Tobacco smoking and gastric cancer: meta-analyses of published data versus pooled analyses of individual participant data (StoP Project)

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Tobacco smoking is one of the main risk factors for gastric cancer, but the magnitude of the association estimated by conventional systematic reviews and meta-analyses might be inaccurate, due to heterogeneous reporting of data and publication bias. We aimed to quantify the combined impact of publication-related biases, and heterogeneity in data analysis or presentation, in the summary estimates obtained from conventional meta-analyses. We compared results from individual participant data pooled-analyses, including the studies in the Stomach Cancer Pooling (StoP) Project, with conventional meta-analyses carried out using only data available in previously published reports from the same studies. From the 23 studies in the StoP Project, 20 had published reports with information on smoking and gastric cancer, but only six had specific data for gastric cardia cancer and seven had data on the daily number of cigarettes smoked. Compared to the results obtained with the StoP database, conventional meta-analyses overvalued the relation between ever smoking (summary odds ratios ranging from 7% higher for all studies to 22% higher for the risk of gastric cardia cancer) and yielded less precise summary estimates (SE ≤ 2.4 times higher). Additionally, funnel plot asymmetry and corresponding hypotheses tests were suggestive of publication bias. Conventional meta-analyses and individual participant data pooled-analyses reached similar conclusions on the direction of the association between smoking and gastric cancer. However, published data tended to overestimate the magnitude of the effects, possibly due to publication biases and limited the analyses by different levels of exposure or cancer subtypes. ***European Journal of Cancer Prevention*** **27:197–204 Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

Systematic reviews of the literature and meta-analyses of the results are central elements of evidence-based practice in medicine and public health, by their potential to yield unbiased summary estimates of different types of effect measures (Egger *et al.*, 2001). However, the validity of findings from conventional meta-analyses is threatened by publication-related biases (Sterne *et al.*, 2000), as well as by inconsistencies across studies regarding the strategies of data analyses and presentation of results (Friedenreich, 1993; Blettner *et al.*, 1999).

Pooled analyses on the basis of individual participant data have been considered the gold standard among the strategies presented to overcome some of the limitations of systematic reviews of published reports (Blettner *et al.*, 1999; Simmonds *et al.*, 2015). In comparison with meta-analyses of published data, pooled analyses of individual participant data allow for access to results not previously published, as well as statistical re-analyses based on more homogeneous definitions of the variables and control of confounding (Riley *et al.*, 2007; Vale *et al.*, 2015; Tudur Smith *et al.*, 2016).

The Stomach Cancer Pooling (StoP) Project (Pelucchi *et al.*, 2015) aims for a better understanding of the etiology of gastric cancer through pooled analyses of individual participant data from more than 14 000 cases and 26 000 controls from studies carried out in 14 countries. The first report from this consortium addressed the relation between smoking and gastric cancer (Praud *et al.*, 2016); it included several studies not considered in previous meta-analyses and yielded more robust estimates on dose–response relationships and stratified analyses by cancer subtype.

In the present study, we aim to quantify the combined impact of publication-related biases and heterogeneity in data analyses or presentation in the summary estimates obtained from conventional meta-analyses. This will be accomplished by a comparison of individual participant data pooled analysis of the studies included in the StoP Project with a conventional meta-analysis carried out using only data available in previously published reports from the same studies.

Patients and methods

Individual participant data meta-analysis

The StoP Project is a consortium of case–control studies (including nested case–control within cohort studies) with at least 80 incident, histologically confirmed, gastric cancer cases (including both gastric cardia and noncardia locations) (Pelucchi *et al.*, 2015).

The first release of the StoP Project dataset included 23 case–control studies, comprising 10 290 (6804 men, 3486 women) cases and 26 145 (15 600 men, 10 545 women) controls from Greece (Lagiou *et al.*, 2004), Italy (four studies) (Buiatti *et al.*, 1989; La Vecchia *et al.*, 1995; Lucenteforte *et al.*, 2008; De Feo *et al.*, 2012), Portugal (Lunet *et al.*, 2007), Russia (Zaridze *et al.*, 1999), Spain (two studies) (Santibanez *et al.*, 2012; Castano-Vinyals *et al.*, 2015), Sweden (three studies, two of which were nested in cohort studies) (Ye *et al.*, 1999; Harris *et al.*, 2013), China (four studies) (Setiawan *et al.*, 2000; Mu *et al.*, 2005; Setiawan *et al.*, 2005; Deandrea *et al.*, 2010), Iran (three studies) (Derakhshan *et al.*, 2008; Pourfarzi *et al.*, 2009; Pakseresht *et al.*, 2011), Japan (Matsuo *et al.*, 2013), Canada (Mao *et al.*, 2002), and the USA (two studies, one of them unpublished; Zhang *et al.*, 1999; Muscat J. *et al.*).

Estimates of the association between cigarette smoking and gastric cancer were calculated using a two-stage modeling approach (Praud *et al.*, 2016). Briefly, in the first stage, the association between smoking and gastric cancer for each study was assessed through multivariable logistic regression models that included, whenever available, terms for age, sex, education/social class, alcohol drinking, fruit and vegetable consumption, study center (for multicenter studies), as well as terms for the matching variables, when applicable. In the second stage, the pooled effects estimates were computed using a random-effect model using the DerSimonian and Laird (2015) method. This was performed for the comparison of the following levels of exposure: (a) ever smokers versus never smokers; (b) current smokers versus never smokers; (c) former smokers versus never smokers; (d) current smokers of less than 10 cigarettes per day versus never smokers; (e) current smokers of between 10 and 20 cigarettes per day versus never smokers; and (f) current smokers of over 20 cigarettes per day versus never smokers.

Heterogeneity was quantified using the I^2 statistic (Higgins and Thompson, 2002).

Meta-analysis of published data

Search strategy

The strategy to identify all published reports of the studies included in the first release of the StoP Project dataset is shown in Supplementary Fig. 1 (Supplemental digital content 1, *http://links.lww.com/EJCP/A177*). We searched PubMed, from inception to the 31 December 2016, and performed forward citation tracking of the reference provided in the StoP Project presentation paper to identify each study, through Google Scholar and Web of Science TM. The responsible investigators for each study were then asked to confirm if all reports had been included and no additional articles were identified.

Data extraction and meta-analysis

The following data were extracted from the original reports: first author, publication year, country, geographic area, number of cases and controls, period of data collection, and odds ratio (OR) for the association between smoking and gastric cancer along with the corresponding confidence intervals. Preference was given to estimates

adjusted for the largest number of confounders, although crude estimates or data to compute them could also be extracted when these were the only available.

The levels of exposure considered were never smokers; former smokers (described in the original reports as 'former smokers' or 'ex-smokers'); and current smokers ('current smokers' or 'smoking more than one cigarette/day, or smoking pipe or cigars').

Data were also extracted according to cancer location within the stomach. For the purpose of analyses, results referring to 'cardia', 'upper third', or 'proximal' stomach cancers were considered equivalent to cancer of the gastric cardia, and 'distal', 'noncardia', or 'all others' as equivalent to cancers not located in the cardia.

Data on specific estimates for different levels of exposure among current smokers, defined based on the number of cigarettes smoked per day, were extracted whenever available. To identify categories of current cigarette consumption corresponding to the exposure closest to less than 10 cigarettes, 10–20 cigarettes, and more than 20 cigarettes per day, we assumed that each category corresponded to an exposure equal to the midpoint of the respective category range and the open-ended categories had the amplitude of the preceding stratum (e.g. for surveys reporting ≤ 14, 14–25, and ≥ 25 cigarettes smoked per day, 7 and 30.5 were the midpoints assigned to the lowest and the highest category, respectively).

For the Italy 1 and Italy 4 studies, data were collected from more than one report providing complementary information. For the China 1 and Italy 1 studies, we selected the reports providing data for the largest sample.

Two investigators (A.F. and S.M.) evaluated independently the selected reports to extract data and differences were discussed until consensus.

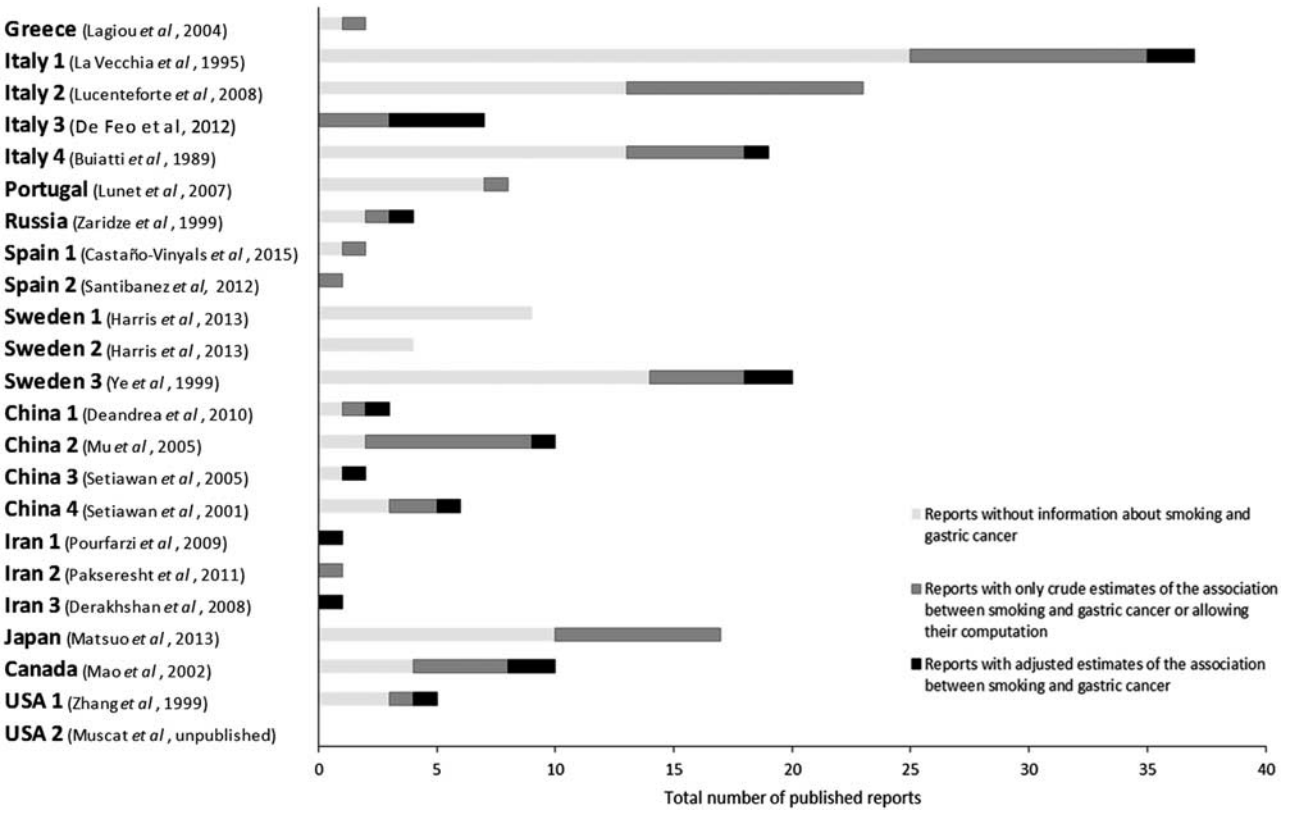
Meta-analyses were carried out to match as closely as possible the analyses described for the individual participant data pooled analyses. The DerSimonian and Laird (2015) method was used to pool the estimates extracted from each study.

Heterogeneity was quantified using the I^2 statistic (Higgins and Thompson, 2002).

Comparison between meta-analyses of published data and of individual participant data

The meta-analyses of published data and individual participant data described previously were compared in

Fig. 1



Studies participating in the Stomach Cancer Pooling (StoP) Project and the corresponding number of published reports and number of reports with information on tobacco smoking and gastric cancer.

Table 1 Comparison between meta-analyses performed with data from the published reports of the Stomach Cancer Pooling (Stop) Project studies and the individual participant data pooled analyses regarding the number of studies, summary estimates, and corresponding precision and heterogeneity

	Meta-analysis of published data				Pooled analysis of individual participant data (StoP)				Ratio MA/StoP			
Smoking category	Number of studies (*N*)	OR (95% CI)	SE	I^2 (%)	Number of studies (*N*)	OR (95% CI)	SE	I^2 (%)	Number of studies	OR	SE	I^2
Ever vs. never												
All estimates*	20	1.28 (1.17–1.41)	0.05	45.8	23	1.20 (1.09–1.32)	0.05	48.4	0.87	1.07	1.00	0.95
Crude estimates	9[a]	1.25 (1.10–1.43)	0.07	44.6								
Adjusted estimates	11[b]	1.33 (1.14–1.53)	0.08	51.3								
Cardia												
All Estimates (adjusted)	6[c]	1.56 (1.18–2.08)	0.14	35.3	17[d]	1.40 (1.16–1.70)	0.10	27.4	0.35	1.11	1.40	1.29
Noncardia												
All estimates (adjusted)	5[e]	1.43 (1.02–2.00)	0.17	80.6	21[f]	1.17 (1.03–1.33)	0.07	46.0	0.24	1.22	2.43	1.75
Smokers of <10 cigarettes/day vs. never												
All Estimates*	6	1.16 (0.92–1.46)	0.12	49.2	21[g]	1.08 (0.91–1.28)	0.09	45.1	0.29	1.07	1.33	1.09
Crude estimates	1[h]	1.39 (0.81–2.37)	0.27	NA								
Adjusted estimates	5[i]	1.13 (0.87–1.47)	0.13	57.0								
Smokers of 10–20 cigarettes/day vs. never												
All estimates (adjusted)	7[j]	1.30 (0.98–1.73)	0.14	70.4	21[g]	1.30 (1.16–1.45)	0.06	18.8	0.33	1.00	2.30	3.74
Smokers of > 20 cigarettes/day vs. never												
All estimates*	7	1.38 (0.97–1.95)	0.18	72.9	20[k]	1.31 (1.09–1.58)	0.09	46.5	0.35	1.05	2.00	1.57
Crude estimates	1[h]	1.30 (0.81–2.09)	0.24	NA								
Adjusted estimates	6[l]	1.39 (0.92–2.11)	0.21	77.3								
Former vs. never												
All estimates*	11	1.09 (1.00–1.19)	0.04	0.0	21[g]	1.14 (0.99–1.31)	0.07	51.3	0.52	0.96	0.57	0.00
Crude estimates	6[m]	1.08 (0.96–1.21)	0.06	0.0								
Adjusted estimates	5[n]	1.13 (0.94–1.34)	0.09	28.4								
Current vs. never												
All estimates*	11	1.30 (1.11–1.53)	0.08	62.3	21[g]	1.26 (1.12–1.41)	0.06	36.7	0.52	1.03	1.33	1.70
Crude estimates	6[m]	1.33 (1.18–1.51)	0.06	0.0								
Adjusted estimates	5[n]	1.25 (0.85–1.83)	0.20	82.2								

CI, confidence interval; MA, meta-analysis; NA, not available; OR, odds ratio; StoP, Stomach Cancer Pooling.
*Computed from pooling crude and adjusted estimates.
[a]Corresponding to China 1, China 4, Greece, Iran 2, Italy 2, Japan, Portugal, Spain 1 and Spain 2 studies providing crude estimates or the necessary information to compute them.
[b]Corresponding to Canada, China 2, China 3, Iran 1, Iran 3, Italy 1, Italy 3, Italy 4, Russia, Sweden 3 and the USA 1 studies providing estimates adjusted for the highest number of confounders.
[c]Corresponding to Canada, Iran 3, Italy 4, Russia, Sweden 3 and the USA 1 studies.
[d]Corresponding to StoP Project studies except Greece, China 1, China 2, China 3, China 4 and Sweden 1.
[e]Corresponding to Canada, Iran 3, Italy 4, Sweden 3 and the USA 1 studies.
[f]Corresponding to StoP Project studies except China 3 and Sweden 1.
[g]Corresponding to StoP Project studies except China 4 and Iran 3.
[h]Corresponding to Italy 2 study.
[i]Corresponding to Canada, China 3, Italy 1, Russia and Sweden 3 studies.
[j]Corresponding to Canada, China 3, Iran 1, Italy 1, Russia, Sweden 3 and the USA 1 studies.
[k]Corresponding to StoP Project studies except China 4, Iran 3 and Sweden 1.
[l]Corresponding to Canada, China 3, Iran 1, Russia, Sweden 3 and the USA 1 studies.
[m]Corresponding to China 1, Iran 2, Italy 1, Italy 2, Spain 1 and Spain 2 studies.
[n]Corresponding to Canada, Iran 1, Italy 4, Russia and Sweden 3 studies.

terms of the number of studies included, the estimates obtained and corresponding precision, as well as heterogeneity of results. For each of these items, the ratios of the values obtained in conventional and individual participant data meta-analyses (ratio MA/StoP) were computed, assuming the latter as the reference.

Funnel plots and Egger's regression asymmetry test were used for the assessment of publication bias (Sterne *et al.*, 2000).

All statistical analyses were carried out using STATA statistical software package version 11.2 (StataCorp., College Station, Texas, USA)

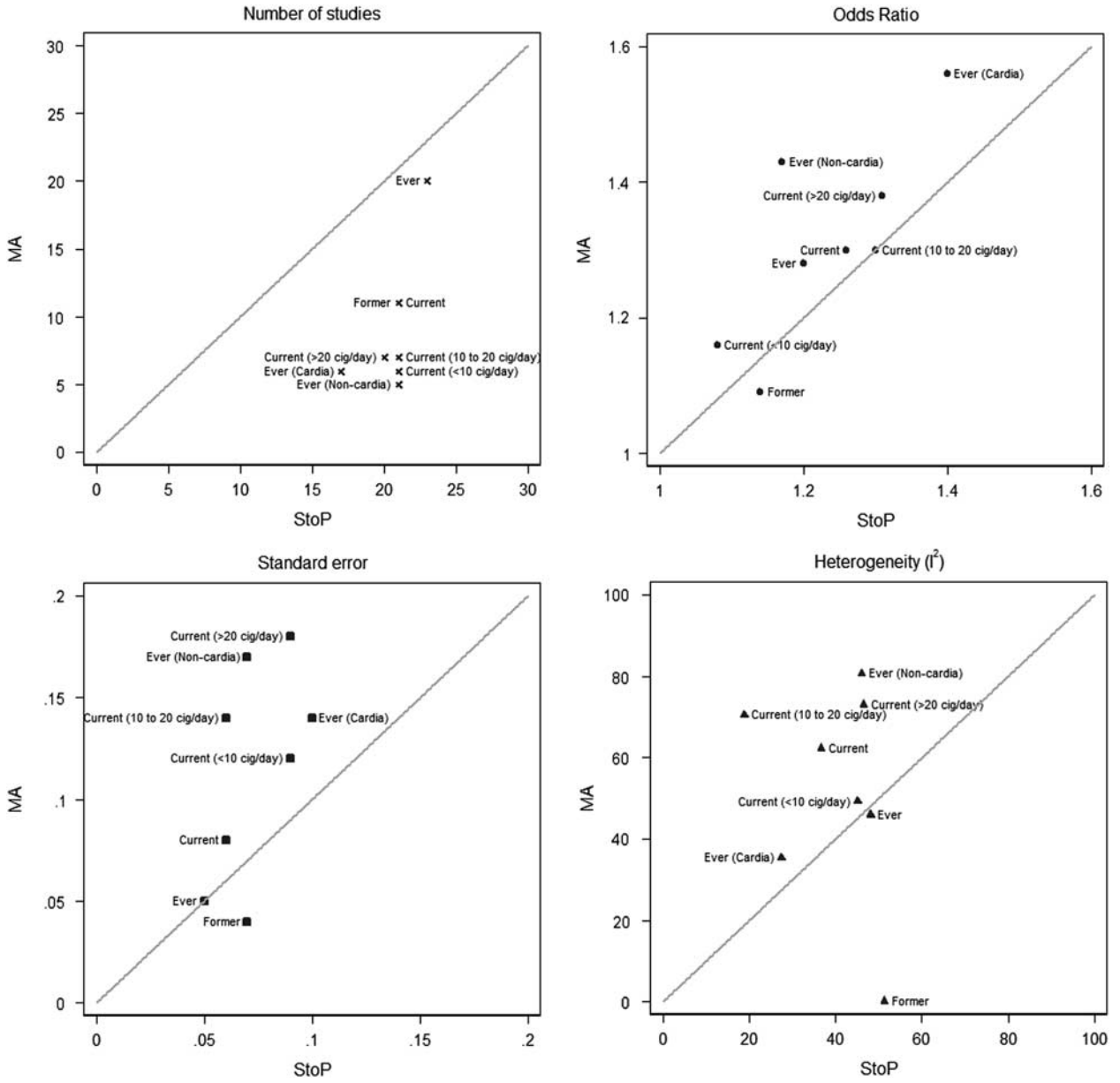
Results

Meta-analysis of published data

A total of 192 reports from the 23 studies participating in the first release of the StoP Project dataset were identified in the systematic literature search: two from Greece, 6 from Italy, eight from Portugal, four from Russia, four from Spain, 29 from Sweden, 22 from China, three from Iran, 18 from Japan, 10 from Canada, and six from the USA (Fig. 1).

The analyses were carried out using information extracted from 25 reports, providing data for 20 of the 23

Fig. 2

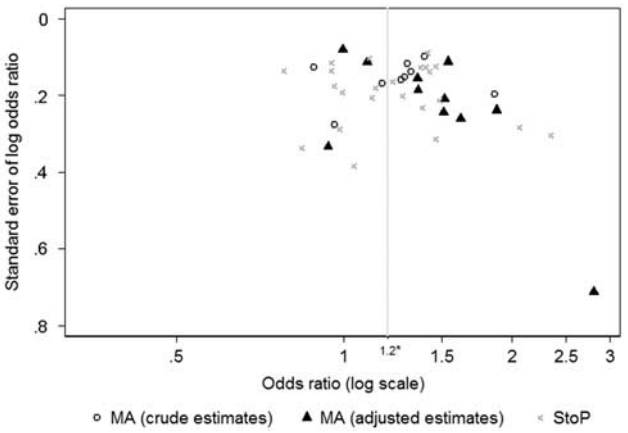


Funnel plot of the Stomach Cancer Pooling (StoP) Project studies evaluating the risk of gastric cancer for ever versus never smokers, considering one estimate per study, using published data and using individual participant data from the StoP Project database. *Summary odds ratio estimate obtained from the pooled analysis of individual participant data (StoP) Egger's regression asymmetry test: MA (crude estimates), $P = 0.876$; MA (adjusted estimates), $P = 0.047$; StoP, $P = 0.807$. MA, meta-analysis of published data; StoP, Individual participant data pooled analysis.

original studies from StoP. Three studies (USA 2, and Sweden 1 and 2) had no published data on the relation between smoking and gastric cancer. The reports from seven studies (Greece, Iran 2, Italy 2, Japan, Portugal, and Spain 1 and 2) provided only crude estimates of the association between smoking and gastric cancer or the necessary information to compute them (Fig. 1). A detailed description of each study and of the corresponding results included in the conventional meta-analysis is provided in Supplementary Table 1 (Supplemental digital content 1, *http://links.lww.com/EJCP/A177*) and the corresponding summary OR estimates for the comparison of ever versus never smokers are presented in Supplementary Table 2 (Supplemental digital content 1, *http://links.lww.com/EJCP/A177*).

Table 1 and Fig. 2 show the comparison between conventional meta-analyses and individual participant data pooled analyses. Both methods reached similar conclusions on the direction of the association, but the estimates obtained with conventional meta-analyses tended to be

Fig. 3



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*Summary odds ratio estimate obtained from the pooled analysis of individual participant data (StoP) Egger's regression asymmetry test: MA (crude estimates), P= 0.876; MA (adjusted estimates), P=0.047; StoP, P=0.807. MA, meta-analysis of published data; StoP, Individual participant data pooled analysis.

higher, less precise, and to present more heterogeneity than the ones calculated using individual participant data.

Data on the comparison between ever and never smokers were available for a larger number of studies (20 out of 23). The summary OR obtained with published data was 7% higher than the one obtained with the StoP data (1.28 vs. 1.20), with a similar SE (ratio MA/StoP = 1.00) and a slightly lower heterogeneity (ratio MA/StoP = 0.95). Among the published reports, there were adjusted OR estimates for 11 studies; the corresponding summary estimates were also higher than those obtained using the StoP data from the same studies (1.33 vs. 1.27).

For specific cancer locations and levels of exposure, the differences between meta-analyses were particularly noticeable. For gastric cardia and noncardia cancers, the ratios MA/StoP were 0.35 and 0.24, respectively, for the number of studies, and the summary OR estimates were 11 and 22% higher, respectively, than the ones from the individual participant data pooled analyses. In terms of the amount of cigarettes smoked per day, only around one-third of the StoP studies had published reports with this information, resulting in estimates more imprecise than the ones from the individual participant pooled analyses. For example, only seven out of 20 studies had published data for smokers of more than 20 cigarettes per day versus never smokers; six provided adjusted OR estimates, also higher than those obtained using the StoP data from the same studies (summary OR: 1.39 vs. 1.22).

For the meta-analysis of published data, a visual inspection of the funnel plot is suggestive of publication bias (Fig. 3) when considering only the studies providing adjusted estimates (Egger's test, $P = 0.047$), whereas a symmetrical funnel plot was obtained for the studies that had only crude estimates (Egger's test, $P = 0.876$) or the individual participant data pooled analysis (Egger's test, $P = 0.807$).

Discussion

The results from the individual participant data pooled analyses tended to show weaker associations than those observed in the corresponding meta-analyses of published data. Our summary OR estimates are also smaller than the ones previously reported; the meta-analysis carried out in 1997 by Tredaniel *et al.* reported a risk of gastric cancer of 1.44 (95% confidence interval: 1.17–1.78) for male ever smokers versus nonsmokers, but included in the variance-weighted analysis only 20 (17 case–control and three cohort) of the 40 studies reviewed, whereas the meta-analysis of 46 case–control studies published between 1997 and 2006 (La Torre *et al.*, 2009) showed a risk estimate of 1.48 (95% confidence interval: 1.28–1.71) for ever smokers. Despite the differences in relation to previous meta-analyses that analyzed selected sets of studies only, the ratio MA/StoP is likely to reflect the order of magnitude of the bias affecting summary estimates from other meta-analyses of published data.

For gastric cancer location, the small number of studies with published information specifically for gastric cardia and noncardia cancers was noteworthy compared with the data available in the StoP Project database. This was also noticed by La Torre *et al.* (2009), who verified that only 13% of the studies included in their meta-analysis had information stratified by cancer location and by Ladeiras-Lopes *et al.* (2008). The latter also highlighted the absence of information on the criteria for classification of gastric cancer subtypes, as well as the different

terms used to define cardia and noncardia locations, as factors that contributed to the heterogeneity between studies, which was also found in our analyses of published data. Tramacere *et al.* (2011) obtained a summary estimate of 1.71 (95% confidence interval: 1.40–2.09) for gastric cardia cancer, when considering only case–control studies, which was also higher than the one obtained in our study.

For some of the published reports, only crude ORs, or the necessary information to compute them, were available. This reflects the fact that assessment of the association between smoking and gastric cancer was not a main objective of those articles, and therefore, no selection bias was expected, as confirmed in the funnel plot analysis. The latter, however, was suggestive of publication bias when only the studies providing adjusted estimates were considered.

Our study does not allow us to disentangle the contribution of publication bias and uncontrolled confounding, or overadjustment of the OR estimates, to the differences between the two strategies of meta-analysis. Nevertheless, within the StoP project, we may expect a more homogeneous control of the effects of major confounders across studies (Egger *et al.*, 1998; Blettner *et al.*, 1999).

A systematic review of empirical comparisons of these two approaches to summarize the evidence from randomized trials has also shown that differences may be small, although sometimes relevant, in addition to the fact that the use of individual participant data allows for more detailed analyses of the available data (Tudur Smith *et al.*, 2016). When reviewing data from observational studies, having access to the individual participant data may be even more important for improving the homogeneity of definition of variables and the control of confounding.

Conclusion

Conventional meta-analyses and individual participant data pooled analyses reached similar conclusions on the direction of the association between smoking and gastric cancer. However, the use of published data tended to overestimate the magnitude of the effects and limited the analyses by different levels of exposure or cancer subtypes. This highlights the importance of consortia of existing datasets to make a more efficient and valid use of resources for research, and specifically the contribution of the StoP Project for a better understanding of the epidemiology of gastric cancer.

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Conflicts of interest

There are no conflicts of interest.

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