

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

Bashir Dabo^{a,*}, Claudio Pelucchi^{b,*}, Matteo Rota^{c,*}, Harshonnati Jain^d, Paola Bertuccio^e, Rossella Bonzi^b, Domenico Palli^f, Monica Ferraroni^b, Zuo-Feng Zhang^g, Aurora Sanchez-Anguiano^a, Yen Thi-Hai Pham^h, Chi Thi-Du Tranⁱ, Anh Gia Pham^j, Guo-Pei Yu^k, Tin C. Nguyen^l, Joshua Muscat^m, Shoichiro Tsuganeⁿ, Akihisa Hidakaⁿ, Gerson S. Hamada^o, David Zaridze^p, Dmitry Maximovitch^p, Manolis Kogevinas^{q,r,s,t}, Nerea Fernández de Larrea^{q,u}, Stefania Boccia^{v,w}, Roberta Pastorino^v, Robert C. Kurtz^x, Areti Lagiyou^y, Pagona Lagiyou^{z,aa}, Jesus Vioque^{q,bb}, M. Constanza Camargo^{cc}, Maria Paula Curado^{dd}, Nuno Lunet^{ee,ff}, Paolo Boffetta^{gg,hh}, Eva Negri^e, Carlo La Vecchia^b and Hung N. Luu^{ii,jj}

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 12477 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* 31: 260–269 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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^aCollege of Public Health, University of South Florida, Tampa, Florida, USA, ^bDepartment of Clinical Sciences and Community Health, University of Milan, Milan, ^cDepartment of Molecular and Translational Medicine, University of Brescia, Brescia, Italy, ^dDepartment of Information Systems and Decision Sciences (ISDS), Muma College of Business, University of South Florida, Tampa, Florida, USA, ^eDepartment of Biomedical and Clinical Sciences, University of Milan, Milan, ^fCancer Risk Factors and Life-Style Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network, ISPRO, Florence, Italy, ^gDepartment of Epidemiology, UCLA Fielding School of Public Health and Jonsson Comprehensive Cancer Center, Los Angeles, California, USA, ^hDepartment of Rehabilitation, Vinmec Hospital Times City, Vinmec Healthcare System, ⁱVietnam Colorectal Cancer and Polyps Research Program, Vinmec Healthcare System, ^jDepartment of Surgical Oncology, Viet-Duc University Hospital, Hanoi, Vietnam, ^kMedical Informatics Center, Peking University, Peking, China, ^lDepartment of Computer Sciences and Engineering, University of Nevada-Reno, Reno, Nevada, ^mDepartment of Public Health Sciences, Tobacco Center of Regulatory Science, Pennsylvania State University College of Medicine, Hershey, Pennsylvania, USA, ⁿEpidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, Japan, ^oNikkei Disease Prevention Center, São Paulo, Brazil, ^pDepartment of Epidemiology and Prevention, Russian N.N. Blokhin Cancer Research Center, Moscow, Russia, ^qCIBER Epidemiología y Salud Pública (CIBERESP), Madrid, ^rISGlobal, ^sIMIM (Hospital del Mar Medical Research Institute), ^tUniversitat Pompeu Fabra (UPF), Barcelona, ^uEnvironmental and Cancer Epidemiology Unit, National Center of Epidemiology, Carlos III Health Institute, Madrid, Spain, ^vSection of Hygiene, University Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, ^wDepartment of Woman and Child Health and Public Health – Public Health Area, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italia, ^xDepartment of Medicine, Memorial Sloan Kettering Cancer Centre, New York, NY, USA, ^yDepartment of Public and Community Health, School of Health Sciences, University of West Attica, ^zDepartment of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens,

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(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 12477 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/m²), 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 (Lagiu *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 12477 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 2012)	160 (26.5)	444 (73.5)	Hospital	61.2±15.3	345 (57.1)	70 (11.6)	18 (3.0)	103 (17.0)	510 (23.4)	216 (9.9)	290 (13.3)	
Italy 4 (Buiatti <i>et al.</i> , 1989)	1016 (46.7)	1159 (53.3)	Population	63.3±9.7	1345 (61.8)	181 (8.3)	69 (3.2)	947 (43.5)	121 (11.4)	119 (11.2)	210 (19.8)	
Greece (Lagiu <i>et al.</i> , 2004)	110 (52.4)	100 (47.6)	Hospital	62.3±12.2	106 (50.5)	17 (8.1)	0	110 (52.4)	168 (4.3)	103 (2.6)	20 (0.5)	
Russia (Zaridze <i>et al.</i> , 2000)	450 (42.4)	611 (57.6)	Hospital	58.3±11.3	541 (51.0)	76 (7.2)	92 (8.7)	356 (33.5)	243 (28.4)	109 (12.7)	49 (5.7)	
Spain 1 (Castano-Vinyals <i>et al.</i> , 2015)	441 (11.4)	3440 (88.6)	Population	64.3±11.6	2182 (56.2)	610 (15.7)	95 (2.4)	346 (8.9)	128 (6.8)	32 (1.1)	294 (9.7)	
Spain 2 (Santibañez <i>et al.</i> , 2012)	401 (46.9)	455 (53.2)	Hospital	63.8±11.0	551 (64.4)	69 (8.1)	31 (3.6)	351 (41)	157 (21.5)	32 (1.1)	12 (4.5)	
Asia	864 (46.0)	1014 (54.0)		61.5±11.2	1229 (65.4)	45 (2.4)	21 (1.1)	128 (6.8)	112 (24.8)	73 (16.1)	0	
China (Setiawan <i>et al.</i> , 2005)	711 (50.0)	711 (50.0)	Population	62.6±11.5	906 (63.7)	19 (1.3)	0	906 (63.7)	45 (16.1)	36 (12.9)	0	
Japan (Machida-Montani <i>et al.</i> , 2004)	153 (33.5)	303 (66.5)	Hospital	57.8±9.4	323 (70.8)	26 (5.7)	21 (4.6)	128 (28.1)	1342 (7.4)	794 (4.4)	931 (5.2)	
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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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 <i>et al.</i> , 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)	12477 (69.1)		60.9±11.5	11182 (61.9)	1504 (8.3)	597 (3.3)	3791 (21.0)	1342 (7.4)	794 (4.4)	931 (5.2)	

^aData not available for the study or region.

^b42% of controls selected from the population but considered as hospital-controlled for the stratified analysis by control type; n: count.

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

	Cases (n=5592)	Controls (n=12477)
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)	44644 (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)
<i>H. Pylori</i> 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 ($P_{\text{heterogeneity}} = 0.04$). 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 ($P_{\text{heterogeneity}} = 0.48$), cancer histological type ($P_{\text{heterogeneity}} = 0.55$), age ($P_{\text{heterogeneity}} = 0.42$), sex ($P_{\text{heterogeneity}} = 0.37$), BMI ($P_{\text{heterogeneity}} = 0.49$), smoking status ($P_{\text{heterogeneity}} = 0.64$), alcohol consumption ($P_{\text{heterogeneity}} = 0.32$), fruit/vegetables intake frequency ($P_{\text{heterogeneity}} = 0.36$), geographical location ($P_{\text{heterogeneity}} = 0.43$), and source of controls ($P_{\text{heterogeneity}} = 0.09$). Moreover, these within strata effects were largely similar to that from the main analysis, and none was statistically significant.

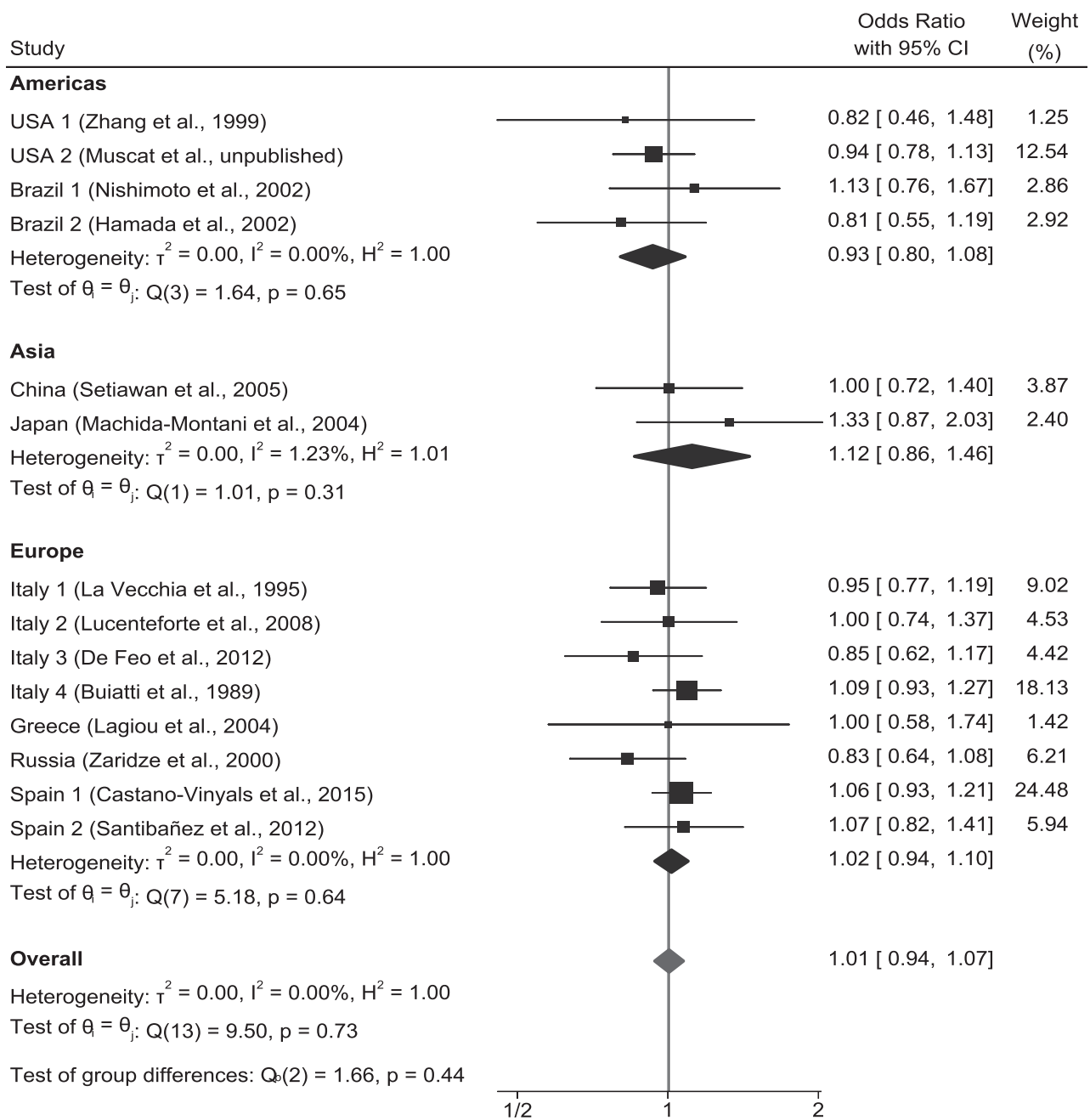
Sensitivity analysis

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 12477 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.

Fig. 1



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 gastroesophageal 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.

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Conflicts of interest

There are no conflicts of interest.

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