Role of smoking in functional dyspepsia and irritable bowel syndrome: three random population-based studies

Nicholas J. Talley[1,2], Nicholas Powell[3], Marjorie M Walker[1,2], Mike P. Jones[2,4], Jukka Ronkainen[5,6], Anna Forsberg[7], Lars Kjellström[8], Per M. Hellström[9], Pertti Aro[10], Bengt Wallner[11], Lars Agréus[12], Anna Andreasson[4,7,13]

[1]University of Newcastle, Newcastle, Australia

[2]NHMRC Centre of Research Excellence in Digestive Health

[3]Division of Digestive Disease, Imperial College, London, UK

[4]Department of Psychology, Macquarie University, North Ryde, Australia

[5]Center for Life Course Health Research, University of Oulu, Finland

[6]Primary Health Care Centre, Tornio, Finland.

[7]Department of Medicine Solna, Karolinska Institutet, Sweden

[8]Gastromottagningen City, Stockholm, Sweden

[9]Department of Medical Sciences. Uppsala University, Uppsala, Sweden

[10]Arokero OY, Tornio, Finland

[11] Department of Surgical and Perioperatve Sciences, Umeå University, Umeå, Sweden

[12]Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Huddinge, Sweden

[13]Stress Research Institute, Department of Psychology, Stockholm University, Stockholm, Sweden

Correspondence:
Nicholas J. Talley AC
Hunter Medical Research Institute
Lot 1, Kookaburra Cct
New Lambton Heights, NSW, 2305, Australia
Email: nicholas.talley@newcastle.edu.au

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Ethics

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Kalixanda 98/99 Local medical ethics committee at Umeå University

LongGERD 2010/443 Regional Ethics Board in Uppsala

Key words: functional dyspepsia, irritable bowel syndrome, postprandial distress, diarrhoea, smoking, snuff

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Summary

Background:

It is uncertain if functional dyspepsia (FD) or irritable bowel syndrome (IBS) are linked to smoking, and smoking cessation is not part of the routine advice provided to these patients.

Aim:

We aimed to assess if smoking is an independent risk factor for FD and IBS.

Methods:

Three population-based endoscopy studies in Sweden with 2560 community individuals in total (mean age 51.5 years, 46% male). IBS (14.9%), FD (33.5%), and associated symptoms were assessed using the validated abdominal symptom questionnaire, and smoking (17.9%) was obtained from standardized questions during a clinic visit. The effect of smoking on symptom status was analysed in an individual person data meta-analysis using mixed effect logistic regression, adjusted for snuffing, age and sex.

Results:

Individuals smoking cigarettes reported significantly higher odds of postprandial distress syndrome (FD-PDS) (OR 11-20 cig/day=1.42, 95% CI 1.04-1.98 p=0.027, OR >20 cig/day=2.16, 95% CI 1.38-3.38, p=0.001) but not epigastric pain. Individuals smoking 20 or more cigarettes per day reported significantly higher odds of IBS-diarrhoea (OR=2.40, 95%CI 1.12-5.16, p=0.025), diarrhoea (OR=2.01, 95%CI 1.28-3.16, p=0.003), urgency (OR=2.21, 95%CI 1.41-3.47, p=0.001) and flatus (OR=1.77, 95%CI 1.14-2.76, p=0.012) than non-smokers. Smoking was not associated with IBS-constipation or IBS-mixed.

Conclusion:

Smoking is an important environmental risk factor for postprandial distress syndrome, the most common functional dyspepsia subgroup, with over a two-fold increased odds of PDS in heavy smokers. The role of smoking in IBS-diarrhoea, but not constipation, is also likely important.

Keywords: IBS-D; irritable bowel syndrome; Functional dyspepsia; FGIDs; postprandial distress; duodenal eosinophilia; eosinophil; duodenum; smoking

Introduction

Globally, functional gastrointestinal disorders (FGIDs) are highly prevalent, and two of the most well recognised are the irritable bowel syndrome (IBS) and functional dyspepsia (FD) [1]. These disorders are important because they are common, and can substantially impact on quality of life, work and relationships [2, 3]. IBS can present with predominant diarrhoea (IBS-D), constipation (IBS-C) or a mixed pattern (IBS-M), while FD may present with early satiety or postprandial fullness (postprandial distress syndrome, PDS) or epigastric pain syndrome (EPS), or a mixed pattern [1-3].

The etiopathogenesis of both IBS and FD is uncertain but environmental and genetic factors are likely relevant. Infections of the gastrointestinal tract represent one important environmental factor, and in post-gastroenteritis there is an increased risk of IBS, FD, or IBS and FD overlap[4]. Other environmental factors have been less well studied in the FGIDs but are potentially important to evaluate as modification of risk may impact disease burden [5].

Older population-based and outpatient studies have suggested smoking is not a risk factor for FD but the major subgroup of PDS was not evaluated [6, 7]. More recent work suggests smokers may have an increased risk of post-infectious FD which is unexplained. [8] A population-based study from Italy reported that smoking is a risk factor for FD [9], but it remains unclear whether this risk is of importance, and whether it applies to all of FD or a subgroup. Studies of current smoking status in IBS have been conflicting and it remains uncertain if this environmental exposure is relevant or not [10]. No studies have evaluated whether snuff use, common in Scandinavia, is also associated with FGIDs.

Smoking cessation is not currently part of the management recommendations for FD or IBS. Our aim was to investigate the association between smoking and IBS or FD (including subtypes) in three similar large general population-based samples that had undergone endoscopy and pool the data to

ensure there was sufficient study power to detect even weak associations. We also evaluated snuff use as a risk factor.

Methods

Participants

The current study includes all participants with interview and complete questionnaire data from three population-based endoscopy studies in Sweden we had conducted: PopCol (n=1158, conducted 2002-2006), Kalixanda (n=1001, conducted 1998-2001) and LongGERD (n=401, conducted 2012), with in total 2560 community subjects. The subjects included were representative of the Swedish population and there was very minimal selection bias in all three cohorts as previously described in detail [11-13].

PopCol

The PopCol study has been previously described in detail [11]. In brief, 3556 persons randomly selected from the Swedish born adult population in two adjacent parishes in Stockholm were sent the validated abdominal symptom questionnaire (ASQ) asking for bothersome abdominal symptoms at any time over the past three months [14]. Out of the 2293 responders, 1673 were reached by phone to invite to an interview with a gastroenterologist. A total of 1244 participants attended the interview and completed further questionnaires including an extended version (asking not only for symptoms over the past three months, but also over the past week and daily) of the ASQ. Of these, 745 participants also agreed to have an ileo-colonoscopy with biopsies. This report includes the 1158 participants who completed the interview and provided complete questionnaire data.

Kalixanda

The Kalixanda study has been described in detail previously [12]. Briefly, the study was performed in two adjacent communities in the northern part of Sweden (Kalix and Haparanda), with a total population of 28 988 inhabitants (as of December 1998). A randomly selected sample of 3000 adults from the two communities was sent the ASQ and the out of 2122 responders who completed the ASQ

1563 were phoned to find 1000 participants willing and able to undergo an esophago-gastro-duodenoscopy (EGD). While attending the clinic for an endoscopy, participants completed the extended version of the ASQ. A total of 1001 participants attended the visit, of whom 1000 had a successful EGD. This report includes the 1001 participants who completed the questionnaire.

LongGERD

The LongGERD study has previously been described in detail[13] . In the study, all inhabitants in Östhammar community, Uppsala, 20 years and above born on day 3, 12 and 24 each month were sent the ASQ. As this was a prospective study on inhabitants born on day 3, 12 and 24 each month, all participants from previous surveys who had moved from the community were also sent the questionnaire. All 947 responders 80 years and younger from the community or from within 200 km from the community were telephoned and asked to complete an EGD. A total of 402 participants agreed, and 388 had a successful EGD; this study included the 401 participants with complete interview and questionnaire data.

Variables

Gastrointestinal symptoms were assessed using the validated ASQ completed at the clinic visit in all three studies.

Irritable bowel syndrome

IBS was defined in PopCol and LongGERD congruent with the Rome criteria [15] as abdominal pain weekly with two of the following: relieved by defecation, associated with changed in stool frequency and/or a change in stool form. IBS was defined in the Kalixanda study as weekly abdominal pain with either diarrhoea, constipation or alternating diarrhoea and constipation the last three months[12].

IBS-D was defined as IBS with reports of bothersome diarrhoea the last three months with no constipation. IBS-C was defined as bothersome constipation in the last three months with no diarrhoea, and IBS-M as bothersome constipation and diarrhoea in the last three months.

Functional dyspepsia

FD was defined congruent with the Rome criteria as presence of EPS and/or PDS [16]. EPS was defined by the presence of any pain modality isolated to the epigastric region. Postprandial distress syndrome PDS was defined as presence of either early satiety and/or postprandial fullness. We separately analysed those who met criteria for both EPS and PDS.

GI symptoms

In addition, the following symptoms were measured by the ASQ: abdominal pain or discomfort, diarrhoea, constipation, passing flatus, borborygmus, urgency and bloating.

Smoking

Smoking was assessed using the question "do you currently smoke?" and smokers were asked how many cigarettes per day they smoked. Smoking was analyzed by dose: smoking up to 10 cigarettes per day, 11 to up to 20 cigarettes per day and 21 cigarettes or more per day, using non-smokers as the reference group.

Snuff

Snuff use was assessed using the question "do you currently snuff?" and snuffers were asked how many crates per week they used. Snuffing was analyzed using non-snuffers as the reference and snuffers using 1 or 2 crates per week, 3 or 4 crates per week, and 5 or more crates per week. The cut-off levels for snuff was used to give approximately the same dose of nicotine as the categories used for smoking. Use of 16 doses of snuff per day corresponds to smoking 18 cigarettes per day and a

nicotine intake of 25 mg [17]. As crates contains 25 doses of snuff, use of 5 crates per week would correspond to the same nicotine intake as smoking 20 cigarettes per day.

Body mass index (BMI)

Weight was measured at the clinic at time of endoscopy. Data on BMI was missing on 10 subjects in Kalixanda and 22 subjects in LongGERD

Anxiety and depression

Anxiety and depression was assessed using the validated hospital anxiety and depression (HAD) scale[18] in all three studies.

Statistics

Distribution of age, sex, BMI, anxiety, depression, smoking status, snuffing status and symptoms per study is presented in Table 1. Differences between studies in dichotomous and categorical variables are calculated using χ^2 test and differences in age using the Kruskal-Wallis test.

The association between smoking and snuff use, and symptoms were calculated in an individual person data (IPD) meta-analysis using mixed effect logistic regression with both smoking and snuffing categories simultaneously as fixed effects and study as random intercept with each symptom status (presence/absence) as the outcome variable. This means that the odds ratios presented for smoking are adjusted for snuff use and vice versa. All analyses were adjusted for age and sex. Other variables considered as potentially confounding were anxiety, depression and BMI but were found to not meet the criteria for potential confounding through not being associated with either smoking or FGID status.

The primary analyses are based on categories of cigarette use due the strongly right-skewed distribution of cigarette and snuff use. However, a linear dose-response is also evaluated by fitting a linear trend through usage categories. Odds ratios >1.0 indicate a given nicotine use is associated with higher odds of an FGID while odds ratios <1.0 indicate an association with lower odds. Potential confounding of the association between anxiety and depression with FGIDs by cigarettes and snuff was evaluated through hierarchical modelling.

In this IPD meta-analysis, between-study variability in symptom prevalence and other measures is reported in Table 1. It is noted that the usual meta-analytic concept of publication bias is not relevant since we are combining the only three studies with the same methodology conducted by the current investigators. As a methodological check, the degree of between-study variance in odds ratios was evaluated via the I^2 measure and by Cochrane's test of homogeneity. These are reported for the statistically significant findings however we note that many I^2 values were zero and only one Cochrane p-value was <0.05.

All analyses were performed in STATA 16 (StataCorp, College Station, Texas). An alpha level of 0.05 was used to determine statistical significance. The combined sample size was determined to provide adequate statistical power (0.8) at the 0.05 (two-tailed) level of statistical power for an odds ratio 2.0 from a baseline probability 0.2 if the Kish design effect was as large as 2.0.

Results

The population characteristics across the three independent cohorts are summarized in Table 1. While there were minor differences for some measures that were statistically significant because of high study power, overall, the populations were comparable in terms of rates of smoking and snuffing.

Gastrointestinal symptoms were somewhat higher in the PopCol study which also included a higher proportion of female subjects.

The association of smoking and IBS and FD adjusted for snuff use, age and sex is summarized in Table 2. There was a greater than two-fold higher odds of FD-PDS (but not FD-EPS) in heavy smokers (more than 20 cigarettes per day) versus non-smokers, and strong evidence of a dose-response effect for FD and separately FD-PDS (Table 3). All statistically significant odds ratios remained so after additionally controlling for HADS anxiety and depression and body mass index (data not shown).

Individuals smoking more than 20 cigarettes per day were at a greater than two-fold increased odds of IBS-diarrhoea versus non-smokers. There was no association between smoking and IBS-constipation (Table 2). There was evidence for a cigarette dose-response in IBS-diarrhoea (p=0.06) but not in IBS overall (Table 3).

Forest plots for the heavy smoking category are presented in Figure 1.

In terms of individual symptoms, individuals smoking more than 10 cigarettes per day reported significantly higher odds of early satiety, but not epigastric pain than non-smokers (Table 4). Individuals smoking more than 20 cigarettes per day had significantly higher odds of diarrhoea, urgency, and bothersome flatus, but not abdominal pain or constipation (Table 4).

A total of n=67 individuals (2.7% of the sample) met criteria for both IBS-diarrhoea and FD-PDS. There was a clear linear dose-response between cigarette smoking category and odds of IBS-diarrhoea and PDS overlap, but no evidence of a linear dose-response for snuff use (Table 3).

Among those with FD, a total of n=63 subjects met criteria for both PDS and EPS. The exclusion of individuals with PDS/EPS overlap had a very negligible effect on the estimated odds ratios or their statistical significance for smoking and PDS, EPS or FD overall (data not shown).

In an analysis assessing smoking in each of the three study cohorts, while there was minor variation between studies with respect to estimated odds ratios there was not enough heterogeneity to suggest incompatible findings between studies for IBS-diarrhoea (average I^2 value across 6 model parameters reported in Table 2 = 0.21, all p>0.1), FD (average I^2 value 0.15, all p>0.2) or PDS (average I^2 value 0.26, all p>0.1).

There was a statistically significant, positive association between increasing scores for both anxiety and depression with the odds of both IBS and FD (all p<0.001), both before and after controlling for cigarette smoking and snuff use. This indicates increased smoking is not accounted for by the association of IBS and FD with anxiety and depression.

Being an ex-smoker was not significantly associated with IBS-diarrhoea (OR=0.79, 95% CI 0.53, 1.18, p=0.25), FD (OR=0.88, 95% CI 0.74, 1.05, p=0.17) or PDS (OR=0.83, 95% CI 0.53, 1.00, p=0.06).

In a post-hoc sensitivity analysis of the positive associations in Table 2, we excluded ex-smokers (n=876) from all the analyses which did not substantially alter the odds ratios or statistical significance, aside from the 11-20 cigarette category for PDS where the OR was 1.27 (95% CI 0.92-1.76). In a second sensitivity analysis for the positive associations in Table 2, we excluded all subjects who were found to have reflux oesophagitis (n=213), peptic ulcer (n=41) or cancer (n=0) at endoscopy, or known inflammatory bowel disease (n=11). The associations of smoking with FD and FD-PDS all remained significant, but the IBS-diarrhoea association was only a trend (OR=2.11, 95% CI 0.88, 5.04).

Snuffing 5 or more crates per week was associated with lower odds of postprandial fullness independent of smoking. Fifty-seven subjects reported both smoking and snuffing. Giving that smoking and snuffing were both associated with FD we investigated if there was an interaction effect between smoking and snuff use and the prevalence of FD-PDS in a post-hoc analysis using smoking status (smoker vs non-smoker), snuffing status (snuffing vs not snuffing) and the interaction between smoking status and snuffing status as fixed effects and study intercept as random effect in a fixed effect regression analysis adjusted for age and sex. No significant interaction between smoking and snuffing in FD-PDS was found (data not shown).

Discussion

In the present study we investigated the association between tobacco use and functional gut disorders (IBS and functional dyspepsia, FD) in three population-based studies from Sweden in an individual person data meta-analysis. Smoking was associated with a significantly increased risk of IBS-diarrhoea and while this only applied to the highest exposure category (more than 20 cigarettes per day), there was a trend for a dose-response relationship (p=0.06). Smoking was also associated with diarrhoea and urgency, and early satiety, although no association with abdominal pain or constipation

was observed. Most impressively, smoking was significantly associated in a dose-dependent manner with FD-PDS, but not FD-EPS. A slightly lower risk of postprandial fullness was reported in snuff users.

In FD, a limited number of studies have explored if there is an association with smoking. In a post-gastroenteritis outbreak of FD in Walkerton, Canada, the risk of FD post infection was significantly higher in smokers as well as women and those with anxiety or depression [8]. In an Italian population-based study, cigarette smoking was an independent risk factor for all comers with FD (OR=1.74, 95% CI 1.11-2.70) [9]. Globally, multiple studies have reported an association between duodenal eosinophilia and FD following the initial report by Talley and Walker [19-21], and smoking was found to be associated with an increased the risk of duodenal eosinophilia in FD in an Australian study[22] . What is new in the present study is the convincing evidence that there is a strong consistent association of FD with smoking, and there is a dose-response effect of smoking in FD, suggesting smoking may play an aetiological role. Cigarette smoking affects the gut mucosa through negative effects on homeostasis, epigenetic modification and composition of gut microbiota [23]. The epigenetic effects of cigarette smoke on immune and epithelial cells and neurons may contribute to symptoms; however, this effect is most studied in inflammatory bowel disease [24], and whether the mechanism linking smoking with FD is via increased microscopic inflammation in the duodenum remains to be clarified. Further, smoking is now known to specifically alter the duodenal microbiome and it is feasible this also plays a key role in the pathogenesis of FD [25-27]. In addition, nicotine may slow gastric emptying representing an alternative mechanism for the development of postprandial distress symptoms[28, 29] although the lack of a positive association with snuff use suggests nicotine may not be the explanation. We observed the percentage of subjects with FD increased from 31% who did not smoke to 48% in the highest frequency smoking group.

Our data suggest there may be an association between smoking and IBS-diarrhoea but not IBS-constipation, but these results need cautious interpretation as causality is less clear. Smoking slows gastric emptying and mouth-cecum transit times but is less likely to alter colonic transit [28-31]. However, while an association with IBS-C might then be expected if smoking is a risk factor, it is also possible delayed small intestinal transit could predispose to small intestinal bacterial overgrowth which has been identified in a subset with IBS and can induce diarrhoea [32]. Further, nicotine reduces pancreatic juice secretion, which may also potentially induce diarrhoea [33]. Notably previous studies have reported conflicting results regarding the association between smoking status and IBS [34]. A systematic review identified 26 articles where smoking was not a risk factor for IBS, while 7 articles reported smoking was significantly more frequent in those with IBS compared to those without [10]. One reason for this may be that smoking in the present study was only associated with diarrhoea and urgency and not abdominal pain, which may lead to different association patterns depending on the proportion with IBS-diarrhoea in any study sample. An alternative hypothesis is smoking increases diarrhoea but the association with IBS is spurious (hence the lack of a relationship with pain), and this cannot be discarded by the current results. Most notably we found less evidence for a dose-response effect with IBS-D, but observed associations between heavy smoking, more than 20 cigarettes per day and IBS. In past studies which only evaluated smoking versus not smoking and found no link [10], any effect of cigarettes may have been too diluted to be observed. While nicotine receptors have been demonstrated on intrinsic and extrinsic nerves in the colon, the effects of nicotine on colonic motor function are likely complex and may depend on gender[31]. Coulie et al. observed that nicotine in healthy subjects increased high amplitude propagated contractions and increased colonic transit but only in high dose[35]. We observed the percentage of subjects with IBS-diarrhoea increased from 4.4% in those who did not smoke to 9.4% in the highest frequency smoking group. However, heavy smoking per se may not cause IBS and diarrhoea; rather, other behaviors or exposures that are increased in both heavy smokers and in IBS (such as a past history of sexual or physical abuse which is linked to higher smoking rates and also IBS) may be the explanation for any association (via

confounding) [36, 37], although this would not explain the strong association between smoking and specific diarrheal symptoms identified in the current study. Further, we did not identify anxiety or depression to be explanations for the links with smoking.

The snuff data also need to be interpreted cautiously. Snuffers were grouped based on crates per week to achieve similar nicotine doses as in the smoking groups. However, several factors influence the actual dose absorbed by an individual and this could not be ascertained in the current study. Snuff was not associated with either early satiety or FD. Similarly we previously reported when only the Kalixanda study was evaluated that snuff use was not linked to peptic ulcer disease or symptoms [38]. The one outlier result was the negative association between snuff and postprandial fullness in the present study, but this may reflect a false positive significant P-value from multiple comparison testing, as there was no dose-response, and smoking was not associated with postprandial fullness. Alternatively, heavy snuff use may reflect recent smoking cessation, as this is one reason for the use of snuff in Sweden. Duodenal eosinophilia is a major risk factor for postprandial distress symptoms in FD and is linked to smoking [22], and therefore smoking cessation might result in less duodenal eosinophilia and less symptoms in snuff users.

The included population-based endoscopy studies had major strengths including random subject selection. Another strength is three independent population- based endoscopy studies were evaluated. The same questionnaire was used in all studies, and symptom assessment applied a well validated tool. The overall response rates in each of the studies was satisfactory; 69% responded to the initial questionnaire survey and 63% of those invited agreed to come in for a face-to-face visit, of whom 80% completed an endoscopy. We have previously comprehensively evaluated each of the study populations for evidence of selection bias which appeared to be very minimal [11-13, 39] . The associations between smoking and symptoms were not confounded by anxiety or depression. Endoscopy had been performed in a major subset of the participants and organic findings explaining

the symptoms were found to be uncommon as previously reported [11-13, 40] plus a sensitivity analysis confirmed excluding organic disease findings and separately, ex-smokers did not alter the results in any substantial way.

The study also had limitations. In Sweden snuff is used in persons also trying to quit smoking which might have interfered with the interpretation of the results. However, this would not explain the general lack of association seen in snuffers. There was minimal study heterogeneity, apart from participants in PopCol being younger with a lower BMI and reporting more anxiety and GI symptoms overall than participants in LongGERD and Kalixanda. The higher prevalence of GI symptoms in the PopCol study may simply reflect the higher proportion of younger women in the sample. We note the IBS-diarrhoea association in particular displayed no dose-response, and a type I error because of multiple testing cannot be fully excluded for this finding. We were required to apply modified Rome III criteria in the current study which is a limitation, but the definitions applied are congruent with Rome definitions and would seem unlikely to explain the associations observed. While a slightly different definition of IBS was applied in the Kalixanda study because this was the information obtained, this should have made very little or no difference to the results which were consistent within studies. We did not set out to undertake a literature wide meta-analysis where the limited available studies are focussed on outpatient or volunteer samples[10, 34]. Our goal in the present study was to assess the relationship between smoking and IBS or FD in the general community (not outpatients), and to ensure sufficient study power we combined all three of our population-based studies; the three studies in the present paper were all conducted by the same authors applying similar protocols and rigorously evaluating random samples of the population. Finally, all studies were performed in Sweden, so generalizability to other countries may be limited.

We conclude smoking but not snuff is an important environmental risk factor for postprandial distress syndrome, the most common functional dyspepsia subgroup, with over two-fold increased odds in heavy smokers. The role of smoking in IBS-diarrhoea is also likely important. Further work to elucidate the mechanisms by which smoking may alter the microbiome and the upper intestinal tract structurally and functionally in FD and IBS are warranted. Specific smoking cessation advice appears warranted in subgroups with FD and IBS but needs to be tested in a clinical trial.

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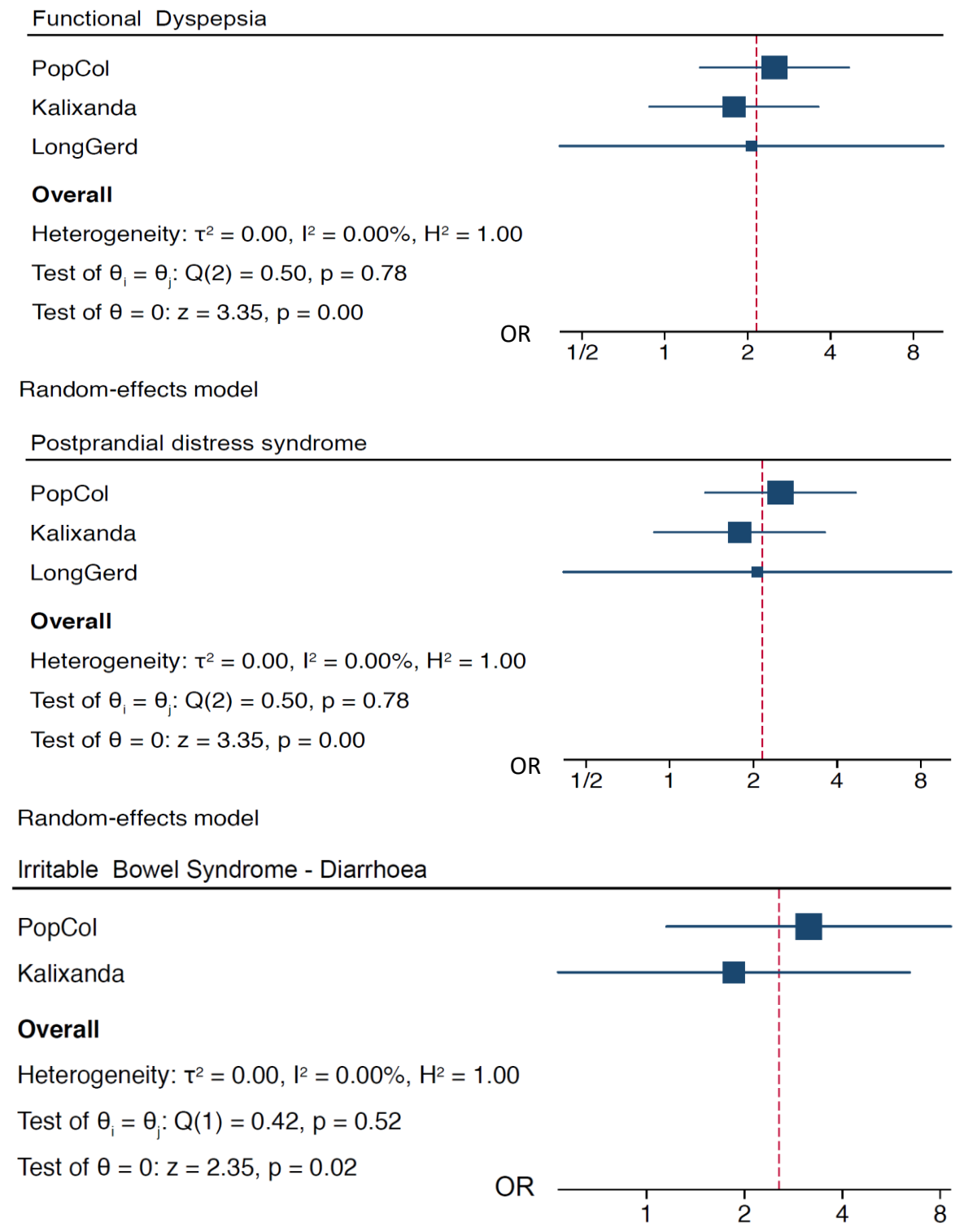

Figure 1: Forest plots of studied cohorts with functional dyspepsia (FD), postprandial distress syndrome subtype of FD, and irritable bowel syndrome (IBS)-diarrhoea (D) assessing heavy smoking (21 cigarettes or more per day). Note there were no subjects who were heavy smokers and had IBS-diarrhoea in the LongGERD study.

Table 1. Population characteristics presented as median (interquartile range IQR) or prevalence (95% CI) in the three different populations

Factor	PopCol	Kalixanda	LongGERD	p-value
Number	1158	1001	401	
Males	501 (43.3%)	488 (48.8%)	194 (48.4%)	0.025
Age, median (IQR)	50 (38, 60)	55 (44, 65)	56 (45, 64)	<0.001
BMI, median (IQR)	23.9 (21.6,26.2)	26.1 (23.8, 28.7)	26.1 (23.9, 29.2)	<0.001
Anxiety (IQR)	4 (2,7)	3 (1,5)	3 (1,6)	<0.001
Depression (IQR)	2 (1,4)	2 (1,4)	3 (1,5)	0.018
Smokers	213 (18.4%)	187 (18.7%)	59 (14.7%)	0.19
Non-smokers	945 (81.6%)	814 (81.3%)	342 (85.5%)	0.16
-10 cig/day	90 (7.8%)	64 (6.4%)	26 (6.5%)	
11-20 cig/day	79 (6.8%)	88 (8.8%)	24 (6.0%)	
20- cig/day	44 (3.8%)	35 (3.5%)	8 (2.0%)	
Snuffers	141 (12.2%)	118 (11.8%)	48 (12.0%)	0.96
Non snuffers	1017 (87.8%)	883 (88.2%)	353 (88.0%)	0.27
1-2 crates/week	58 (5.0%)	64 (6.4%)	16 (4.0%)	
2-3 crates/week	45 (3.9%)	30 (3.0%)	17 (4.2%)	
5- crates/week	38 (3.3%)	24 (2.4%)	15 (3.7%)	
Both smoker and snuffer	27 (2.3%)	22 (2.2%)	8 (2.0%)	0.92
IBS	179 (15.5%)	157 (15.7%)	37 (10.6%)	0.055
IBS-Diarrhoea	58 (5.0%)	45 (4.5%)	16 (4.4%)	0.81
IBS-Constipation	44 (3.8%)	44 (4.4%)	6 (1.6%)	0.059
IBS-Mixed	77 (6.7%)	68 (6.8%)	13 (3.6%)	0.073
Diarrhoea	389 (33.6%)	217 (24.8%)	67 (22.5%)	<0.001
FD	452 (39.1%)	282 (28.4%)	115 (30.0%)	<0.001
FD-Postprandial distress	397 (34.3%)	233 (23.5%)	96 (25.1%)	<0.001
FD-Epigastric pain	90 (7.9%)	67 (6.8%)	29 (8.0%)	0.55

IBS= irritable bowel syndrome; FD=functional dyspepsia

Table 2. Individual person data meta-analysis of the association between smoking and snuffing and irritable bowel syndrome (IBS) and functional dyspepsia (FD), adjusted for age and sex

Smoking cigarettes per day vs non-smoking	**OR**	**95 % CI**		**p**	**Snuffing crates per week vs non-snuffing**	**OR**	**95 % CI**		**p**
IBS (all)									
-10 cig/day	1.06	.70	1.59	0.9	1-2	.84	.51	1.40	0.51
11-20 cig/day	1.13	.76	1.67	0.55	2-3	.89	.47	1.69	0.73
20- cig/day	1.51	.87	2.62	0.15	5-	.90	.45	1.80	0.77
IBS-Diarrhoea									
-10 cig/day	1.40	.72	2.69	0.32	1-2	.36	.26	1.63	0.36
11-20 cig/day	1.12	.55	2.28	0.75	2-3	.94	.37	2.48	0.94
20- cig/day	**2.40**	**1.12**	**5.16**	**0.025**	5-	.87	.32	2.62	0.87
IBS-Constipation									
-10 cig/day	.57	.25	1.33	0.19	1-2	.94	.37	2.37	0.89
11-20 cig/day	.63	.29	1.38	0.25	2-3	1.02	.31	3.37	0.97
20- cig/day	.68	.21	2.21	0.52	5-	1			
IBS-Mixed									
-10 cig/day	1.17	.66	2.08	0.58	1-2	1.33	.67	2.63	0.42
11-20 cig/day	1.41	.82	2.44	0.22	2-3	.70	.21	2.31	0.56
20- cig/day	1.16	.46	2.96	0.75	5-	1.93	.79	4.70	0.15
FD (all)									
-10 cig/day	1.16	.84	1.61	0.37	1-2	1.07	.73	1.55	0.74
11-20 cig/day	1.22	.89	1.67	0.22	2-3	.89	.55	1.43	0.63
20- cig/day	**2.14**	**1.38**	**3.33**	**0.001**	5-	.63	.36	1.09	0.097
FD-Epigastric pain									
-10 cig/day	.96	.54	1.72	0.90	1-2	1.18	.62	2.25	0.62
11-20 cig/day	.52	.25	1.08	0.08	2-3	1.56	.75	3.22	0.24
20- cig/day	1.12	.51	2.47	0.79	5-	.78	.28	2.20	0.64
FD-Postprandial distress									
-10 cig/day	1.14	.81	1.60	0.45	1-2	.88	.59	1.32	0.54
11-20 cig/day	**1.43**	**1.04**	**1.98**	**0.027**	2-3	.67	.40	1.14	0.14
20- cig/day	**2.16**	**1.38**	**3.38**	**0.001**	5-	.60	.33	1.08	0.088

IBS=irritable bowel syndrome, FD= functional dyspepsia, OR= Odds ratio

Table 3. Linear trends in dose-response of cigarettes and snuff for the irritable bowel syndrome (IBS), functional dyspepsia (FD) and subgroups

Disorder	Cigarettes	Snuff
IBS (all)	1.10 (0.95, 1.26) p=0.2	0.97 (0.80, 1.17) p=0.8
IBS-C	0.78 (0.56, 1.08) p=0.1	0.60 (0.32, 1.12) p=0.1
IBS-D	**1.23 (0.99, 1.52) p=0.06**	0.94 (0.71, 1.26) p=0.7
FD (all)	**1.20 (1.08, 1.34) p=0.001**	0.90 (0.79, 1.04) p=0.2
PDS	**1.24 (1.11, 1.38) p<0.001**	0.84 (0.72, 0.98) p=0.03
EPS	0.90 (0.72, 1.11) p=0.3	1.05 (0.83, 1.33) p=0.7
IBS-D/FD-PDS overlap	**1.43 (1.11, 1.84) p=0.005**	0.92 (0.61, 1.40) p=0.7

Note: All trends adjusted for age and sex

C=constipation; D=diarrhoea; PDS =postprandial distress syndrome; EPS=epigastric pain syndrome

Table 4. Individual person data meta-analysis of the association between smoking and snuffing and gastrointestinal symptoms, adjusted for age and sex

Smoking cigarettes per day vs non-smoking	OR	95 % CI		p	Snuffing crates per week vs non-snuffing	OR	95 % CI		p
Abdominal pain									
-10 cig/day	1.06	.77	1.47	0.70	1-2	1.10	.77	1.58	0.59
11-20 cig/day	.95	.70	1.30	0.75	2-3	.83	.53	1.29	0.40
20- cig/day	1.39	.89	2.18	0.15	5-	.77	.48	1.25	0.29
Diarrhoea									
-10 cig/day	.86	.60	1.23	0.41	1-2	1.09	.73	1.63	0.68
11-20 cig/day	.92	.65	1.31	0.65	2-3	1.10	.68	1.78	0.69
20- cig/day	**2.01**	**1.28**	**3.16**	**0.003**	5-	1.23	.73	2.07	0.43
Constipation									
-10 cig/day	1.06	.74	1.51	0.75	1-2	1.17	.76	1.78	0.48
11-20 cig/day	1.04	.74	1.48	0.81	2-3	.55	.28	1.10	0.089
20- cig/day	1.12	.66	1.89	0.68	5-	.73	.36	1.45	0.37
Straining									
-10 cig/day	.99	.71	1.39	0.96	1-2	1.05	.71	1.57	0.80
11-20 cig/day	.84	.60	1.18	0.31	2-3	.89	.53	1.49	0.67
20- cig/day	.78	.47	1.31	0.35	5-	.80	.45	1.42	0.44
Urgency									
-10 cig/day	.76	.53	1.09	0.14	1-2	.88	.59	1.33	0.55
11-20 cig/day	1.04	.75	1.45	0.82	2-3	1.00	.61	1.63	0.99
20- cig/day	**2.21**	**1.41**	**3.47**	**0.001**	5-	.95	.55	1.63	0.85
Borborygmus									
-10 cig/day	.77	.54	1.09	0.14	1-2	1.16	.79	1.70	0.44
11-20 cig/day	1.13	.82	1.55	0.46	2-3	1.16	.73	1.85	0.53
20- cig/day	1.44	.91	2.28	0.12	5-	1.08	.64	1.80	0.78
Bothersome passing flatus									
-10 cig/day	.78	.55	1.09	0.15	1-2	.98	.68	1.43	0.93
11-20 cig/day	1.07	.78	1.46	0.69	2-3	.75	.47	1.22	0.25
20- cig/day	**1.77**	**1.14**	**2.76**	**0.012**	5-	.93	.57	1.54	0.79
Bloating									
-10 cig/day	1.21	.88	1.67	0.25	1-2	.94	.65	1.37	0.74
11-20 cig/day	1.14	.84	1.56	0.40	2-3	.83	.51	1.33	0.43
20- cig/day	1.56	.99	2.44	0.055	5-	.68	.40	1.17	0.17
Postprandial fullness									
-10 cig/day	1.03	.72	1.49	0.86	1-2	.65	.40	1.04	0.071
11-20 cig/day	1.22	.86	1.73	0.26	2-3	.66	.38	1.17	0.16
20- cig/day	1.44	.87	2.37	0.15	5-	**.47**	**.24**	**.95**	**0.034**
Early satiety									
-10 cig/day	1.17	.77	1.77	0.45	1-2	.86	.51	1.45	0.58
11-20 cig/day	**1.90**	**1.32**	**2.74**	**0.001**	2-3	1.02	.54	1.93	0.95
20- cig/day	**2.58**	**1.56**	**4.26**	**0.000**	5-	1.04	.52	2.08	0.91

OR= Odds ratio

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1+5
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			8
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-10
Bias	9	Describe any efforts to address potential sources of bias	12-13
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8,11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	12-14
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15

Discussion			13
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.