 68% of controls, reported ever consuming alcohol, with a pooled OR of 1.10 (95% CI, 0.99–1.21) as compared to never drinkers. When analyzing drinking intensity (Fig. 1), we found a significant association between heavy drinking and gastric cancer risk, the ORs for >4 up to 6 drinks/day being 1.26 (95% CI, 1.08–1.48), and 1.48 (95% CI, 1.29–1.70) for consumption of >6 drinks/day as compared with never drinkers, with a significant trend in risk ($p < 0.01$). When data were analyzed through an aggregated dataset with a one-stage approach, results were materially unchanged, the ORs being 1.29 (95% CI, 1.14–1.47) for >4 up to 6 drinks/day and 1.48 (95% CI, 1.31–1.68) for >6 drinks/day.

The distribution of beverage consumption differed substantially. Among drinkers of only one type of beverage, wine was the most common reported beverage (66.1 and 64.2% among cases and controls, respectively), followed by spirits (20.7 and 17.6% among cases and controls, respectively) and beer (13.1 and 18.1% among cases and controls, respectively).

A significant excess risk was found for spirits-only drinkers of >1 drink/day (pooled OR 1.66, 95% CI 1.23–2.22), while the pooled OR was 1.44 (95% CI 0.98–2.11) for wine-only drinkers of >3 drinks/day and 1.27 (95% CI 0.89–1.82) for beer-only drinkers of >1 drink/day, in the absence, however, of a significant trend (Table 2).

Data on duration of alcohol drinking were available in a total of 8 studies. A significant increased risk (pooled OR 1.28, 95% CI 1.08–1.51) of gastric cancer was observed for subjects drinking alcohol from >20 to 40 years, while the pooled ORs for the highest duration of consumption (>40 years) was 1.13 (95% CI, 0.97–1.33). We found a significant excess risk for subjects quitting drinking for <5 years (pooled OR 1.93, 95% CI 1.39–2.68), taking current drinkers as a reference, then the risk decreased towards unity.

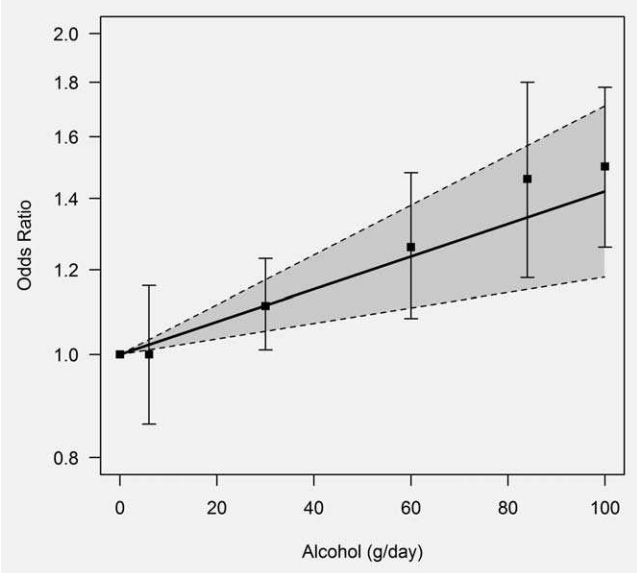

Figure 2. Best fitting fractional polynomial model (continuous line) with its 95% CIs (dashed lines) describing the dose rate-risk relationship between average lifetime alcohol drinking and gastric cancer risk. ORs (represented by squares) and their 95% CIs (represented by vertical bars) estimates deriving from the categorical analysis are also reported.

The best fitting dose rate-risk relationship between average lifetime alcohol drinking and gastric cancer risk was $\ln(OR) = -2.65E\text{-}6 \cdot dose^{-2} + 0.003518 \cdot dose$ (Fig. 2). The random-effects pooled model-based estimates of the OR were 1.02 (95% CI, 1.01–1.03), 1.11 (95% CI, 1.05–1.17), 1.24 (95% CI, 1.11–1.38), 1.34 (95% CI, 1.15–1.57) and 1.42 (95% CI, 1.15–1.57) for consumption of 6 (*i.e.*, ≤1 drink/day), 30 (*i.e.*, >1 to 4 drinks/day), 60 (*i.e.*, >4 to 6 drinks/day), 84 (*i.e.*, >6 to 8 drinks/day) and 100 (*i.e.*, >8 drinks/day) grams of alcohol per day, respectively.

Stratified analyses according to drinking intensity are reported in Table 3. No significant differences in risk estimates were observed by sex, age and geographic area, while never smokers drinking >4 drinks/day had almost a two-fold excess risk of gastric cancer (OR 1.87, 95% CI 1.35–2.58). Although pooled estimates did not significantly differ across levels of socioeconomic status, an increased risk for heavy drinkers (OR 1.47, 95% CI 1.21–1.79) was evident for subjects with low socioeconomic status. When considering heavy drinkers, risks were somewhat higher for cardia (OR 1.61, 95% CI 1.11–2.34) than non-cardia (OR 1.28, 95% CI 1.13–1.45) gastric cancers and in intestinal-type (OR 1.54, 95% CI 1.20–1.97) than in diffuse-type (OR 1.29, 95% CI 1.05–1.58) gastric cancers. Similar pooled estimates were observed in *H. pylori* infected (heavy drinkers, OR = 1.52, 95% CI 1.16–2.00) and non-infected (heavy drinkers, OR = 1.69, 95% CI 0.95–3.01) subjects, while the pooled OR for heavy drinkers was 1.42 (95% CI 1.11–1.83) when the analysis was restricted to *H. pylori* positive controls (all cases supposed to be infected). In addition, in the restricted group of non-cardia gastric cancer cases, *H. pylori* infected heavy drinkers (OR = 1.39, 95% CI 1.10–1.76) and non-infected heavy drinkers, (OR = 1.39, 95% CI 0.88–2.20) subjects had similar gastric cancer risks. No differences in risk estimates were found between studies with controls enrolled in hospital (heavy drinkers, OR = 1.33, 95% CI 1.12–1.59) and those in the general population (heavy drinkers, OR = 1.47, 95% CI 1.18–1.82).

Similar results emerged in stratified analyses when considering wine only drinkers (Supporting Information Table S2).

Discussion

This uniquely large collaborative pooled analysis in the StoP Project consortium found an association between heavy alcohol drinking (defined as consumption of >4 drinks/day, approximately 50 g/day of ethanol) and the risk of gastric cancer. A significant excess risk of ∼50% emerged for drinkers of >6 drinks/day. Adjustment for socioeconomic status and fruit and vegetables consumption allows for possible confounding by poor nutrition, an established gastric cancer risk factor associated with heavy alcohol drinking.[41] Notably, when stratifying by socioeconomic status, no significant differences in pooled estimates emerged. When considering drinkers of each specific type of beverages only, we found a significantly increased risk for spirits-only drinkers, even though in our data the most commonly consumed beverage was wine. No consistent relation was observed for duration of alcohol drinking, and the risk of quitters was not reduced as compared with current drinkers. This is not surprising, since for alcohol drinking the effect of duration is less clear than that of dose also on strongly alcohol-related cancers, such as head and neck neoplasms.[42]

Our results are in the wave of an accumulating evidence of an association between heavy alcohol drinking and gastric cancer risk.[9–11,43] A meta-analysis by Tramacere *et al.*[10] – based on 15 cohort and 44 case-control studies – found a 20% increased risk of gastric cancer (RR 1.20, 95% CI 1.01–1.44) for 4 or more alcoholic drinks per day, consistent with our results, but was unable to investigate the role of higher alcohol doses, nor the effects of specific beverages. The European Prospective Investigation into Cancer and Nutrition (EPIC) study[9] found a significant hazard ratio (HR) of 1.65 (95% CI 1.06–2.58) for ethanol intake measured at baseline, and a HR of 1.50 (95% CI 0.90–2.51) for average lifetime drinking of >60 g/day, in line with our findings. A recent report from the Korean Multi-center Cancer Cohort[11] found a HR of 1.36 (95% CI 0.95–1.96) for a consumption of >55 g per occasion, and interestingly, using a case-cohort design, a HR of 3.27 (95% CI 1.01–10.56) in *H. pylori* non-infected heavy drinkers, although based on a few cases only. Our findings, however, do not support a different effect of heavy alcohol drinking in subjects infected and noninfected by *H. pylori*.

Results from stratified analyses did not show a substantial difference between geographic regions in the magnitude of risk for the highest consumption level. The 60% not significant excess risk observed in Asian studies suggests a gene-environment interaction between ALDH2 and alcohol

Table 3. Pooled ORs and 95% CIs for gastric cancer according to alcohol drinking in strata of sex, age, cigarette smoking, socioeconomic status, geographic area, cancer site, cancer histotype, *H. Pylori* infection and controls recruitment

	Never	Light drinkers (≤1 drink/day)		Moderate drinkers (>1 to 4 drinks/day)		Heavy drinkers (>4 drinks/day)			
	Ca:Co	Ca:Co	OR (95% CI)	Ca:Co	OR (95% CI)	Ca:Co	OR[1] (95% CI)	p^2	p^3
Overall	2,096:6,117	2,239:7,816	1.00 (0.86–1.16)	2,632:5,812	1.11 (1.01–1.23)	1,171:2,098	1.36 (1.22–1.52)	<0.01	
Sex									
Men	846:2,376	1,416:4,346	1.02 (0.85–1.22)	1,995:4,383	1.10 (0.98–1.24)	1,113:1,967	1.44 (1.24–1.68)	0.53	0.17
Women	1,250:3,741	823:3,470	0.99 (0.83–1.18)	637:1,429	1.11 (0.92–1.33)	58:131	1.41 (0.97–2.06)	0.50	
Age									
≤55	576:2,116	538:2,708	0.89 (0.66–1.19)	624:1,810	1.13 (0.85–1.51)	353:827	1.73 (1.14–2.63)	0.17	0.44
>55 to 65	590:1,687	625:2,047	0.98 (0.79–1.20)	840:1,827	1.07 (0.91–1.25)	411:732	1.22 (1.00–1.49)	0.65	
>65	930:2,311	1,076:3,060	1.09 (0.89–1.34)	1,168:2,175	1.16 (1.02–1.33)	407:539	1.49 (1.23–1.82)	0.91	
Cigarette smoking									
Never	1,280:3,863	837:3,381	1.03 (0.82–1.28)	832:1,909	1.14 (0.97–1.33)	239:393	1.87 (1.35–2.58)	0.08	0.25
Former	375:1,165	738:2,574	1.10 (0.86–1.40)	890:2,104	1.41 (1.09–1.83)	384:752	1.64 (1.10–2.44)	<0.01	
Current	399:1,028	567:1,713	0.91 (0.76–1.10)	821:1,708	0.93 (0.78–1.12)	524:933	1.14 (0.93–1.40)	0.95	
Socioeconomic status[4]									
Low	940:2,232	1,143:3,040	0.99 (0.83–1.19)	1,449:2,216	1.11 (0.97–1.27)	511:678	1.47 (1.21–1.79)	0.96	0.67
Intermediate	442:1,441	471:2,114	0.90 (0.75–1.08)	597:1,515	1.10 (0.87–1.39)	311:639	1.25 (0.80–1.96)	0.01	
High	180:962	325:1,796	0.85 (0.57–1.26)	236:1,093	1.11 (0.83–1.47)	101:318	1.31 (0.90–1.90)	0.01	
Geographic area									
Europe	958:2,666	1,232:4,019	1.07 (0.87–1.33)	1,921:3,730	1.19 (1.05–1.35)	741:1,269	1.34 (1.14–1.58)	0.59	0.54
Asia	736:1,786	331:979	0.83 (0.70–0.98)	340:936	0.98 (0.71–1.36)	258:467	1.59 (0.87–2.90)	0.03	
North America	402:1,665	676:2,818	1.07 (0.87–1.33)	371:1,146	1.08 (0.90–1.29)	172:362	1.46 (1.14–1.85)	0.70	
Site[5]									
Cardia	172:5,582	355:7,541	0.97 (0.65–1.44)	312:5,730	1.00 (0.81–1.24)	179:2,077	1.61 (1.11–2.34)	0.05	0.19
Non cardia	1,606:5,582	1,634:7,541	0.98 (0.84–1.15)	2,195:5,730	1.16 (0.94–1.44)	936:2,077	1.28 (1.13–1.45)	0.61	
Histotype[6]									
Intestinal	397:4,792	477:6,672	0.99 (0.72–1.37)	758:4,745	1.13 (0.95–1.35)	249:1,617	1.54 (1.20–1.97)	0.89	0.35
Diffuse	531:4,792	465:6,672	1.01 (0.85–1.21)	557:4,745	1.03 (0.88–1.20)	282:1,617	1.29 (1.05–1.58)	0.94	
Undifferentiated	536:4,792	596:6,672	0.78 (0.67–0.89)	695:4,745	1.14 (0.88–1.47)	306:1,617	1.50 (1.23–1.83)	0.59	
***H. pylori* infection[7]**									
H. pylori positive	374:870	413:1,340	0.77 (0.63–0.96)	444:1,092	1.14 (0.92–1.41)	321:478	1.52 (1.16–2.00)	0.45	0.24
H. pylori negative	185:516	152:491	0.86 (0.60–1.23)	123:318	0.97 (0.46–2.07)	114:189	1.69 (0.95–3.01)	0.11	

Table 3. Pooled ORs and 95% CIs for gastric cancer according to alcohol drinking in strata of sex, age, cigarette smoking, socioeconomic status, geographic area, cancer site, cancer histotype, *H. Pylori* infection and controls recruitment (Continued)

	Never	Light drinkers (≤1 drink/day)		Moderate drinkers (>1 to 4 drinks/day)		Heavy drinkers (>4 drinks/day)			
	Ca:Co	Ca:Co	OR (95% CI)	Ca:Co	OR (95% CI)	Ca:Co	OR[1] (95% CI)	p^2	p^3
Only *H. pylori* positive controls[8]	942:870	938:1,340	0.75 (0.60–0.94)	823:1,092	0.94 (0.79–1.12)	644:478	1.42 (1.11–1.83)	0.16	
***H. pylori* infection in noncardia gastric cancer cases[9]**									
H. pylori positive	320:813	338:1,289	0.81 (0.69–0.95)	395:1,092	1.01 (0.84–1.23)	280:478	1.39 (1.10–1.76)	0.61	0.89
H. pylori negative	94:389	89:391	0.89 (0.64–1.25)	105:318	1.11 (0.68–1.82)	89:189	1.39 (0.88–2.20)	0.59	
Only *H. pylori* positive controls[8]	771:813	754:1,289	0.79 (0.60–1.05)	736:1,092	0.96 (0.79–1.16)	554:478	1.43 (1.09–1.87)	0.45	
Controls[10]									
Hospital based	1,193:3,148	879:2,149	1.22 (0.97–1.54)	1,021:2,446	1.14 (0.97–1.34)	663:1,237	1.33 (1.12–1.59)	0.24	0.73
Population based	802:2,803	1,346:5,634	0.84 (0.72–0.98)	1,468:3,204	1.05 (0.92–1.20)	336:625	1.47 (1.18–1.82)	0.50	

[1]Pooled ORs were computed using random-effects models. Study-specific ORs were adjusted, when available and feasible, for sex, age, race/ethnicity, social class, tobacco smoking, fruit and vegetable consumption and study center for multicentric studies.
[2]*p* Values for test of OR heterogeneity across studies.
[3]*p* Values for test of interaction derived from a meta-regression model.
[4]The studies Italy 3 (De Feo *et al.*, 2012)[18] and Japan (Matsuo *et al.*, 2013)[31] were not considered due to a high fraction of missing values for socioeconomic status.
[5]The studies China 1 (Deandrea *et al.*, 2010)[27] and China 2 (Mu *et al.*, 2005)[28] were not considered as they did not collect data on cancer subsite.
[6]The studies Greece (Lagiou *et al.*, 2004),[16] Italy 1 (La Vecchia *et al.*, 1995),[19] Sweden 1 (Harris *et al.*, 2013),[25] Sweden 2 (Harris *et al.* 2013),[25] China 1 (Deandrea *et al.* 2010)[27] and China 2 (Mu *et al.* 2005)[28] were not considered as they did not collect data on histological type.
[7]Considered studies: Portugal (Lunet *et al.*, 2007),[21] Russia (Zaridze *et al.*, 2000),[22] Spain 1 (Castano-Vinyals *et al.*, 2015),[23] Sweden 3 (Ye *et al.*, 1999),[26] China 2 (Mu *et al.*, 2005)[28] and Japan (Matsuo *et al.*, 2013).[31] The studies Italy 3 (De Feo *et al.*, 2012)[18] and Spain 2 (Santibanez *et al.*, 2012)[24] were not considered because no information on *H. pylori* infection was available for controls, or controls were all *H. pylori* negative.
[8]Pooled ORs were computed considering all cases and only controls positive to *H. pylori* infection.
[9]Considered studies: Portugal (Lunet *et al.*, 2007),[21] Russia (Zaridze *et al.*, 2000),[22] Spain 1 (Castano-Vinyals *et al.*, 2015),[23] Sweden 3 (Ye *et al.*, 1999)[26] and Japan (Matsuo *et al.*, 2013).[31]
[10]The Russian study (Zaridze *et al.*, 2000)[22] was not considered in this analysis because it included both hospital and general population controls.
Ca, cases; Co, controls.
StoP Project consortium

consumption.[31] ALDH2 polymorphisms were found to modify the susceptibility to the development of gastric cancer associated with alcohol intake, especially in case of ALDH2 *1/*2 genotype.[44]

This pooled analysis reported similar findings in men and women and across various age groups. When considering heavy drinkers (>4 drinks/day), we found an almost two-fold increased risk in never smokers (OR 1.87 95% CI 1.35–2.58), while the corresponding risks in former (OR 1.64, 95% CI 1.10–2.44) and current smokers (OR 1.14, 95% CI 0.93–1.40) were lower. This finding suggests no or marginal confounding by smoking status, and argues against the hypothesis that the excess risk in heavy drinkers is due to the correlation between heavy alcohol drinking and tobacco smoking, an established risk factor for gastric cancer risk.[15]

Only a few studies investigated the relation between alcohol drinking and gastric cancer by anatomic location (cardia *vs.* noncardia gastric cancer),[9,10,45] or according to histological type.[9] Our data showed somewhat stronger associations for heavy drinking in cardia (OR 1.61, 95% CI 1.11–2.34) than in noncardia (OR 1.28, 95% CI 1.13–1.45) gastric cancers and in intestinal-type (OR 1.54, 95% CI 1.20–1.97) than in diffuse-type (OR 1.29, 95% CI 1.05–1.58) cancers. Regarding cancer subsite, our results are in contrast with those of the EPIC study,[9] that found a three-fold increased risk for noncardia cancers for consumption of 60 g/day or more of alcohol, and no significantly increased risk for cardia cancers, while the Netherlands Cohort Study[45] did not find any difference. When analyzing cancer histological type, the EPIC study reported an increased, although not significant, risk (HR 1.95) for intestinal-type cancers, in the absence of association for diffuse-type cancer. Our results were based on over 6,000 noncardia and 1,000 cardia gastric cancer cases, and over 1,800 cases each of intestinal and diffuse histological type of gastric cancer.

When analyzing the dose rate-risk relationship using flexible models—*i.e.* by considering alcohol as a continuous variable—we found that the best fitting fractional polynomial was the one with powers (–2,1), showing a linear trend without a threshold effect,[9,43] which resulted in an estimated 4% significant increased risk of gastric cancer for every additional drink of alcohol per day.

Our results showed an almost two fold excess risk among former drinkers who had stopped drinking for <5 years, but the risk decreased towards unity afterwards. This apparently paradoxical finding could be partly explained by the fact that some cases could have quit drinking after the onset of symptoms or immediately after the diagnosis of gastric cancer (i.e., reverse causation).[46]

The mechanisms by which (heavy) alcohol consumption exerts its carcinogenic effect are various and not fully understood. Acetaldehyde, the first metabolite of ethanol, is a human carcinogen able to induce DNA lesions, generate free radicals and bind to enzymes involved in DNA repair and antioxidant protection.[47] Moreover, chronic and heavy (~40 g/day) intake of alcohol markedly induces expression of cytochrome P-4502E1 (CYP2E1) in the gastrointestinal mucosa of rodents and in humans,[48] contributing to the formation of reactive oxygen species in the gastrointestinal tract, and to the activation of procarcinogens like nitrosamines. It should be also recognized that the nutritional status of heavy drinkers is impaired due to primary and secondary malnutrition, leading to deficiencies of core nutrients that in turn may contribute to the carcinogenic process.[48]

Our analyses included studies with hospital controls, which are more prone to selection bias, but the results were consistent across different sources of study controls. Moreover, differences across studies in the formulation of their questions on lifetime alcohol consumption may represent a source of heterogeneity. In 13 out of 20 studies[19–21,23–25,27–31] including the one with unpublished data, never drinkers were defined as lifelong abstainers, while in the remaining 7 studies[16–18,22,26,32,33] as long time (*i.e.* up to 20 years) non-drinkers including infrequent occasional drinkers (<1 times per month). It is however unlikely that this had meaningfully influenced our results.

Underreporting of alcohol intake may also have affected our results, since social acceptance of alcohol consumption may vary across countries, as well as consumption of specific beverages and their ethanol content.[49] However, no substantial inconsistencies emerged across studies, particularly in heavy drinkers, as confirmed by the low I^2 statistic for heterogeneity between studies.

The "StoP Project" includes original and individual data on alcohol drinking on ~10,000 cases and 26,000 controls and provide us a unique opportunity to investigate and accurately quantify the dose rate-risk relationship between alcohol drinking and gastric cancer risk, overall and in strata of potential confounders, or according to tumor location and histology. The individual level approach has several advantages as compared with study-level meta-analysis, specifically the availability of detailed and uniform information on important covariates.[50]

We were able to adjust for socioeconomic status and consumption of fruit and vegetables in the majority of studies, and we investigated the possible confounding effect of *H. pylori* infection. These sensitivity analyses confirmed the results of the main analysis, thus providing further evidence of a role of heavy alcohol drinking independent from that of *H. pylori*.

In conclusion, the results of this pooled-analysis of epidemiological studies support a detrimental, although modest, effect of heavy alcohol drinking on gastric cancer risk. The almost two-fold increased risk in heavy drinkers among never smokers, as well as the consistent results when restricting the analyses to *H. pylori* positive subjects, support an independent role of heavy alcohol drinking on gastric cancer risk.

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