

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

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

**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* XXX: 000–000 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

European Journal of Cancer Prevention XXX, XXX:000–000

**Keywords:** diabetes, gastric cancer, risk factors

<sup>a</sup>College of Public Health, University of South Florida, Tampa, Florida, USA, <sup>b</sup>Department of Clinical Sciences and Community Health, University of Milan, Milan, <sup>c</sup>Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy, <sup>d</sup>Department of Information Systems and Decision Sciences (ISDS), Muma College of Business, University of South Florida, Tampa, Florida, USA, <sup>e</sup>Department of Biomedical and Clinical Sciences, University of Milan, Milan, <sup>f</sup>Cancer Risk Factors and Life-Style Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network, ISPRO, Florence, Italy, <sup>g</sup>Department of Epidemiology, UCLA Fielding School of Public Health and Jonsson Comprehensive Cancer Center, Los Angeles, California, USA, <sup>h</sup>Department of Rehabilitation, Vinmec Hospital Times City, Vinmec Healthcare System, <sup>i</sup>Vietnam Colorectal Cancer and Polyps Research Program, Vinmec Healthcare System, <sup>j</sup>Department of Surgical Oncology, Viet-Duc University Hospital, Hanoi, Vietnam, <sup>k</sup>Medical Informatics Center, Peking University, Peking, China, <sup>l</sup>Department of Computer Sciences and Engineering, University of Nevada-Reno, Reno, Nevada, <sup>m</sup>Department of Public Health Sciences, Tobacco Center of Regulatory Science, Pennsylvania State University College of Medicine, Hershey, Pennsylvania, USA, <sup>n</sup>Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, Japan, <sup>o</sup>Nikkei Disease Prevention Center, São Paulo, Brazil, <sup>p</sup>Department of Epidemiology and Prevention, Russian N.N. Blokhin Cancer Research Center, Moscow, Russia, <sup>q</sup>CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, <sup>r</sup>ISGlobal, <sup>s</sup>MIM (Hospital del Mar Medical Research Institute), <sup>t</sup>Universitat Pompeu Fabra (UPF), Barcelona, <sup>u</sup>Environmental and Cancer Epidemiology Unit, National Center of Epidemiology, Carlos III Health Institute, Madrid, Spain, <sup>v</sup>Section of Hygiene, University Department of Life Sciences and Public Health, Università Cattolica del Sacro Cuore, <sup>w</sup>Department of Woman and Child Health and Public Health – Public Health Area, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italia, <sup>x</sup>Department of Medicine, Memorial Sloan Kettering Cancer Centre, New York, NY, USA, <sup>y</sup>Department of Public and Community Health, School of Health Sciences, University of West Attica, <sup>z</sup>Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens,

This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Athens, Greece, <sup>aa</sup>Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA, <sup>bb</sup>Department of Public Health, Miguel Hernandez University, FISABIO-ISABIAL, Campus San Juan, Alicante, Spain, <sup>cc</sup>Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, USA, <sup>dd</sup>Centro Internacional de Pesquisa, A. C. Camargo Cancer Center, São Paulo, Brazil, <sup>ee</sup>Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina da Universidade do Porto, Al. Prof. Hernâni Monteiro, <sup>ff</sup>EPIUnit – Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas, Porto, Portugal, <sup>gg</sup>Stony Brook Cancer Center, Stony Brook University, New York, New York, USA, <sup>hh</sup>Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy, <sup>ii</sup>UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh and <sup>jj</sup>Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Correspondence to Hung N. Luu, MD, PhD, Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, UPMC Hillman Cancer Center, UPMC Cancer Pavilion, Suite 4C, Room 466, 5150 Centre Avenue, Pittsburgh, PA 15232, USA

Tel: +1 412-623-3386; e-mail: luuh@upmc.edu

\*Bashir Dabo, Claudio Pelucchi, Matteo Rota, Paolo Boffetta, Eva Negr, Carlo La Vecchia, and Hung N. Luu contributed equally to the writing of this article.

Received 18 April 2021 Accepted 23 April 2021

## 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 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  $\geq 30 \text{ kg/m}^2$ ), 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  $\geq 25$ ), 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 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)	1134 (9.1)	653 (5.3)	637 (5.1)	
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)	33 (4.2)	57 (7.3)	64 (8.2)	
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)	59 (9.8)	49 (8.1)	4 (0.9)	
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)	510 (23.4)	216 (9.9)	290 (13.3)	
Greece (Lagiou <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)	121 (11.4)	119 (11.2)	210 (19.8)	
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)	168 (4.3)	103 (2.6)	20 (0.5)	
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)	243 (28.4)	109 (12.7)	49 (5.7)	
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)	109 (12.7)	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)	1134 (9.1)	653 (5.3)	637 (5.1)	
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	128 (6.8)	1134 (9.1)	653 (5.3)	637 (5.1)	
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)	1134 (9.1)	653 (5.3)	637 (5.1)	
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 <sup>b</sup>	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)	

<sup>a</sup>Data not available for the study or region.

<sup>b</sup>4.2% 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)
<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 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		OR (95% CI) <sup>a</sup>	<i>P</i> <sub>between-study</sub>	<i>P</i> <sub>interaction</sub>
	No	Yes			
	Case/control	Case/control			
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 <sup>2</sup> ) <sup>b</sup>					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 <sup>c</sup>					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 <sup>d</sup>					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	
<i>H. pylori</i> serostatus <sup>e</sup>					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 <sup>f</sup>					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 <sup>g</sup>					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.

<sup>a</sup>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).

<sup>b</sup>Variable was not available for Brazil 1, Brazil 2, Italy 3, and USA 2 studies.

<sup>c</sup>Variable was not available for China, Italy 3, Russia, and Spain 1 studies.

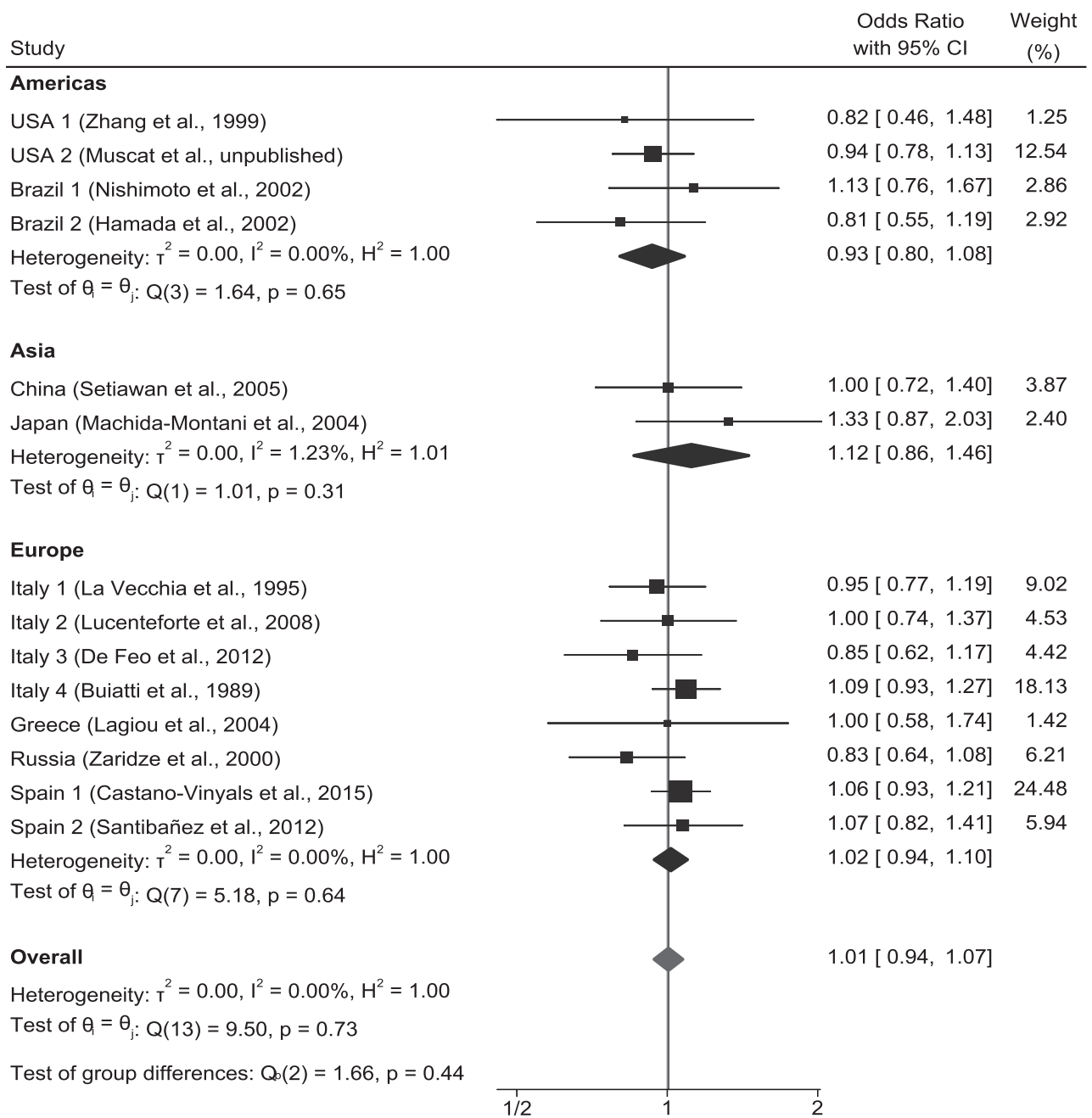
<sup>d</sup>Variable was not available/not usable for USA 2, Brazil 1, and Brazil 2 studies.

<sup>e</sup>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.

<sup>f</sup>Variable was not available/not usable for Brazil 2, China, and Greece studies.

<sup>g</sup>Studies considered: Italy 2, Italy 3, Italy 4, Russia, Spain 1, Spain 2, and USA 1.

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.

## Acknowledgements

This work was supported by Associazione Italiana per la Ricerca sul Cancro (AIRC), Project no. 21378 (Investigator Grant); Fondazione Italiana per la Ricerca sul Cancro (FIRC); Italian League for the Fight Against Cancer (LILT); European Cancer Prevention (ECP) Organization; and University of Pittsburgh Medical Center (UPMC) Start-up Grant (to H.N.L.).

## Conflicts of interest

There are no conflicts of interest.

## References

- Bajaj S, Prasad S, Gupta A, Singh VB (2012). Oral manifestations in type-2 diabetes and related complications. *Indian J Endocrinol Metab* **16**:777–779.
- Biranjia-Hurdoyal SD, Seetulsingh-Goorah SP (2016). Performances of four *Helicobacter pylori* serological detection kits using stool antigen test as gold standard. *PLoS One* **11**:e0163834.
- Buiatti E, Palli D, Decarli A, Amadori D, Avellini C, Bianchi S, *et al.* (1989). A case-control study of gastric cancer and diet in Italy. *Int J Cancer* **44**:611–616.
- Burke DL, Ensor J, Riley RD (2017). Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med* **36**:855–875.
- Castañó-Vinyals G, Aragonés N, Pérez-Gómez B, Martín V, Llorca J, Moreno V, *et al*; MCC-Spain Study Group. (2015). Population-based multicase-control study in common tumors in Spain (MCC-Spain): rationale and study design. *Gac Sanit* **29**:308–315.
- Cheung KS, Chan EW, Chen L, Seto WK, Wong ICK, Leung WK (2019). Diabetes increases risk of gastric cancer after *Helicobacter pylori* eradication: a territory-wide study with propensity score analysis. *Diabetes Care* **42**:1769–1775.
- Cheung KS, Chan EW, Wong AYS, Chen L, Wong ICK, Leung WK (2018). Long-term proton pump inhibitors and risk of gastric cancer development after treatment for *Helicobacter pylori*: a population-based study. *Gut* **67**:28–35.
- Currie CJ, Poole CD, Gale EA (2009). The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. *Diabetologia* **52**:1766–1777.
- Dandona P, Thusu K, Cook S, Snyder B, Makowski J, Armstrong D, Nicotera T (1996). Oxidative damage to DNA in diabetes mellitus. *Lancet* **347**:444–445.
- De Feo E, Simone B, Persiani R, Cananzi F, Biondi A, Arzani D, *et al.* (2012). A case-control study on the effect of apolipoprotein E genotypes on gastric cancer risk and progression. *BMC Cancer* **12**:494.
- DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. *Control Clin Trials* **7**:177–188.
- El-Serag HB, Hampel H, Javadi F (2006). The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. *Clin Gastroenterol Hepatol* **4**:369–380.
- Espelt A, Goday A, Franch J, Borrell C (2012). Validity of self-reported diabetes in health interview surveys for measuring social inequalities in the prevalence of diabetes. *J Epidemiol Community Health* **66**:e15.
- Friberg E, Orsini N, Mantzoros CS, Wolk A (2007). Diabetes mellitus and risk of endometrial cancer: a meta-analysis. *Diabetologia* **50**:1365–1374.
- Ge Z, Ben Q, Qian J, Wang Y, Li, Y (2011). Diabetes mellitus and risk of gastric cancer: a systematic review and meta-analysis of observational studies. *Eur J Gastroenterol Hepatol* **23**:1127–1135.
- Goto A, Morita A, Goto M, Sasaki S, Miyachi M, Aiba N, *et al*; Saku Cohort Study Group. (2013). Validity of diabetes self-reports in the Saku diabetes study. *J Epidemiol* **23**:295–300.
- Hamada GS, Kowalski LP, Nishimoto IN, Rodrigues JJ, Iriya K, Sasazuki S, *et al*; São Paulo–Japan Cancer Project Gastric Cancer Study Group. (2002). Risk factors for stomach cancer in Brazil (II): a case-control study among Japanese Brazilians in São Paulo. *Jpn J Clin Oncol* **32**:284–290.
- Huxley R, Ansary-Moghaddam A, Berrington de González A, Barzi F, Woodward M (2005). Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer* **92**:2076–2083.
- Ikeda F, Doi Y, Yonemoto K, Ninomiya T, Kubo M, Shikata K, *et al.* (2009). Hyperglycemia increases risk of gastric cancer posed by *Helicobacter pylori* infection: a population-based cohort study. *Gastroenterology* **136**:1234–1241.
- International Agency for Research on Cancer (IARC) (1994). Infection with *Helicobacter pylori*. In: *IARC monographs on the Evaluation of Carcinogenic Risks to Humans. Schisto-somiasis, Liver Flukes and Helicobacter pylori*. IARC, Lyon: France **61**:177–241.
- Jun JK, Gwack J, Park SK, Choi YH, Kim Y, Shin A, *et al.* (2006). Fasting serum glucose level and gastric cancer risk in a nested case-control study. *J Prev Med Public Health* **39**:493–498.
- Kabir UY, Askew A, Jiang Y, Bhuyan SS, Ezekekwe E, Dobalian A (2020). Moderate psychological distress as a barrier to breast cancer screening among women. *J Hosp Adm* **9**.
- Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F (2014). Gastric cancer: descriptive epidemiology, risk factors, screening, and prevention. *Cancer Epidemiol Biomarkers Prev* **23**:700–713.

- Kim TJ, Lee H, Min YW, Min BH, Lee JH, Son HJ, *et al.* (2016). Diabetic biomarkers and the risk of proximal or distal gastric cancer. *J Gastroenterol Hepatol* **31**:1705–1710.
- Lagiou P, Samoli E, Lagiou A, Peterson J, Tzonou A, Dwyer J, Trichopoulos D (2004). Flavonoids, vitamin C and adenocarcinoma of the stomach. *Cancer Causes Control* **15**:67–72.
- Larsson SC, Orsini N, Wolk A (2005). Diabetes mellitus and risk of colorectal cancer: a meta-analysis. *J Natl Cancer Inst* **97**:1679–1687.
- Li P, Zhang C, Gao P, Chen X, Ma B, Yu D, *et al.* (2018). Metformin use and its effect on gastric cancer in patients with type 2 diabetes: a systematic review of observational studies. *Oncol Lett* **15**:1191–1199.
- Liao S, Li J, Wei W, Wang L, Zhang Y, Li J, *et al.* (2011). Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. *Asian Pac J Cancer Prev* **12**:1061–1065.
- Lin SW, Freedman ND, Hollenbeck AR, Schatzkin A, Abnet CC (2011). Prospective study of self-reported diabetes and risk of upper gastrointestinal cancers. *Cancer Epidemiol Biomarkers Prev* **20**:954–961.
- Liu Y, De A (2015). Multiple imputation by fully conditional specification for dealing with missing data in a large epidemiologic study. *Int J Stat Med Res* **4**:287–295.
- Lorenzi M, Montisano DF, Toledo S, Barrieux A (1986). High glucose induces DNA damage in cultured human endothelial cells. *J Clin Invest* **77**:322–325.
- Lucenteforte E, Scita V, Bosetti C, Bertuccio P, Negri E, La Vecchia C (2008). Food groups and alcoholic beverages and the risk of stomach cancer: a case-control study in Italy. *Nutr Cancer* **60**:577–584.
- Machida-Montani A, Sasazuki S, Inoue M, Natsukawa S, Shaura K, Koizumi Y, *et al.* (2004). Association of *Helicobacter pylori* infection and environmental factors in non-cardia gastric cancer in Japan. *Gastric Cancer* **7**:46–53.
- Marimuthu SP, Vijayaragavan P, Moysich KB, Jayaprakash V (2011). Diabetes mellitus and gastric carcinoma: is there an association? *J Carcinog* **10**:30.
- Miao ZF, Xu H, Xu YY, Wang ZN, Zhao TT, Song YX, Xu HM (2017). Diabetes mellitus and the risk of gastric cancer: a meta-analysis of cohort studies. *Oncotarget* **8**:44881–44892.
- Nishimoto IN, Hamada GS, Kowalski LP, Rodrigues JG, Iriya K, Sasazuki S, *et al*; São Paulo–Japan Cancer Project Gastric Cancer Study Group. (2002). Risk factors for stomach cancer in Brazil (I): a case-control study among non-Japanese Brazilians in São Paulo. *Jpn J Clin Oncol* **32**:277–283.
- Peleteiro B, La Vecchia C, Lunet N (2012). The role of *Helicobacter pylori* infection in the web of gastric cancer causation. *Eur J Cancer Prev* **21**:118–125.
- Peleteiro B, Lopes C, Figueiredo C, Lunet N (2011). Salt intake and gastric cancer risk according to *Helicobacter pylori* infection, smoking, tumour site and histological type. *Br J Cancer* **104**:198–207.
- Pelucchi C, Lunet N, Boccia S, Zhang ZF, Praud D, Boffetta P, *et al.* (2015). The Stomach Cancer Pooling (StoP) Project: study design and presentation. *Eur J Cancer Prev* **24**:16–23.
- Pollak M (2012). The insulin and insulin-like growth factor receptor family in neoplasia: an update. *Nat Rev Cancer* **12**:159–169.
- Rawla P, Barsouk A (2019). Epidemiology of gastric cancer: global trends, risk factors and prevention. *Prz Gastroenterol* **14**:26–38.
- Rubin DB. *Multiple imputation for nonresponse in surveys*, Vol 81 Hoboken: John Wiley & Sons, 2004.
- Santibañez M, Alguacil J, de la Hera MG, Navarrete-Muñoz EM, Llorca J, Aragonés N, *et al*; PANESOES Study Group. (2012). Occupational exposures and risk of stomach cancer by histological type. *Occup Environ Med* **69**:268–275.
- Schneider AL, Pankow JS, Heiss G, Selvin E (2012). Validity and reliability of self-reported diabetes in the Atherosclerosis Risk in Communities Study. *Am J Epidemiol* **176**:738–743.
- Setiawan VW, Yu GP, Lu QY, Lu ML, Yu SZ, Mu L, *et al.* (2005). Allium vegetables and stomach cancer risk in China. *Asian Pac J Cancer Prev* **6**:387–395.
- Singh PP, Singh S (2013). Statins are associated with reduced risk of gastric cancer: a systematic review and meta-analysis. *Ann Oncol* **24**:1721–1730.
- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al.* (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* **71**:209–249.
- Tian T, Zhang LQ, Ma XH, Zhou JN, Shen J (2012). Diabetes mellitus and incidence and mortality of gastric cancer: a meta-analysis. *Exp Clin Endocrinol Diabetes* **120**:217–223.
- Tseng CH, Tseng FH (2014). Diabetes and gastric cancer: the potential links. *World J Gastroenterol* **20**:1701–1711.
- La Vecchia C, D'Avanzo B, Negri E, Decarli A, Benichou J (1995). Attributable risks for stomach cancer in northern Italy. *Int J Cancer* **60**:748–752.
- Vigneri P, Frasca F, Sciacca L, Pandini G, Vigneri R (2009). Diabetes and cancer. *Endocr Relat Cancer* **16**:1103–1123.
- Wells GA, Shea B, O'Connell DA, Peterson J, Welch V, Losos M, *et al.* (2011). The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analyses. *Ottawa Hospital Research Institute* [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). Accessed March 15, 2020.
- Wieser V, Moschen AR, Tilg H (2013). Inflammation, cytokines and insulin resistance: a clinical perspective. *Arch Immunol Ther Exp (Warsz)* **61**:119–125.
- Ye X, Fu J, Yang Y, Gao Y, Liu L, Chen S (2013). Frequency-risk and duration-risk relationships between aspirin use and gastric cancer: a systematic review and meta-analysis. *PLoS One* **8**.
- Yoon JM, Son KY, Eom CS, Durrance D, Park SM (2013). Pre-existing diabetes mellitus increases the risk of gastric cancer: a meta-analysis. *World J Gastroenterol* **19**:936–945.
- Yuan X, Liu T, Wu L, Zou ZY, Li C (2015). Validity of self-reported diabetes among middle-aged and older Chinese adults: the china health and retirement longitudinal study. *BMJ Open* **5**:e006633.
- Zaridze D, Borisova E, Maximovitch D, Chkhikvadze V (2000). Alcohol consumption, smoking and risk of gastric cancer: case-control study from Moscow, Russia. *Cancer Causes Control* **11**:363–371.
- Zhang ZF, Kurtz RC, Klimstra DS, Yu GP, Sun M, Harlap S, Marshall JR (1999). *Helicobacter pylori* infection on the risk of stomach cancer and chronic atrophic gastritis. *Cancer Detect Prev* **23**:357–367.
- Zheng J, Rutegård M, Santoni G, Wallner B, Johansson I, Sund M, *et al.* (2019). Prediabetes and diabetes in relation to risk of gastric adenocarcinoma. *Br J Cancer* **120**:1147–1152.