The association between diabetes and gastric cancer: results from the Stomach Cancer Pooling Project Consortium

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Background   Prior epidemiologic studies on the association between diabetes and gastric cancer risk provided inconclusive findings, while traditional, aggregate data meta-analyses were characterized by high between-study heterogeneity.

Objective   To investigate the association between type 2 diabetes and gastric cancer using data from the 'Stomach Cancer Pooling (StoP) Project', an international consortium of more than 30 case–control and nested case–control studies, which is large and provides harmonized definition of participants' characteristics across individual studies. The data have the potential to minimize between-study heterogeneity and provide greater statistical power for subgroup analysis.

Methods   We included 5592 gastric cancer cases and 12 477 controls from 14 studies from Europe, Asia, North America, and South America in a two-stage individual-participant data meta-analysis. Random-effect models were used to estimate summary odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) by pooling study-specific ORs.

Results   We did not find an overall association between diabetes and gastric cancer (pooled OR=1.01, 95% CI, 0.94–1.07). However, the risk of cardia gastric cancer was significantly higher among individuals with type 2 diabetes (OR=1.16, 95% CI, 1.02–1.33). There was no association between diabetes and gastric cancer risk in strata of *Helicobacter pylori* infection serostatus, age, sex, BMI, smoking status, alcohol consumption, fruit/vegetable intake, gastric cancer histologic type, and source of controls.

Conclusion   This study provides additional evidence that diabetes is unrelated to gastric cancer overall but may be associated with excess cardia gastric cancer risk. *European Journal of Cancer Prevention* XXX: 000–000 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

In 2020, it was estimated that more than one million new cases of gastric cancer (or stomach cancer) were diagnosed worldwide and approximately 769 000 deaths were attributable to the disease, making it the fifth most common human malignancy and the fourth leading cause of cancer death (Sung *et al.*, 2021). Globally, the age-standardized incidence of gastric cancer among males and females were 15.8 and 7.0 per 100 000, respectively, while the respective mortality rates were 11.0 and 4.9 per 100 000 (Sung *et al.*, 2021)

Helicobacter pylori is the major human stomach carcinogen [International Agency for Research on Cancer (IARC), 1994]. One of the proposed mechanisms for the initiation and development of gastric cancer is oxidative stress via inflammation induced by infection with *H. pylori*, which leads to DNA damage by reactive oxygen species and subsequent tissue neoplasia (Vigneri *et al.*, 2009). Because metabolic syndromes/disorders, including obesity and type 2 diabetes mellitus, are also associated with low-grade systemic pro-inflammation, they may as well play important roles in gastric cancer carcinogenesis (Vigneri *et al.*, 2009).

While epidemiologic studies have shown that individuals with diabetes mellitus have an increased risk of cancer in various organs/tissues including the pancreas (Huxley *et al.*, 2005), breast (Liao *et al.*, 2011), endometrium (Friberg *et al.*, 2007), colon/rectum (Larsson *et al.*, 2005), and liver (El-Serag *et al.*, 2006), data on the association between diabetes and gastric cancer risk are inconclusive. A meta-analysis by Tian *et al.* (2012) found a modest and marginally significant association between diabetes and the risk of gastric cancer [relative risk (RR) = 1.11, 95% CI, 1.00−1.24, I^2 = 79.5%]. In a stratified analysis, this association was stronger in studies conducted in Asia (RR = 1.19, 95% CI, 1.07−1.32, I^2 = 29.8%) and on patients with type 2 diabetes (RR = 1.14, 95% CI, 1.01−1.30, I^2 = 84.8%).

In another meta-analysis of 21 observational studies, including 4 case−control and 17 cohort studies, Ge *et al.* (2011) reported no significant association between diabetes and gastric cancer (RR = 1.09, 95% CI, 0.98−1.22, I^2 = 81.2%). In stratified analysis, diabetic women were found to have 18% excess risk of gastric cancer (RR = 1.18, 95% CI, 1.01−1.39), whereas no association was observed in men. Also, a recent meta-analysis of 22 studies and 13 538 incident gastric cancer cases (Miao *et al.*, 2017) found no association between diabetes mellitus and gastric cancer (RR = 1.10, 95% CI, 0.94−1.29, I^2 = 22.9% in men and 1.00 (0.90−1.11), I^2 = 97.2% in women). However, in stratified analysis by geographic region, a significant positive association was found between diabetes and gastric cancer among women in Western countries (RR = 1.31, 95% CI, 1.09−1.57, I^2 = 0.0%). Furthermore, this association was stronger among nonsmokers (RR = 1.58, 95% CI, 1.04−2.39, I^2 = 91.1% in men and 1.60 (1.02−2.50), I^2 = 90.5% in women).

While heterogeneity in meta-analysis is often inescapable, between-study variability in these aggregate meta-analyses was too high that a different approach is needed to summarize the true relationship between diabetes mellitus and gastric cancer risk. The Stomach Cancer Pooling (StoP) Project, an international consortium of more than 30 epidemiological gastric cancer studies, provides a unique opportunity to perform such type of study, through individual-level data that were harmonized to produce a more homogeneous definition of participants characteristics (Pelucchi *et al.*, 2015). In addition, the large dataset provides strong power for valid subgroup analyses. In the current study, we investigated the association between type 2 diabetes mellitus and gastric cancer by pooling individual-level data from case−control studies in the StoP Project consortium.

Methods

Study population and sample size

Details of the purpose and procedures of the StoP project have been provided elsewhere (Pelucchi *et al.*, 2015). Briefly, data for the current analysis were based on the second release of the StoP project consortium data, which includes 31 gastric cancer case−control and nested case−control studies worldwide. A total of 14 participating studies with data on type 2 diabetes were included in our analysis. Four of the studies were from Italy (Buiatti *et al.*, 1989; La Vecchia *et al.*, 1995; Lucenteforte *et al.*, 2008; De Feo *et al.*, 2012), two from Spain (Santibañez *et al.*, 2012; Castaño-Vinyals *et al.*, 2015), one each from Greece

(Lagiou *et al.*, 2004), Russia (Zaridze *et al.*, 2000), China (Setiawan *et al.*, 2005), and Japan (Machida-Montani *et al.*, 2004), and two each were from the USA (Zhang *et al.*,1999; one is unpublished) and Brazil (Hamada *et al.*, 2002; Nishimoto *et al.*, 2002). These constituted a total of 5592 gastric cancer cases and 12 477 controls. Only one study had published a report on the association between diabetes and gastric cancer previously (La Vecchia *et al.*, 1995). The original data from each study were obtained after a signed data transfer agreement was given by the principal investigators. The consortium harmonized all data based on a predetermined format.

The University of Milan Institutional Review Board (IRB) provided the ethical approval for the StoP project (reference 19/15 – 01 April 2015). Participating studies were approved by their local IRBs.

Study outcome
Cases were individuals with histologically confirmed incident gastric cancer. All the studies included data on cancer anatomical subsite (cardia and noncardia) and histologic subtype (i.e. intestinal, diffuse, and others, including mixed, undifferentiated, and unclassified type) except a Chinese study (Setiawan *et al.*, 2005) (for both subsite and histologic type) and three other studies (La Vecchia *et al.*, 1995; Lagiou *et al.*, 2004; Machida-Montani *et al.*, 2004) which did not include information on cancer histology. The outcome for our main analysis was any type of gastric cancer, regardless of a subsite or histologic classification. We performed additional analyses with each gastric cancer histologic type and subsite as (polytomous) outcome.

Controls were recruited from the same source population and within the same periods as the cases. In nine studies, the controls were selected at the same health facility as the cases and, depending on the study, included patients with various noncancer conditions. The Japanese study (Machida-Montani *et al.*, 2004) selected controls among participants in a health checkup program. Three studies recruited controls from the general population (Buiatti *et al.*, 1989; Setiawan *et al.*, 2005; Castaño-Vinyals *et al.*, 2015), while one study (Hamada *et al.*, 2002) had a mixed source of controls (58% from a hospital near the cases source and 42% from the community).

Exposure
Data on the history of type 2 diabetes mellitus (diagnosed by a health professional or treated) were collected using a structured questionnaire in all 14 studies. The questionnaires were administered by trained interviewers in all the studies except the Russian study (Zaridze *et al.*, 2000) – for which it was self-administered – and two others (Zhang *et al.*, 1999; Machida-Montani *et al.*, 2004) – for which the information on the procedure used to administer the questionnaire was not provided. Exposure data were collected in the same way and within the same period for cases and controls in all the studies.

Statistical analysis and covariates
We adopted the two-stage individual-participant data pooling approach (Burke *et al.*, 2017). At the initial stage, we used unconditional logistic regression to estimate odds ratios (ORs) and the corresponding 95% confidence intervals (95% CIs) for the association between diabetes and gastric cancer in each study, using maximum likelihood method. Depending on availability (no more than 30% missing data) and feasibility, the logistic regression models were adjusted for age (i.e. <55, 55–65, and >65 years), race/ethnicity (i.e. White, Black/African American, Asian, Hispanic/Latino, and other races), sex, BMI (i.e. <18.5, 18.5–24.9, 25–29.9, and ≥30 kg/m^2), alcohol consumption (i.e. never, low, and moderate/high), tobacco smoking status (i.e. never, former, and current), *H.* pylori infection serostatus, history of gastric ulcer, fruit/vegetable intake (using study-specific tertiles), and study site (for studies with multiple sites). Some variables were re-categorized to avoid scant data in some studies, and also for the stratified analyses. Any implausibility or inconsistency in observations was reconciled by the investigators for each individual study.

We replaced the occasional missing data in study covariates using multiple imputations by fully conditional specification (Liu and De, 2015). Under the assumption of missing at random, 10 imputed datasets were generated for each study, with the missing observations replaced with values selected from the separate conditional distribution of each imputed variable. A logistic regression model was then fitted on each of the 10 imputed datasets to obtain estimates, which were combined using Rubin's rule (Rubin, 2004) to produce regression coefficient and corresponding standard error for each study. The imputation models contained the same set of covariates (and the outcome) as the analysis models. The resulting study-specific regression coefficients were then combined in the second (pooling) stage using inverse-variance weighted random effect models (Burke *et al.*, 2017) to produce summary ORs and 95% CI estimates.

For the analysis with cancer anatomical subsite and histologic type as outcomes, we fitted polytomous logistic regression models for each study in the analysis phase of the first stage, following multiple imputations. Between-study heterogeneity was assessed using the Method-of-Moments estimator and quantified using I^2 (proportion of total model variance due to between-study variability) (DerSimonian and Laird, 1986). We performed subgroup analyses to evaluate possible differences in the association between type 2 diabetes and gastric cancer across strata of sex, age, BMI (i.e. <25 and ≥25), smoking status, alcohol consumption, fruit/vegetable intake, *H. pylori* infection serostatus, cancer subsite, cancer histological subtype, geographical region and source of controls (i.e. hospital versus general population). The study with the mixed source of controls (Nishimoto *et al.*, 2002) was considered to have used hospital controls only. Statistical

significance of differences across strata was assessed in a meta-regression model.

We conducted a number of sensitivity analyses to assess the robustness of our results, even though the two-stage analysis method was adopted *a priori* to avoid bias (Burke *et al.*, 2017), and we took steps to check the quality of the imputed data, including examination of the differences between the observed, imputed and completed datasets and comparison of their distributions using Kernel density plots (Liu and De, 2015). First, we fitted a single unconditional, fixed-effect logistic regression model using the entire data, controlling for study and other covariates that were available across all the studies. Missing data were also replaced in this analysis using the same approach as the main analysis. Second, we restricted the main analysis to studies that scored at least six on the Newcastle−Ottawa scale (NOS) for assessing the quality of case−control studies (Wells *et al.*, 2011), [all except one (Lagiou *et al.*, 2004)] to see if study quality had any impact on our results. To rule out the potential effect of differences in exposure data collection on our analysis, we excluded the study that used a self-administered questionnaire to collect data on the history of diabetes (Zaridze *et al.*, 2000) and two others (Zhang *et al.*, 1999; Machida-Montani *et al.*, 2004) for which usage of professional interviewers to administer the questionnaire could not be confirmed. Finally, to rule out potential misclassification of *H. pylori* infection serostatus among cases, we included only *H. pylori* seropositive controls in the logistic model for the two-stage main analysis, under the assumption that *H. pylori* infection was a necessary cause of gastric cancer.

The LOGISTIC, MI, and MI ANALYZE procedures in SAS (version 9.4) were performed in the first stage of the analysis, using a macro specifically developed for this purpose. The METAREG package in Stata (version 16) was used to fit the random-effect and meta-regression models in the second stage (the pooling stage).

Results

Participants' characteristics

The current analysis included 5592 gastric cancer cases and 12 477 controls. Table 1 reports selected characteristics of the participating studies. European studies account for two-thirds of the participants (68.7%), and Italy had the largest proportion among countries (35.5%). The rest of the participants were from Asia (10.4%), North America (16.9%), and South America (4.0%).

The summary of key sociodemographic and health characteristics of the cases and controls is presented in Table 2. A larger proportion of controls (8.8%) than cases (7.3%) had type 2 diabetes. Mean age at study entry was slightly higher for cases (62.2 years) than for controls (60.4 years). Gastric cancer cases were also more likely to be male patients, of low socioeconomic status, moderate to high consumers of alcohol, current smokers as well as having a history of peptic ulcer disease, and gastritis.

Table 1   Characteristics and outcomes of the participating studies in the current analysis

	Cases, n (%)	Controls, n (%)	Type of control	Age at entry (mean±SD)	Male, n (%)	Diabetes, n (%)	Cancer subsite		Histologic type		
							Cardia, n (%)	Noncardia, n (%)	Intestinal, n (%)	Diffuse, n (%)	Other, n (%)
Europe	3577 (28.8)	8837 (71.2)		61.1±12.0	7188 (57.9)	1194 (9.6)	326 (2.6)	3191 (26.0)	1134 (9.1)	653 (5.3)	637 (5.1)
Italy 1 (La Vecchia et al., 1995)	769 (27.0)	2081 (73.0)	Hospital	55.5±11.6	1689 (59.3)	113 (4.0)	11 (0.4)	758 (26.6)	33 (4.2)	57 (7.3)	64 (8.2)
Italy 2 (Lucenteforte et al., 2008)	230 (29.6)	547 (70.4)	Hospital	60.2±11.2	429 (55.2)	58 (7.5)	10 (1.3)	220 (28.3)	59 (9.8)	49 (8.1)	4 (0.9)
Italy 3 (De Feo et al., 2012)	160 (26.5)	444 (73.5)	Hospital	61.2±15.3	345 (57.1)	70 (11.6)	18 (3.0)	103 (17.0)	[a]	[a]	[a]
Italy 4 (Buiatti et al., 1989)	1016 (46.7)	1159 (53.3)	Population	63.3±9.7	1345 (61.8)	181 (8.3)	69 (3.2)	947 (43.5)	510 (23.4)	216 (9.9)	290 (13.3)
Greece (Lagiou et al., 2004)	110 (52.4)	100 (47.6)	Hospital	62.3±12.2	106 (50.5)	17 (8.1)	0	110 (52.4)	[a]	[a]	[a]
Russia (Zaridze et al., 2000)	450 (42.4)	611 (57.6)	Hospital	58.3±11.3	541 (51.0)	76 (7.2)	92 (8.7)	356 (33.5)	121 (11.4)	119 (11.2)	210 (19.8)
Spain 1 (Castano-Vinyals et al., 2015)	441 (11.4)	3440 (88.6)	Population	64.3±11.6	2182 (56.2)	610 (15.7)	95 (2.4)	346 (8.9)	168 (4.3)	103 (2.6)	20 (0.5)
Spain 2 (Santibañez et al., 2012)	401 (46.9)	455 (53.2)	Hospital	63.8±11.0	551 (64.4)	69 (8.1)	31 (3.6)	351 (41)	243 (28.4)	109 (12.7)	49 (5.7)
Asia	864 (46.0)	1014 (54.0)		61.5±11.2	1229 (65.4)	45 (2.4)	21 (1.1)	128 (6.8)	[a]	[a]	[a]
China (Setiawan et al., 2005)	711 (50.0)	711 (50.0)	Population	62.6±11.5	906 (63.7)	19 (1.3)	[a]	[a]	[a]	[a]	[a]
Japan (Machida-Montani et al., 2004)	153 (33.5)	303 (66.5)	Hospital	57.8±9.4	323 (70.8)	26 (5.7)	21 (4.6)	128 (28.1)	[a]	[a]	[a]
North America	832 (27.3)	2214 (72.7)		59.8±10.2	2265 (74.4)	194 (6.4)	225 (7.4)	189 (6.2)	51 (1.7)	32 (1.1)	294 (9.7)
USA 1 (Zhang et al., 1999)	132 (50.0)	132 (50.0)	Hospital	57.7±13.9	156 (59.1)	15 (5.7)	64 (24.2)	68 (25.8)	51 (19.3)	32 (12.1)	12 (4.5)
USA 2 (Muscat et al., unpublished)	700 (25.2)	2082 (74.8)	Hospital	60.0±9.8	2109 (75.8)	179 (6.4)	161 (5.8)	121 (4.3)	0	0	282 (10.1)
South America	319 (43.6)	412 (56.4)		61.1±10.0	500 (68.4)	71 (9.7)	25 (3.4)	283 (38.7)	157 (21.5)	109 (15.0)	0
Brazil 1 (Nishimoto et al., 2002)	226 (50.0)	226 (50.0)	Hospital	58.3±7.7	326 (72.1)	30 (6.6)	19 (4.2)	198 (43.8)	112 (24.8)	73 (16.1)	0
Brazil 2 (Hamada et al., 2002)	93 (33.3)	186 (66.7)	Hospital[b]	65.5±11.4	174 (62.4)	41 (14.7)	6 (2.1)	85 (30.5)	45 (16.1)	36 (12.9)	0
Total	5592 (31.0)	12 477 (69.1)		60.9±11.5	11 182 (61.9)	1504 (8.3)	597 (3.3)	3791 (21.0)	1342 (7.4)	794 (4.4)	931 (5.2)

[a]Data not available for the study or region.
[b]42% of controls selected from the population but considered as hospital-controlled for the stratified analysis by control type. *n*: count.

Table 2 Distribution of cases and controls by selected covariates in the current analysis

	Cases (*n*=5592)	Controls (*n*=12 477)
Diabetes		
No	5064 (90.6)	11 246 (90.1)
Yes	408 (7.3)	1096 (8.8)
Missing	120 (2.2)	135 (1.1)
Age (mean±SD)	62.2±10.8	60.4±11.8
Age categories (years)		
≤55	1423 (25.5)	3947 (31.6)
55–65	1538 (27.5)	3372 (27.0)
≥65	2631 (47.1)	5158 (41.3)
BMI		
≤18.5	169 (3.0)	184 (1.5)
18.5–25	2066 (37.0)	4202 (33.7)
25–30	1400 (25.0)	3907 (31.3)
≥30	1099 (19.7)	2151 (17.2)
Missing	858 (15.3)	2033 (16.3)
Sex		
Male	3603 (64.4)	7579 (60.7)
Female	1989 (35.6)	4898 (39.3)
Race/ethnicity		
White	2333 (41.7)	7108 (57.0)
Black/African American	88 (1.6)	217 (1.7)
Asian	105 (1.9)	199 (1.6)
Hispanic/Latino	56 (1.0)	73 (0.6)
Other	13 (0.2)	36 (0.3)
Missing	2997 (53.6)	4844 (38.8)
Education (completed)		
Less than high school	2449 (43.8)	3285 (26.3)
High school	1521 (27.2)	44 644 (37.2)
College graduate	419 (7.5)	1535 (12.3)
Missing	1203 (21.5)	3013 (24.2)
Socioeconomic status		
Low	3096 (55.4)	5464 (43.8)
Intermediate	1794 (32.1)	4529 (36.3)
High	594 (10.6)	2151 (17.2)
Missing	108 (1.9)	333 (2.7)
Smoking		
Never	2333 (41.7)	5478 (44.0)
Former	1458 (26.1)	3482 (28.0)
Current	1723 (30.8)	3387 (27.2)
Missing	78 (1.4)	130 (1.0)
Drinking		
Never	1173 (21.0)	3469 (28.0)
Low	711 (12.7)	1474 (12.0)
Moderate	1623 (29.0)	3126 (25.1)
High	854 (15.3)	1665 (13.3)
Missing	1231 (22.0)	2743 (22.0)
History of gastritis		
No	2466 (44.1)	6017 (48.2)
Yes	711 (12.7)	586 (4.7)
Missing	2415 (43.2)	5874 (47.1)
History of gastric ulcer		
No	2869 (51.3)	5075 (40.7)
Yes	407 (7.3)	238 (2.0)
Missing	2316 (41.4)	7164 (57.4)
History of peptic ulcer		
No	2055 (36.8)	7298 (58.5)
Yes	852 (15.2)	975 (7.8)
Missing	2685 (48.0)	4204 (33.7)
Vegetable and fruit intake		
Low	1487 (26.6)	2754 (22.1)
Intermediate	1494 (26.7)	3181 (25.5)
High	1774 (31.7)	3749 (30.1)
Missing	837 (15.0)	2793 (22.3)
***H. Pylori* seroprevalence**		
Negative	377 (6.7)	728 (5.8)
Positive	891 (16.0)	2601 (21.0)
Missing	4324 (77.3)	9148 (73.3)

n: count.

Association between type 2 diabetes mellitus and gastric cancer

Table 3 shows the pooled ORs and 95% CIs for the association between gastric cancer and diabetes for all participants – also shown in (Fig. 1), and stratified by age, BMI, smoking status, drinking frequency, fruits/vegetable intake, *H. pylori* infection serostatus, study geographical location, cancer anatomical site, histologic subtype as well as type (source) of controls. Overall, compared to diabetes-free individuals, there was no association between diabetes and gastric cancer (pooled OR = 1.01, 95% CI, 0.94–1.07).

Pooled OR estimates were significantly different by cancer anatomical site ($P_{heterogeneity}$ = 0.04). Those with diabetes had a significantly higher risk of cardia gastric cancer compared to those without diabetes (OR = 1.16, 95% CI, 1.02–1.33), while no association was observed between diabetes and noncardia gastric cancer (OR = 1.03, 95% CI, 0.95–1.12). We did not find a significant difference in the association across the strata of *H. pylori* infection serostatus ($P_{heterogeneity}$ = 0.48), cancer histological type ($P_{heterogeneity}$ = 0.55), age ($P_{heterogeneity}$ = 0.42), sex ($P_{heterogeneity}$ = 0.37), BMI ($P_{heterogeneity}$ = 0.49), smoking status ($P_{heterogeneity}$ = 0.64), alcohol consumption ($P_{heterogeneity}$ = 0.32), fruit/vegetables intake frequency ($P_{heterogeneity}$ = 0.36), geographical location ($P_{heterogeneity}$ = 0.43), and source of controls ($P_{heterogeneity}$ = 0.09). Moreover, these within strata effects were largely similar to that from the main analysis, and none was statistically significant.

Sensitivity analysis

Our analysis using a single, fixed-effect logistic regression model for the whole data, controlling for study and other covariates, yielded similar results as the main, two-stage analysis (OR = 0.99, 95% CI, 0.94–1.08). Also, the results from the main analysis did not change appreciably after excluding one study with a score of only 5 on the NOS (OR = 1.01, 95% CI, 0.94–1.07), as well as following the removal from the analysis of three studies which either used a self-administered questionnaire to assess diabetes history or had unverified means of administering the questionnaire (OR = 1.01, 95% CI, 0.95–1.09). Similarly, the model containing only *H. pylori* seropositive controls did not differ from the model with all the controls included (OR = 1.00, 95% CI, 0.94–1.12).

Discussion

In this pooled analysis of individual-level data on 5592 gastric cancer cases and 12 477 controls from 14 studies within the StoP consortium, we found a null association between type 2 diabetes and gastric cancer risk. When the analysis was stratified by cancer subsite, we found an increased risk of gastric cancer among patients with cardia tumors. The null association remained, and was consistent, across strata of *H. pylori* infection serostatus, sex, age, BMI, smoking status, alcohol consumption, fruit/vegetables intake, geographical location, cancer histological type, and source of controls.

Our results add to the growing evidence on the potential role of diabetes in gastric cancer pathogenesis. Consistent with our finding, some recent (aggregate-data) meta-analyses also found a minor direct but nonstatistically significant overall association between type 2 diabetes and gastric cancer; which was; however, significant for certain subgroups among the participants (Ge *et al.*, 2011; Marimuthu *et al.*, 2011; Miao *et al.*, 2017). Only one of the meta-analyses (Ge *et al.*, 2011) included any of the studies in this analysis (94% of cancer cases from one of the Italian studies) (La Vecchia *et al.*, 1995). However, other meta-analyses (Tian *et al.*, 2012; Yoon *et al.*, 2013) and a recent large cohort study (Cheung *et al.*, 2019) found overall significant positive associations. The differences between our results and those from other studies could be due to dissimilarities in design, analysis approach, or between-study heterogeneity. For example, Cheung *et al.* (2019) used a cohort design with homogenous population who previously received *H. pylori* eradication therapy. They also controlled for more potential confounders than included in our models and performed propensity score analysis. Lack of adjustment for use of medications in our models, such as metformin, aspirin, and statins, which are known to have an inverse association with gastric cancer (Currie *et al.*, 2009; Singh and Singh, 2013; Ye *et al.*, 2013; Li *et al.*, 2018), could have biased our results towards the

Table 3 Pooled odds ratios (ORs) and 95% confidence intervals (CIs) for the association between diabetes and gastric cancer, stratified by selected characteristics in the current analysis

| | Diabetes | | | | |
| | No | Yes | | | |
	Case/control	Case/control	OR (95% CI)[a]	$P_{between-study}$	$P_{interaction}$
Overall	4697/10828	375/1060	1.01 (0.94–1.07)	0.73	
Sex					0.37
Men	3365/6803	265/701	1.06 (0.97–1.16)	0.53	
Women	1799/4443	143/395	0.94 (0.84–1.05)	0.80	
Age (years)					0.42
≤55	1353/3801	44/112	1.09 (0.88–1.35)	0.81	
>55–<65	1399/3050	104/283	1.04 (0.85–1.25)	0.17	
≥65	2312/4395	260/701	1.00 (0.90–1.09)	0.62	
BMI (kg/m^2)[b]					0.49
<25	2112/4135	120/245	0.97 (0.85–1.12)	0.43	
≥25	2158/5254	225/686	1.04 (0.94–1.15)	0.65	
Smoking status					0.64
Never	2096/4936	183/476	1.01 (0.90–1.13)	0.39	
Former	1298/3066	131/400	1.06 (0.93–1.20)	0.75	
Current	1601/3141	88/203	1.01 (0.86–1.18)	0.95	
Alcohol consumption[c]					0.32
Never	1072/3073	101/391	0.88 (0.72–1.07)	0.52	
Low	665/1398	6/73	1.17 (0.85–1.61)	0.12	
Moderate/high	2284/4417	190/371	1.10 (0.91–1.33)	0.08	
Fruit/vegetable intake[d]					0.36
Low	1358/2482	86/239	1.00 (0.86–1.16)	0.61	
Intermediate	1368/2869	103/274	1.02 (0.89–1.18)	0.83	
High	1582/3396	147/305	1.03 (0.88–1.26)	0.27	
H. pylori serostatus[e]					0.48
Positive	695/2235	87/358	1.02 (0.90–1.15)	0.59	
Negative	289/658	30/69	0.94 (0.71–1.25)	0.36	
Geographic region					0.44
Europe	3252/7933	314/880	1.02 (0.94–1.10)	0.64	
Asia	734/882	21/24	1.12 (0.86–1.46)	0.31	
Americas	1078/2431	73/192	0.93 (0.80–1.08)	0.65	
Cancer subsite[f]					0.03
Cardia	533/10405	56/1048	1.16 (1.02–1.33)	0.37	
Noncardia	3283/10405	304/1048	1.03 (0.95–1.12)	0.57	
Histological type[g]					0.55
Intestinal	1054/5963	130/798	1.07 (0.96–1.20)	0.42	
Diffuse	625/5963	56/798	1.00 (0.86–1.17)	0.47	
Other	594/5963	53/798	1.02 (0.86–1.20)	0.97	
Control type					0.09
Hospital	3194/6688	227/467	0.95 (0.87–1.04)	0.77	
Population	1870/4558	181/629	1.07 (0.97–1.18)	0.90	

CI, confidence interval; OR, odds ratio.

[a]Pooled ORs were obtained using random-effects models. ORs were adjusted, when possible (in a study), for age, race/ethnicity, sex, BMI, socioeconomic status, tobacco smoking status, level of alcohol consumption, frequency of fruit/vegetable intake, history of gastric ulcer, and study site (for multicenter studies).

[b]Variable was not available for Brazil 1, Brazil 2, Italy 3, and USA 2 studies.

[c]Variable was not available for China, Italy 3, Russia, and Spain 1 studies.
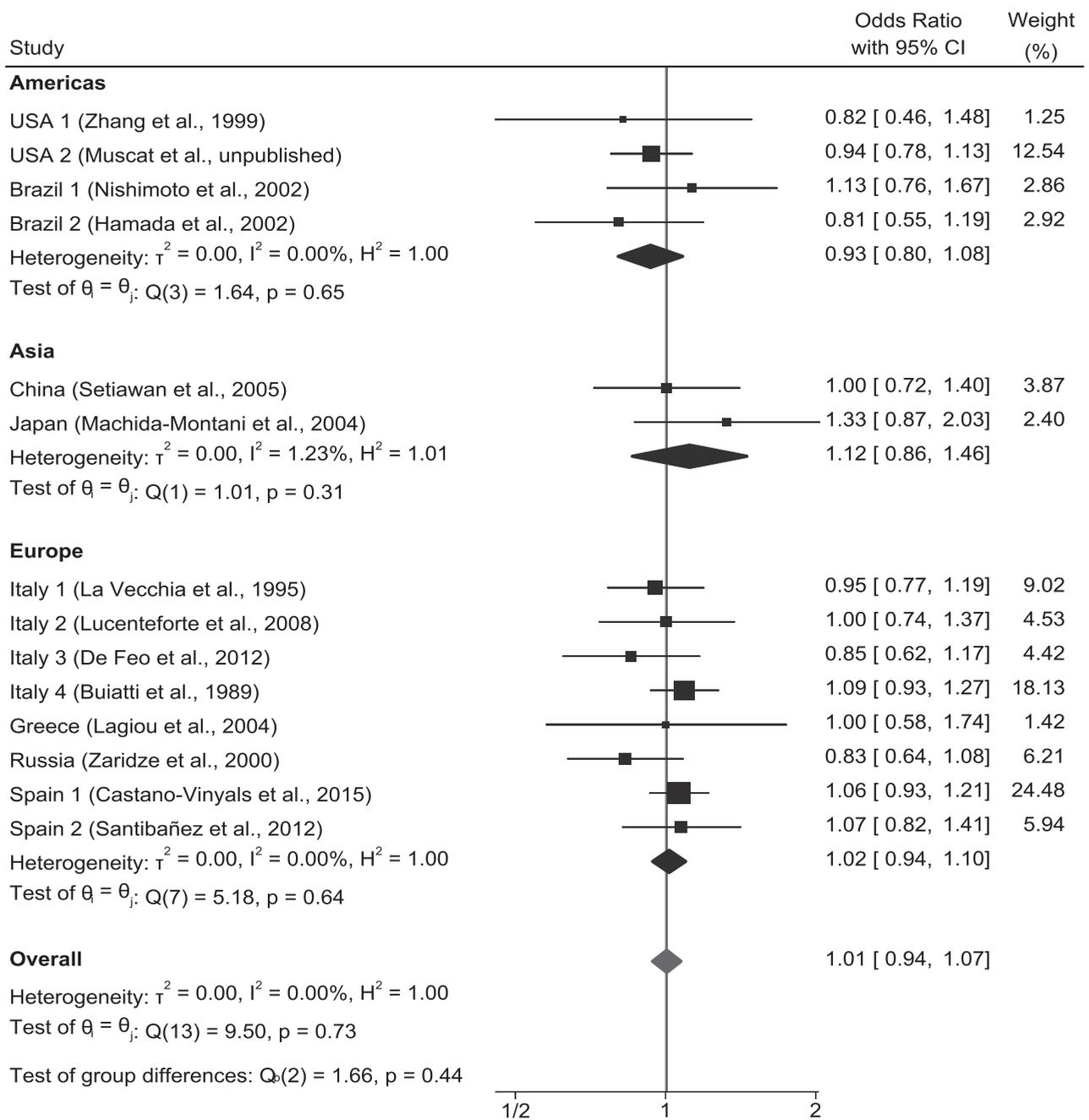
[d]Variable was not available/not usable for USA 2, Brazil 1, and Brazil 2 studies.

[e]Studies considered: Brazil 1, Brazil 2, Japan, Russia, and Spain 1. Italy 3 excluded because all controls in the study had missing data on *H. pylori* infection serostatus.

[f]Variable was not available/not usable for Brazil 2, China, and Greece studies.

[g]Studies considered: Italy 2, Italy 3, Italy 4, Russia, Spain 1, Spain 2, and USA 1.

Fig. 1

Study		Odds Ratio with 95% CI	Weight (%)
Americas			
USA 1 (Zhang et al., 1999)		0.82 [0.46, 1.48]	1.25
USA 2 (Muscat et al., unpublished)		0.94 [0.78, 1.13]	12.54
Brazil 1 (Nishimoto et al., 2002)		1.13 [0.76, 1.67]	2.86
Brazil 2 (Hamada et al., 2002)		0.81 [0.55, 1.19]	2.92
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$		0.93 [0.80, 1.08]	
Test of $\theta_i = \theta_j$: Q(3) = 1.64, p = 0.65			
Asia			
China (Setiawan et al., 2005)		1.00 [0.72, 1.40]	3.87
Japan (Machida-Montani et al., 2004)		1.33 [0.87, 2.03]	2.40
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 1.23\%$, $H^2 = 1.01$		1.12 [0.86, 1.46]	
Test of $\theta_i = \theta_j$: Q(1) = 1.01, p = 0.31			
Europe			
Italy 1 (La Vecchia et al., 1995)		0.95 [0.77, 1.19]	9.02
Italy 2 (Lucenteforte et al., 2008)		1.00 [0.74, 1.37]	4.53
Italy 3 (De Feo et al., 2012)		0.85 [0.62, 1.17]	4.42
Italy 4 (Buiatti et al., 1989)		1.09 [0.93, 1.27]	18.13
Greece (Lagiou et al., 2004)		1.00 [0.58, 1.74]	1.42
Russia (Zaridze et al., 2000)		0.83 [0.64, 1.08]	6.21
Spain 1 (Castano-Vinyals et al., 2015)		1.06 [0.93, 1.21]	24.48
Spain 2 (Santibañez et al., 2012)		1.07 [0.82, 1.41]	5.94
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$		1.02 [0.94, 1.10]	
Test of $\theta_i = \theta_j$: Q(7) = 5.18, p = 0.64			
Overall		1.01 [0.94, 1.07]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$			
Test of $\theta_i = \theta_j$: Q(13) = 9.50, p = 0.73			
Test of group differences: $Q_b(2) = 1.66$, p = 0.44			

1/2   1   2

Random-effects DerSimonian-Laird model

Study-specific and pooled odds ratios and their respective 95% confidence intervals for the association between diabetes and gastric cancer risk in the Stomach Cancer Pooling (StoP) Project Consortium. CI, confidence interval.

null. This is because diabetic patients would more likely have required therapy with these drugs. But, like our study, Cheung *et al.* (2019) also found a positive association between diabetes mellitus and cancers located in the cardia region of the stomach. Our analysis improved on traditional meta-analyses by pooling individual-level data and using the same definition of variables across individual studies, which probably reduced between-study heterogeneity in our results. But the meta-analyses by Yoon *et al.* (2013) and Tian *et al.* (2012), which also found a significant positive association between diabetes and gastric cancer, were based on aggregate data. The latter study (Tian *et al.*, 2012) was characterized by very high between-study heterogeneity ($I^2 = 84.8\%$ for type

2 diabetes mellitus and 79.5% for any type of diabetes mellitus). Also, only two studies in the work by Yoon *et al.* (2013) controlled for *H. pylori* infection status in their analyses. Nevertheless, regardless of the statistical significance, the positive direction of the association reported by most published meta-analyses to date suggests diabetes could be, potentially, an independent risk factor for gastric cancer. And our study, among the first pooled analyses of individual data to evaluate the impact of type 2 diabetes on gastric cancer risk, also showed a similar trend for cardia cancer.

Of importance, we investigated the effect of diabetes mellitus on gastric cancer risk across strata of key covariates. Our study is the first meta-analysis – to the best of our knowledge – to evaluate the association according to gastric cancer subsite and *H. pylori* infection status by pooling individual-level data from many studies. To date, only four reports have been published on the association by gastric tumor location (Lin *et al.*, 2011; Kim *et al.*, 2016; Cheung *et al.*, 2019; Zheng *et al.*, 2019). None of them included as many gastric cancer cases as we had in our analysis. Consistent with our results, Lin *et al.* (2011) and, more recently, Cheung *et al.* (2019) found a significantly higher risk of cardia gastric cancer among individuals with diabetes, with respective hazard ratios and 95% CIs of 1.89 (1.43–2.50) and 3.5 (1.45–7.97). On the other hand, Kim *et al.* (2016) and Zheng *et al.* (2019) each reported a null association (hazard ratio = 0.64, 95% CI, 0.14–2.94; and hazard ratio = 0.94, 95% CI, 0.57–1.54, respectively). There are several differences between these studies and ours that might explain why the results differ. Both studies used cohort design and included fewer gastric cancer cases. Moreover, the participants in Kim *et al.* (2016) study included individuals who visited a hospital for a routine checkup, who were possibly less prone to risky behaviors regarding both diabetes mellitus and gastric cancer, such as sedentary lifestyle, smoking, and alcohol intake. While Zheng *et al.* (2019) combined diabetic patients and those with prediabetes in the same exposure group in their analysis.

The link between type 2 diabetes mellitus and gastric cancer, in general, is still not fully understood, but several potential biological explanations have been suggested, including shared risk factors (such as obesity); hyperinsulinemia and resistance to insulin; *H. pylori* infection; comorbidities (e.g. via diet or lifestyle changes); use of medications (e.g. metformin, aspirin, statins, and insulin) and hyperglycemia (Lorenzi *et al.*,1986; Dandona *et al.*,1996; Pollak, 2012; Wieser *et al.*, 2013; Tseng and Tseng, 2014; Cheung *et al.*, 2018). It is also not clear what might be responsible for the difference being observed in the cardia and noncardia gastric cancer risk, but a recent hypothesis suggests that the answer might lie in the distinct cancer etiopathogenetic mechanisms for the two stomach subsites (Cheung *et al.*, 2019). *H. pylori* infection (through atrophic gastritis and hypochlorhydria),

low socioeconomic status, and dietary factors are known to be associated more with noncardia gastric cancers. Whereas obesity (particularly severe type) and gastro-esophageal reflux disease (GERD) are risk factors that are almost unique to cardia cancers (Karimi *et al.*, 2014). The observed higher risk of cardia gastric cancer among individuals with type 2 diabetes might be due to their greater predisposition to obesity and GERD (Rawla and Barsouk, 2019). Furthermore, treating *H. pylori* infection might improve corpus inflammation, thereby restoring gastric acid production and compound GERD (Cheung *et al.*, 2019). However, Lin *et al.* (2011) did not find any difference in the risk of proximal gastric adenocarcinoma due to diabetes across strata of BMI, suggesting that other factors independent of obesity could be involved in the pathogenesis of cardia cancer. Further research is needed to test these hypotheses using more comprehensive data on obesity and *H. pylori* infection than used in this analysis and other published studies, to be collected long before cancer diagnosis.

Our study is also among the few to have examined potential differences in gastric cancer risk due to diabetes according to strata of *H. pylori* infection (Jun *et al.*, 2006; Ikeda *et al.*, 2009). Like our study, Jun *et al.* (2006) found a similar, null association between diabetes mellitus and gastric cancer among both *H. pylori* positive and negative individuals. However, Ikeda *et al.* (2009) reported a significant increase in gastric cancer risk among *H. pylori*-infected diabetic patients who had baseline glycated hemoglobin levels above 6.0%. These conflicting results highlight the importance of investigating differences by *H. pylori* infection status in gastric cancer risk among diabetes mellitus patients in future studies.

A key strength of our study is the use of a harmonized, high-quality individual-level data to obtain pooled estimates, which might have resulted in the very low between-study heterogeneity observed in our models compared to prior aggregate data meta-analyses. Most of our analysis models had I^2 below 5% and none had above 30%. We used larger samples in our subgroup analyses than used in many previous studies, which ensured adequate power for effect size estimation. Moreover, our sample was inclusive, coming from eight countries on four continents. We had also included *H. pylori* infection serostatus, an important factor for gastric cancer, as a covariate in our models, in addition to other well-established risk factors for gastric cancer, which was rarely accomplished in previous studies. The similarity between our main results and those from the various sensitivity analyses we conducted shows our models were robust.

Our current study also has limitations. We assessed diabetes status by self-report, which is known to have high specificity but low to moderate sensitivity in some of the countries our analysis represents (Espelt *et al.*, 2012; Schneider *et al.*, 2012; Goto *et al.*, 2013; Yuan *et al.*, 2015)

and might have led to misclassification of the variable. However, the use of professional interviewers to administer questionnaires by most of the studies in our analysis could have limited this bias. Also, the prevalence rates of diabetes among majority of the controls in our analysis were comparable to the respective countries' averages at the time the data were collected. Additionally, the sensitivity of diabetes mellitus self-report is known to be education dependent (Yuan *et al.*, 2015) and we adjusted for educational status of participants in our models. We could have misclassified *H. pylori* infection status by assessing it using antibodies and, for the cases, following a gastric cancer diagnosis. Serological diagnosis of *H. pylori* infection, in general, has limited validity (Biranjia-Hurdoyal and Seetulsingh-Goorah, 2016) and could be unreliable at gastric cancer diagnosis as the infection tends to diminish with cancer progression (Peleteiro *et al.*, 2012). However, the results from our sensitivity analysis with *H. pylori* seropositive controls only in the model suggest misclassification of *H. pylori* infection status, if present, was nondifferential for cases. Our results were also susceptible to selection bias due to the use of hospital controls by most of the studies in our analyses. However, the similarity of ORs between studies that used hospital controls and those with controls from the general population, as well as across levels of other sociodemographic characteristics suggests this bias was unlikely to have occurred. Due to absent or limited data, we were not able to adjust for other established correlates of diabetes and gastric cancer in our models, including medications use, salt intake, glycemic control, family history of gastric cancer, and factors known to affect diabetes or cancer-related health-seeking behaviors, such as mental wellbeing (Peleteiro *et al.*, 2011; Bajaj *et al.*, 2012; Tseng and Tseng, 2014; Kabir *et al.*, 2020). However, our inclusion of *H. pylori* infection serostatus, fruit/vegetable consumption, and history of gastric ulcer as covariates in study-specific logistic regression models is a significant improvement in many previous studies.

In conclusion, results from our large pooled analysis of individual-level data from 14 international case−control studies showed no overall association between diabetes and gastric cancer. The subgroup analysis; however, suggested that diabetes could be a risk factor for cardia gastric cancer. There is a need for further research to understand the underlying mechanism for the dissimilarity in the diabetes-associated cardia and noncardia gastric cancer risk.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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