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Tobacco smoking and the risk of pancreatitis: A systematic review and meta-analysis of prospective studies

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ABSTRACT

Background: Tobacco smoking has been associated with increased risk of pancreatitis in several studies, however, not all studies have found an association and it is unclear whether there is a dose-response relationship between increasing amount of tobacco smoked and pancreatitis risk. We conducted a systematic review and meta-analysis of prospective studies on tobacco smoking and pancreatitis to clarify the association.

Methods: PubMed and Embase databases were searched for relevant studies up to April 13th, 2019. Prospective studies that reported adjusted relative risk (RR) estimates and 95% confidence intervals (CIs) for the association between tobacco smoking and pancreatitis were included and summary RRs were calculated using a random effects model.

Results: Ten prospective studies were included. The summary RR for acute pancreatitis was 1.49 (95% CI: 1.29–1.72, $I^2 = 68\%$, n = 7) for current smokers, 1.24 (95% CI: 1.15–1.34, $I^2 = 0\%$, n = 7) for former smokers, and 1.39 (95% CI: 1.25–1.54, $I^2 = 69\%$, n = 7) for ever smokers compared to never smokers. Similar results were observed for chronic pancreatitis and acute/chronic pancreatitis combined. The summary RR per 10 cigarettes per day was 1.30 (95% CI: 1.18–1.42, $I^2 = 42\%$, n = 3) and per 10 pack-years in current smokers was 1.13 (95% CI: 1.08–1.17, $I^2 = 14\%$, n = 4) for acute pancreatitis and results were similar for chronic pancreatitis and acute/chronic pancreatitis combined.

Conclusions: These results suggest that tobacco smoking increases the risk of acute and chronic pancreatitis and acute and chronic pancreatitis combined and that there is a dose-response relationship between increasing number of cigarettes and pack-years and pancreatitis risk.

Introduction

Pancreatitis is an inflammatory disorder of the pancreas which predisposes to pancreatic cancer [1,2] and has been associated with premature mortality as well [2,3]. The large international variation in pancreatitis rates, from 4 up to >100 cases per 100000 persons per year [4], coupled with the rapid changes in the incidence of pancreatitis over time [5,6] suggest that environmental risk factors may be of importance in the etiology of the disease. High alcohol intake [2,7], obesity [2], diabetes [2], and a history of gallstones [2,7] are among the established or suspected risk factors for pancreatitis.

Tobacco smoking has been associated with increased risk of diabetes [8] and gallstones [9], which are important risk factors for pancreatitis [2] and smoking is an established risk factor for pancreatic cancer [10], for which pancreatitis is an established risk factor. On the other hand people who smoke also frequently drink more alcohol, and it is possible that alcohol consumption potentially could confound an association between smoking and pancreatitis. Several [2,7,11–17], but not all [7] studies have shown an increased risk of pancreatitis among smokers. However, in some

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of these studies associations were not observed with acute pancreatitis [16], gallstone-related pancreatitis [11,17], or chronic pancreatitis [2]. Although a previous meta-analysis found a positive association between smoking and pancreatitis risk [18], most of the included studies were case-control or cross-sectional studies, study designs which can be affected by recall bias and selection bias and from which it is difficult to establish a temporal relationship between smoking and pancreatitis risk. In addition, no dose-response analyses were conducted. Establishing a dose-response relationship between increasing amount of tobacco smoked and pancreatitis risk would strengthen the evidence base. Several additional prospective studies have been published on tobacco smoking and pancreatitis risk since that meta-analysis came out [2,16,17], including nearly 400 000 participants and >4100 cases, and for this reason we conducted an updated meta-analysis of studies on the topic with the aim of clarifying the strength of the association between tobacco smoking and pancreatitis, clarify the strength and shape of the dose-response relationship between increasing number of cigarettes smoked per day or pack-years of smoking and pancreatitis, and investigate potential confounding and sources of heterogeneity using subgroup and meta-regression analyses.

Material and methods

Search strategy

We searched PubMed and Embase databases up to April 13th, 2019 for eligible studies. The search terms used are provided in the supplementary text. We followed PRISMA criteria for reporting meta-analyses [19]. In addition, the reference lists of the identified publications were searched for further studies.

Study selection and inclusion criteria

We included published retrospective and prospective cohort studies and nested case-control studies within cohorts that investigated the association between tobacco smoking and the risk of pancreatitis and provided adjusted relative risk (RR) estimates and 95% confidence intervals (CIs) in the publication. A list of the excluded studies and the exclusion reasons can be found in Supplementary Table 1. The screening of the literature search was conducted by DA and YMS.

Data extraction

The following data were extracted from each study: The first author's name, publication year, country where the study was conducted, the name of the study, study period and duration of follow-up, sample size, number of cases, smoking variable, comparison and subgroup, RRs and 95% CIs for smoking compared to not smoking and variables adjusted for in the analysis. The data extraction was conducted by DA and checked for accuracy by YMS.

Statistical methods

Random effects models were used to calculate summary RRs (95% CIs) of pancreatitis for current, former and ever smoking compared to never smoking [20]. The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted using random effects weights. A two-tailed $p < 0.05$ was considered statistically significant.

For the linear dose-response analysis we used the method by Greenland and Longnecker [21] to estimate linear trends and 95% CIs from the natural logarithm of the RRs across categories of cigarettes smoked per day and pack-years. When cigarettes per day and pack-years were reported by ranges we estimated the midpoint by calculating the average of the lower and upper bound. A potential nonlinear association was investigated using restricted cubic splines with three knots at 10%, 50% and 90% percentiles of the distribution, which was combined using multivariate meta-analysis [22,23].

Heterogeneity between studies was evaluated using Q and I^2 statistics [24]. I^2 is a measure of how much of the heterogeneity that is due to between study variation rather than chance. I^2-values of 25%, 50% and 75% indicates low, moderate and high heterogeneity respectively. We conducted main analyses (all studies combined) and stratified by study characteristics such as sex, duration of follow-up, geographic location, number of cases, study quality and by adjustment for confounding factors to investigate potential sources of heterogeneity. Study quality was assessed using the Newcastle Ottawa scale which rates studies according to selection, comparability and outcome assessment with a score range from 0 to 9 [25].

Publication bias was assessed using Egger's test [26] and Begg-Mazumdar's test [27] and by inspection of the funnel plots. The statistical analyses were conducted using the software package Stata, version 13.0 software (StataCorp, Texas, US).

Results

We identified 10 population-based prospective studies (9 publications) [2,7,11–17] that could be included in the analysis of tobacco smoking and pancreatitis risk (Fig. 1, Table 1). One publication provided results for two studies combined [15]. Five studies were from Europe, four studies were from the US and two studies were from Asia (Table 1).

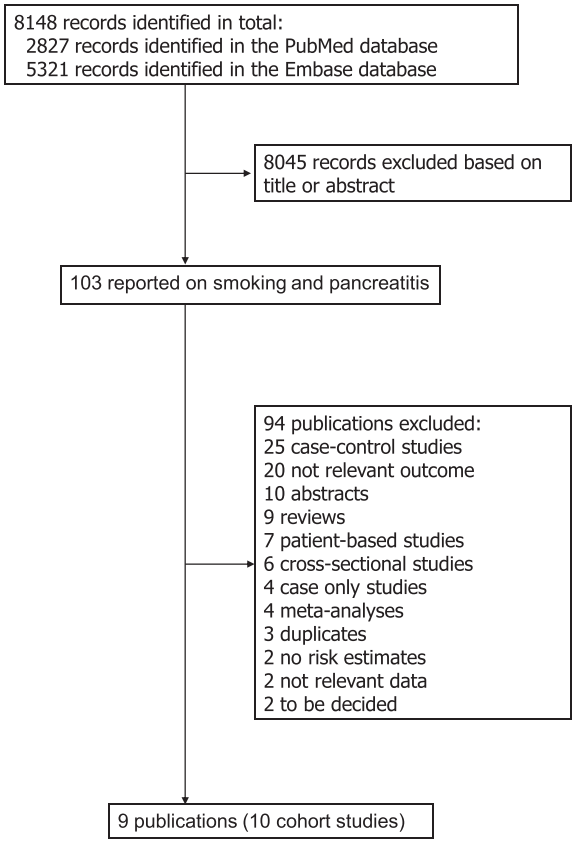

Fig. 1. Flow-chart of study selection.

Table 1
Prospective studies of tobacco smoking and pancreatitis

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Type of diabetes, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
Morton C et al, 2004, USA	Kaiser Permanente Medical Care Program	1978-1985 - 1998, ~16.5 years follow-up	128934 men and women: 439 pancreatitis cases 168/125/110 gallstone/ alcohol/ idiopathic pancreatitis cases	Cigarette smoking, gallstone-related pancreatitis	Never	1.0	Age, sex, race, BMI, education, alcohol
					Former	1.2 (0.7-2.2)	
					Current, <1 pack/day	0.9 (0.3-2.2)	
					Current, ≥1 pack/day	1.3 (0.5-3.1)	
				Cigarette smoking, alcohol-related pancreatitis	Never	1.0	
					Former	1.7 (0.9-3.1)	
					Current, <1 pack/day	2.7 (1.5-4.9)	
					Current, ≥1 pack/day	4.9 (2.2-11.2)	
				Cigarette smoking, idiopathic pancreatitis	Never	1.0	
					Former	1.6 (0.96-2.6)	
					Current, <1 pack/day	1.9 (1.1-3.3)	
					Current, ≥1 pack/day	3.1 (1.4-7.2)	
Lindkvist B et al, 2008, Sweden	The Malmo Preventive Project	1974-1992 - 1999, ~17.9 years follow-up	33211 men and women, age 45.6 years: 179 acute pancreatitis cases	Smoking status and tobacco dose	Never	1.00	Age, sex, Malmo Modification of the Michigan Alcoholism Screening Test, BMI
					Former	1.09 (0.66-1.80)	
					Current	2.14 (1.48-3.09)	
					Current, <20 cig/d	1.84 (1.19-2.85)	
					Current, 20-30	3.19 (2.03-5.00)	
					Current, >30	2.87 (1.57-5.24)	
Tolstrup JS et al, 2009, Denmark	Copenhagen City Heart Study	1976-78, 81-83, 91-94 − 2007, 20.2 years follow-up	9573 women and 8332 men, age 20-95 years: 235 pancreatitis cases 160 acute pancreatitis cases 97 chronic pancreatitis cases	Smoking status, women	Never	1.0	Age, sex, education, BMI, alcohol
					Former	1.4 (0.8-2.6)	
					Current, 1-14 g/d	1.7 (0.9-3.0)	
					15-24	2.6 (1.5-4.7)	
					≥25	2.3 (0.8-6.2)	
				Smoking status, men	Never	1.0	
					Former	2.1 (0.9-5.2)	
					Current, 1-14 g/d	1.5 (0.6-3.9)	
					15-24	2.6 (1.1-6.2)	
					≥25	4.1 (1.7-9.9)	
				Smoking status, acute pancreatitis	Never	1.0	
					Former	2.3 (1.3-4.1)	
					Current, 1-14 g/d	2.0 (1.1-3.6)	
					15-24	2.8 (1.5-5.0)	
					≥25	3.8 (1.9-7.5)	
				Smoking status, chronic pancreatitis	Never	1.0	
					Former	0.9 (0.4-2.0)	
					Current, 1-14 g/d	1.1 (0.5-2.3)	
					15-24	2.0 (1.0-4.1)	
					≥25	3.3 (1.5-7.3)	
				Smoking status, total pancreatitis	Never	1.0	
					Former	1.7 (1.0-2.7)	
					Current, 1-14 g/d	1.5 (0.9-2.5)	
					15-24	2.5 (1.5-3.9)	
					≥25	3.3 (1.9-5.8)	
				Pack-years, acute pancreatitis	Never	1.0	
					<15 pack-yrs, curr.	1.3 (0.7-2.7)	
					15-29	2.2 (1.2-3.8)	
					30-44	2.8 (1.6-5.1)	

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Table 1 (*continued*)

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Type of diabetes, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
					45-59	3.2 (1.6-6.2)	
					≥60	2.9 (1.4-6.3)	
					Ex., <30 yrs	2.0 (1.1-3.7)	
					≥30	2.7 (1.5-5.1)	
				Pack-years, chronic pancreatitis	Never	1.0	
					<15 pack-yrs, curr.	1.1 (0.4-2.6)	
					15-29	1.2 (0.5-2.6)	
					30-44	2.3 (1.1-4.8)	
					45-59	3.1 (1.3-7.1)	
					≥60	4.1 (1.8-9.7)	
					Ex., <30 yrs	0.8 (0.3-2.3)	
					≥30	1.1 (0.4-2.3)	
				Pack-years, total pancreatitis	Never	1.0	
					<15 pack-yrs, curr.	1.4 (0.8-2.4)	
					15-29	1.7 (1.0-2.8)	
					30-44	2.5 (1.5-4.2)	
					45-59	3.2 (1.8-5.7)	
					≥60	3.7 (2.0-6.8)	
					Ex., <30 yrs	1.5 (0.9-2.7)	
					≥30	2.2 (1.3-3.9)	
Gonzalez-Perez A et al, 2010, United Kingdom	The Health Improvement Network	1996-2006, 4.0 years follow-up	285525 men and women, age 20-79 years: 374 acute pancreatitis cases 4327 controls	Smoking status	Never	1.00	Age, sex, Townsend Index, ischemic heart disease, exposure to antibiotics, H2 blockers, proton pump inhibitors, NSAIDs, other antihypertensive drugs, alcohol, diabetes, antidiabetic drugs, gastrointestinal disease, BMI, paracetamol, ACE inhibitors
					Former	1.14 (0.89-1.47)	
					Current	1.48 (1.06-2.06)	
Sadr-Azodi O et al, 2012, Sweden	Swedish Mammography Cohort and Cohort of Swedish Men	1997 - 2009, 12 years follow-up	84667 men and women, age 46-84 years: 307 non-gallstone related acute pancreatitis cases 234 gallstone-related acute pancreatitis cases	Smoking status, all	Never	1.00	Age, sex, BMI, diabetes, educational level, monthly alcohol consumption
					Former	1.19 (0.97-1.46)	
					Current	1.33 (1.07-1.66)	
				Pack-years	Never	1.00	
					Former, <20 pack-years	1.14 (0.90-1.45)	
					Former, ≥20 pack-years	1.33 (0.99-1.79)	
					Current, <20 pack-years	1.11 (0.80-1.54)	
					Current, ≥20 pack-years	1.53 (1.17-2.01)	
				Smoking cessation, years from smoking cessation	Never	1.00	
					<10 years from cessation	1.37 (0.99-1.90)	
					10-14.9	1.28 (0.83-1.96)	
					15-19.9	1.25 (0.83-1.89)	
					20-24.9	1.14 (0.75-1.74)	
					25-29.9	0.95 (0.58-1.54)	

					≥30.0	1.07 (0.77-1.50)	
				Smoking status, non-gallstone-related pancreatitis	Never	1.00	
					Former	1.47 (1.11-1.94)	
					Current	1.83 (1.37-2.44)	
				Pack-years	Never	1.00	
					Former, <20 pack-years	1.36 (0.98-1.88)	
					Former, ≥20 pack-years	1.78 (1.21-2.60)	
					Current, <20 pack-years	1.46 (0.95-2.23)	
					Current, ≥20 pack-years	2.29 (1.63-3.22)	
				Smoking cessation, years from smoking cessation	Never	1.00	
					<10 years from cessation	1.95 (1.29-2.94)	
					10-14.9	1.70 (1.00-2.91)	
					15-19.9	1.72 (1.03-2.87)	
					20-24.9	1.20 (0.66-2.15)	
					25-29.9	1.14 (0.61-2.15)	
					≥30.0	1.07 (0.67-1.73)	
				Smoking status, gallstone-related pancreatitis	Never	1.00	
					Former	0.95 (0.62-1.26)	
					Current	0.88 (0.70-1.29)	
				Pack-years	Never	1.00	
					Former, <20 pack-years	0.96 (0.68-1.37)	
					Former, ≥20 pack-years	0.91 (0.55-1.50)	
					Current, <20 pack-years	0.80 (0.47-1.36)	
					Current, ≥20 pack-years	0.83 (0.51-1.34)	
				Smoking cessation, years from smoking cessation	Never	1.00	
					<10 years from cessation	0.85 (0.48-1.49)	
					10-14.9	0.88 (0.43-1.82)	
					15-19.9	0.80 (0.39-1.66)	
					20-24.9	1.13 (0.62-1.66)	
					25-29.9	0.77 (0.36-1.66)	
					≥30.0	1.11 (0.69-1.77)	
Lin HH et al, 2014, Taiwan	National Health Interview Survey in Taiwan	2001-2005, 3 years follow-up	35642 men and women, age >18 years: 66 pancreatitis cases	Smoking status	Never	1.00	Age, sex, alcohol, education, physical activity, household income, gallstone or bile duct stone
					Current	1.13 (0.62-2.06)	
					Ever	1.14 (0.63-2.06)	
				Cigarettes smoked per day	Never	1.00	
					≤5 cigarettes/day	2.06 (0.78-5.49)	
					>5-15	0.71 (0.26-1.92)	
					>15-25	0.96 (0.42-2.21)	
					>25	1.82 (0.72-4.62)	
				Years of smoking	Never	1.00	
					≤10 years	0.80 (0.17-3.76)	
					>10-20	1.38 (0.51-3.72)	
					>20	1.15 (0.57-2.32)	
				Pack-years of smoking	Never	1.00	
					≤10 pack-years	1.32 (0.56-3.12)	
					>10-20	0.98 (0.38-2.52)	
					>20	1.16 (0.53-2.54)	
Prizment AE et al, 2015, USA	Iowa Women's Health Study	1986-2004, ~18 years follow-up		Smoking status, acute pancreatitis	Never	1.00	
					Former	1.25 (0.97-1.61)	

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Table 1 (*continued*)

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Type of diabetes, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
			36436 women, age ≥65 years: 511 acute pancreatitis cases 149 chronic pancreatitis cases		Current	1.02 (0.81-1.28)	Age, time of Medicare enrolment, BMI
				Pack-years of smoking	0 pack-years	1.00	
					1-19	0.86 (0.65-1.15)	
					20-39	1.32 (1.01-1.73)	
					≥40	1.25 (0.91-1.70)	
				Smoking status, chronic pancreatitis	Never	1.00	
					Former	1.59 (1.02-2.47)	
					Current	1.64 (1.11-2.41)	
				Pack-years of smoking	0 pack-years	1.00	
					1-19	1.46 (0.92-2.30)	
					20-39	1.51 (0.92-2.48)	
					≥40	2.03 (1.23-3.34)	
Setiawan VW et al, 2016, USA	The Multiethnic Cohort Study	1993-1996 - 2012, 10.1 years follow-up	145886 men and women, age 45-75 years: 1065 gallstone-related acute pancreatitis cases 1222 non-gallstone-related acute pancreatitis cases 523 recurrent acute/ chronic pancreatitis cases	Smoking status, gallstone-related acute pancreatitis, men	Never	1.00	BMI, alcohol, diabetes, vigorous activity, education
					Former	1.22 (0.98-1.51)	
					Current	0.95 (0.68-1.32)	
				Pack-years	Never	1.00	
					Former, <20 pack-years	1.20 (0.95-1.51)	
					Former, ≥20 pack-years	1.26 (0.93-1.70)	
					Current, <20 pack-years	0.94 (0.62-1.45)	
					Current, ≥20 pack-years	0.95 (0.61-1.48)	
				Smoking status, non-gallstone-related acute pancreatitis cases	Never	1.00	
					Former	1.21 (0.97-1.51)	
					Current	1.87 (1.44-2.43)	
				Pack-years	Never	1.00	
					Former, <20 pack-years	1.25 (0.99-1.57)	
					Former, ≥20 pack-years	1.10 (0.80-1.50)	
					Current, <20 pack-years	1.87 (1.37-2.56)	
					Current, ≥20 pack-years	1.87 (1.34-2.60)	
				Smoking status, recurrent acute pancreatitis and chronic pancreatitis	Never	1.00	
					Former	1.25 (0.89-1.78)	
					Current	1.72 (1.12-2.66)	
				Pack-years	Never	1.00	
					Former, <20 pack-years	1.28 (0.89-1.85)	
					Former, ≥20 pack-years	1.17 (0.72-1.90)	
					Current, <20 pack-years	1.96 (1.18-3.24)	
					Current, ≥20 pack-years	1.47 (0.84-2.60)	
				Smoking status, gallstone-related acute pancreatitis, women	Never	1.00	
					Former	1.16 (0.95-1.41)	
					Current	1.20 (0.92-1.56)	
				Pack-years	Never	1.00	
					Former, <20 pack-years	1.11 (0.90-1.36)	

					Former, ≥20 pack-years	1.46 (1.01-2.13)	
					Current, <20 pack-years	1.18 (0.87-1.62)	
					Current, ≥20 pack-years	1.24 (0.80-1.90)	
				Smoking status, non-gallstone-related acute pancreatitis cases	Never	1.00	
					Former	1.35 (1.13-1.61)	
					Current	1.63 (1.30-2.04)	
				Pack-years	Never	1.00	
					Former, <20 pack-years	1.27 (1.05-1.53)	
					Former, ≥20 pack-years	1.83 (1.34-2.50)	
					Current, <20 pack-years	1.45 (1.11-1.91)	
					Current, ≥20 pack-years	2.01 (1.45-2.80)	
				Smoking status, recurrent acute pancreatitis and chronic pancreatitis	Never	1.00	
					Former	1.28 (0.97-1.68)	
					Current	2.31 (1.70-3.14)	
				Pack-years	Never	1.00	
					Former, <20 pack-years	1.20 (0.89-1.61)	
					Former, ≥20 pack-years	1.75 (1.07-2.85)	
					Current, <20 pack-years	1.89 (1.29-2.75)	
					Current, ≥20 pack-years	3.22 (2.12-4.87)	
Pang Y et al, 2018, China	China Kadoorie Biobank Study	2004-2008 - 2015, 9.2 years follow-up	209237 men, age 30-79 years: 421 acute pancreatitis cases 299 other pancreatitis cases	Smoking status, acute pancreatitis	Never	1.00 (0.75-1.33)	Age, sex, region, education, alcohol, medication (aspirin, ACE-I, beta blockers, statins, diuretics, calcium antagonists, metformin, insulin), obesity, physical inactivity, gallbladder disease, diabetes
					Occasional	1.26 (0.93-1.73)	
					Former	1.34 (0.93-1.92)	
					Current	1.45 (1.28-1.64)	
				Cigarettes per day	Never	1.00 (0.75-1.34)	
					<20 cig/d	1.27 (1.06-1.52)	
					20-24	1.39 (1.16-1.67)	
					≥25	1.97 (1.59-2.44)	
				Smoking status, other pancreatitis	Never	1.00 (0.70-1.42)	
					Occasional	1.17 (0.79-1.72)	
					Former	1.09 (0.68-1.73)	
					Current	1.47 (1.28-1.70)	
				Cigarettes per day	Never	1.00 (0.70-1.43)	
					<20 cig/d	1.13 (0.91-1.41)	
					20-24	1.57 (1.28-1.94)	
					≥25	1.88 (1.45-2.44)	
				Smoking status, chronic pancreatitis	Never	1.00	
					Current	1.60 (0.61-4.19)	

ACE-I=angiotensin converting enzyme inhibitors, BMI =Body mass index, NSAIDs=non-steroidal anti-inflammatory drugs

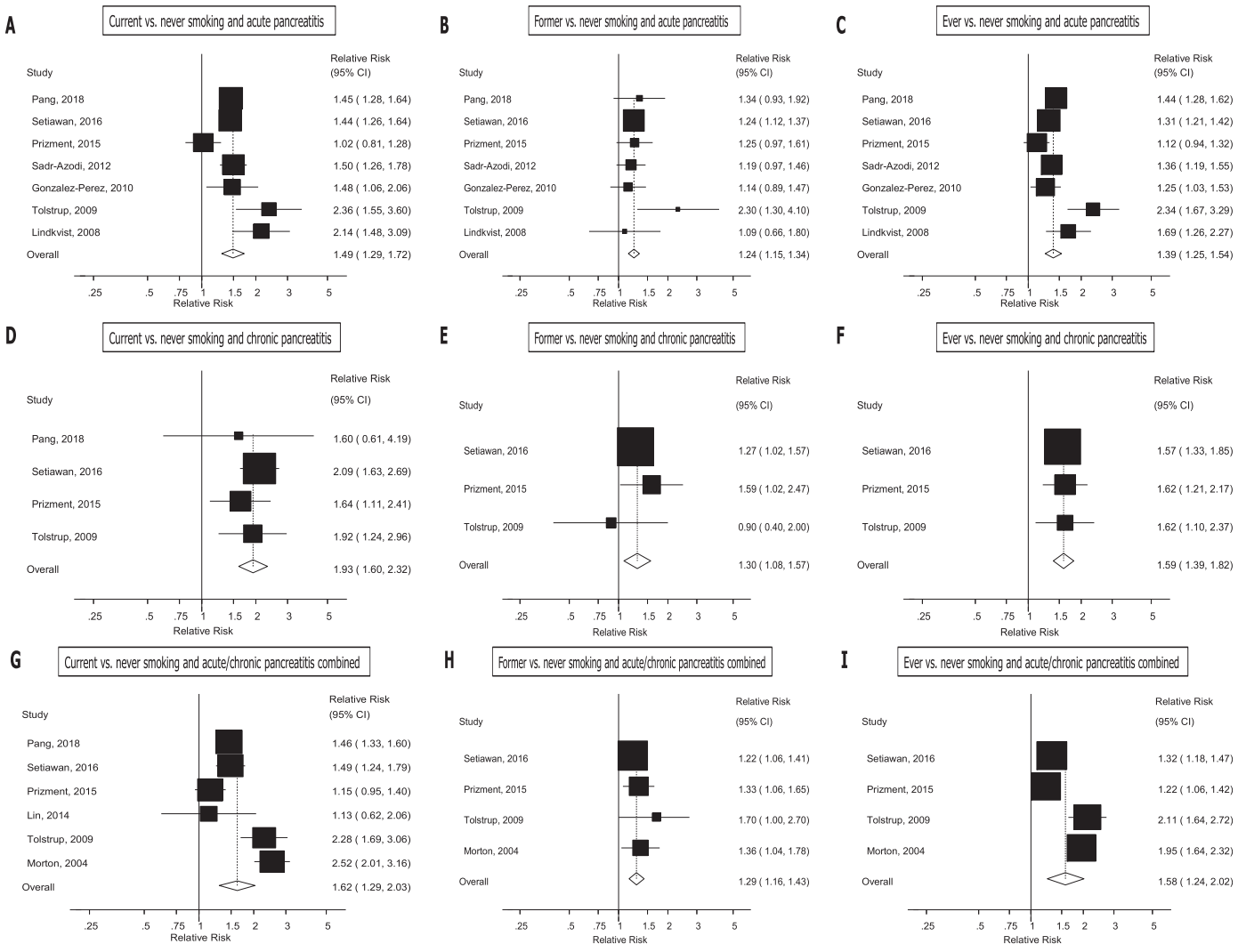

Fig. 2. Smoking status and acute, chronic and acute/chronic pancreatitis.

Acute pancreatitis

Eight cohort studies (7 publications, 7 risk estimates) [2,12–17] were included in the analyses of current, former and ever smoking vs. never smoking and risk of acute pancreatitis (5131 cases, 833 120 participants). The summary RR was 1.49 (95% CI: 1.29–1.72, $I^2 = 67.9\%$, $p_{heterogeneity} = 0.005$) for current smokers, 1.24 (95% CI: 1.15–1.34, $I^2 = 0\%$, $p_{heterogeneity} = 0.49$) for former smokers, and 1.39 (95% CI: 1.25–1.54, $I^2 = 68.9\%$, $p_{heterogeneity} = 0.004$) for ever smokers (Fig. 2a–c). There was no evidence of publication bias with Egger's test or Begg's test for current smokers ($p = 0.40$ and $p = 0.13$, respectively), former smokers ($p = 0.45$ and $p = 0.37$, respectively), or ever smokers ($p = 0.27$ and 0.23, respectively) (Supplementary Fig. 1-3). The results were not materially altered in sensitivity analyses excluding one study at a time from the analyses (Supplementary fig. 4-6).

Three cohort studies [2,12,13] were included in the dose-response analysis of cigarettes per day and risk of acute pancreatitis and the summary RR per 10 cigarettes per day was 1.30 (95% CI: 1.18–1.42, $I^2 = 42.3\%$, $p_{heterogeneity} = 0.18$) (Fig. 3a). There was no evidence of a nonlinear association between cigarettes smoked per day and risk of acute pancreatitis, $p_{nonlinearity} = 0.35$ (Fig. 3d).

Four cohort studies [13,15–17] were included in the dose-response analysis of pack-years of smoking in current smokers and risk of acute pancreatitis and the summary RR per 10 pack-years was 1.13 (95% CI: 1.08–1.17, $I^2 = 13.7\%$, $p_{heterogeneity} = 0.32$) (Fig. 3b). There was evidence of a nonlinear association between pack-years and risk of acute pancreatitis, $p_{nonlinearity} = 0.04$, with a stronger increase in risk between 0 and 20 pack-years than above that level (Fig. 3e).

Three cohort studies [13,15,17] were included in the dose-response analysis of pack-years of smoking among former smokers and risk of acute pancreatitis and the summary RR per 10 pack-years was 1.12 (95% CI: 1.07–1.17, $I^2 = 0\%$, $p_{heterogeneity} = 0.53$) (Fig. 3c). There was no evidence of a nonlinear association between pack-years in former smokers and risk of acute pancreatitis, $p_{nonlinearity} = 0.14$ (Fig. 3e).

Chronic pancreatitis

Four [2,13,16,17], three [13,16,17] and three [13,16,17] cohort studies were included in the analysis of current (4037 cases, 710 541 participants), former (2958 cases, 200 227 participants) and ever smoking (2958 cases, 200 227 participants) vs. never smoking and risk of chronic pancreatitis, respectively. The summary RR was 1.93 (95% CI: 1.60–2.32, $I^2 = 0\%$, $p_{heterogeneity} = 0.75$)

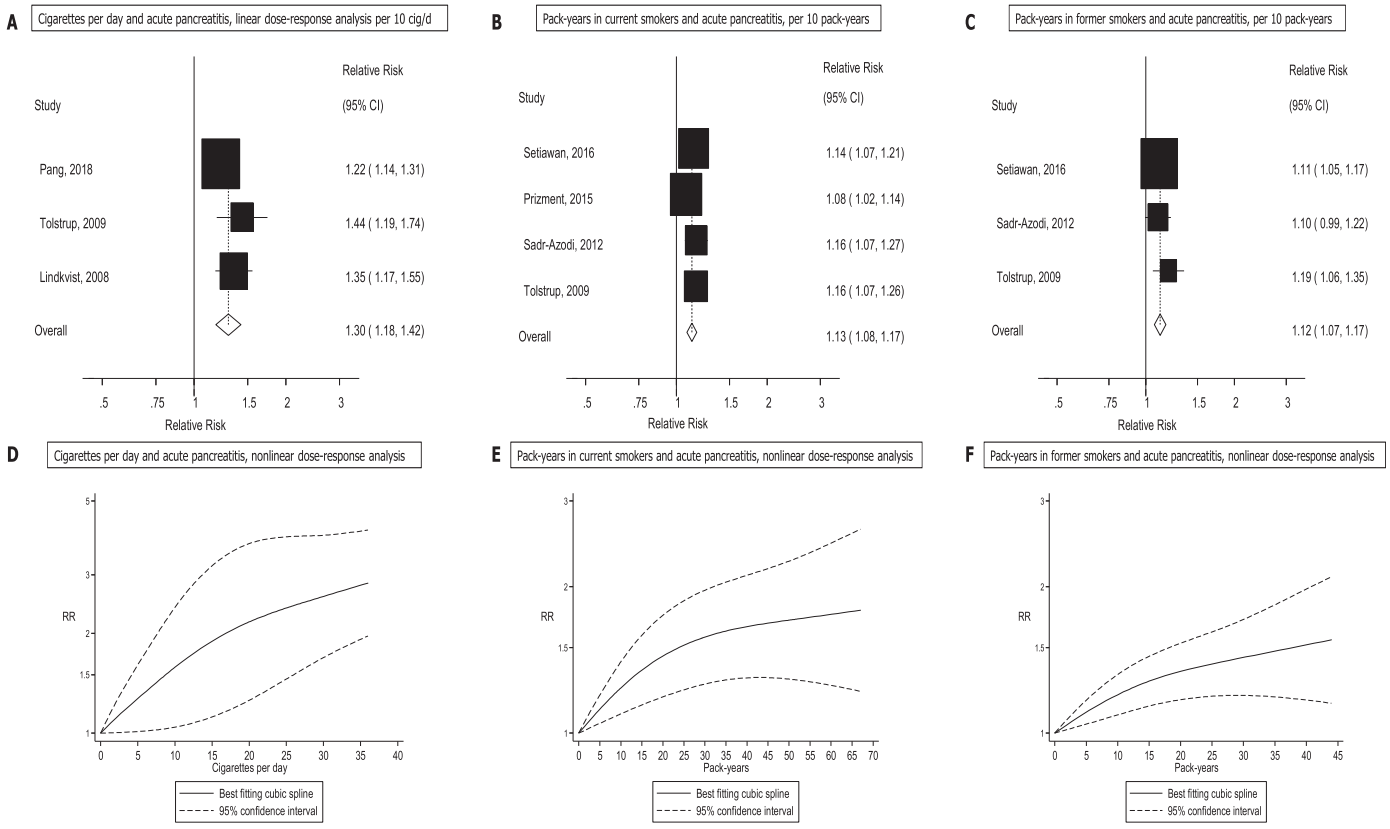

Fig. 3. Cigarettes per day and pack years and risk of acute pancreatitis.

for current smokers, 1.30 (95% CI: 1.08–1.57, $I^2 = 0\%$, $p_{heterogeneity} = 0.44$) for former smokers, and 1.59 (95% CI: 1.39–1.82, $I^2 = 0\%$, $p_{heterogeneity} = 0.98$) for ever smokers (Fig. 2d–f). Most of the results were similar in sensitivity analyses excluding one study at a time (Supplementary fig. 7-9).

Three studies [13,16,17] were included in the analysis of pack-years in current smokers and risk of chronic pancreatitis and the summary RR per 10 pack-years was 1.22 (95% CI: 1.11–1.33, $I^2 = 0\%$, $p_{heterogeneity} = 0.44$) (Figure Fig. 4a). The test for nonlinearity was not significant, $p_{nonlinearity} = 0.27$ (Fig. 4c).

Two studies [13,17] were included in the analysis of pack-years in current smokers and risk of chronic pancreatitis and the summary RR per 10 pack-years was 1.10 (95% CI: 0.99–1.21, $I^2 = 0\%$, $p_{heterogeneity} = 0.49$) (Fig. 4b). The test for nonlinearity was not significant, $p_{nonlinearity} = 0.48$ (Fig. 4d).

Acute and chronic pancreatitis combined

Six [2,7,11,13,16,17], four [11,13,16,17] and three [11,13,16,17] cohort studies were included in the analysis of current (4542 cases, 875 117 participants), former (3397 cases, 329 161 participants) and ever smoking (3397 cases, 329 161 participants) vs. never smoking and risk of acute and chronic pancreatitis combined, respectively. The summary RR was 1.62 (95% CI: 1.29–2.03, $I^2 = 86.1\%$, $p_{heterogeneity}<0.0001$) for current smokers, 1.29 (95% CI: 1.16–1.43, $I^2 = 0\%$, $p_{heterogeneity} = 0.57$) for former smokers, and 1.58 (95% CI: 1.24–2.02, $I^2 = 89.2\%$, $p_{heterogeneity}<0.0001$) for ever smokers (Fig. 3g–i). There was no evidence of publication bias with Egger's test or Begg's test for current smokers ($p = 0.60$ and $p = 0.71$, respectively) (Supplementary fig. 10). The results persisted in sensitivity analyses excluding one study at a time (Supplementary Fig. 11-13).

Three cohort studies [7,11,13] were included in the dose-response analysis of cigarettes per day and risk of acute and chronic pancreatitis combined and the summary RR per 10 cigarettes per day was 1.28 (95% CI: 1.05–1.57, $I^2 = 74.3\%$, $p_{heterogeneity} = 0.02$) (Fig. 5a). There was no evidence of a nonlinear association between cigarettes smoked per day and risk of acute pancreatitis, $p_{nonlinearity} = 0.87$ (Fig. 5d).

Four studies [7,13,16,17] were included in the analysis of pack-years in current smokers and risk of acute and chronic pancreatitis combined and the summary RR per 10 pack-years was 1.14 (95% CI: 1.08–1.21, $I^2 = 59.9\%$, $p_{heterogeneity} = 0.06$) (Fig. 5b). The test for nonlinearity was not significant, $p_{nonlinearity} = 0.12$ (Fig. 5e).

Two studies [13,17] were included in the analysis of pack-years in former smokers and risk of acute and chronic pancreatitis combined and the summary RR per 10 pack-years was 1.12 (95% CI: 1.07–1.18, $I^2 = 0\%$, $p_{heterogeneity} = 0.37$) (Fig. 5c). The test for nonlinearity was not significant, $p_{nonlinearity} = 0.14$ (Fig. 5f).

Gallstone and non-gallstone-related pancreatitis

Three studies [11,15,17] were included in the analyses of current, former and ever smoking and risk of gallstone-related and non-gallstone-related pancreatitis and the summary RR for gallstone-related pancreatitis was 1.03 (95% CI: 0.87–1.22, $I^2 = 0\%$, $p_{heterogeneity} = 0.49$) for current smokers, 1.16 (95% CI: 1.02–1.31, $I^2 = 0\%$, $p_{heterogeneity} = 0.51$) for former smokers, and 1.08 (95% CI: 0.91–1.27, $I^2 = 39.7\%$, $p_{heterogeneity} = 0.19$) for ever smokers, and for non-gallstone-related pancreatitis was 1.98 (95% CI: 1.55–2.53, $I^2 = 63\%$, $p_{heterogeneity} = 0.07$) for current smokers, 1.40 (95% CI: 1.19–1.64, $I^2 = 26.4\%$, $p_{heterogeneity} = 0.26$) for former smokers, and

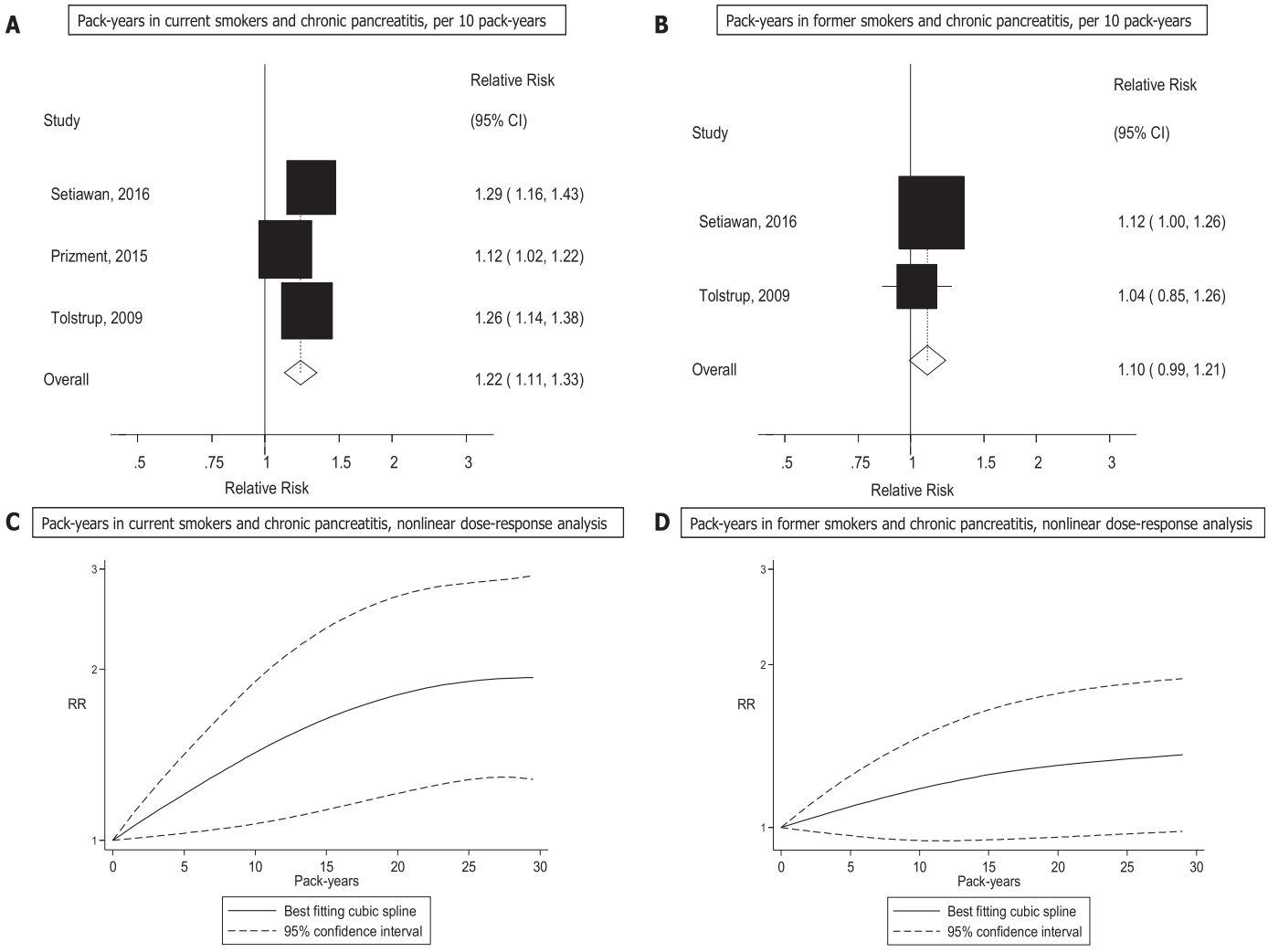

Fig. 4. Pack-years and risk of chronic pancreatitis.

1.72 (95% CI: 1.35–2.20, $I^2 = 81.5\%$, $p_{heterogeneity} = 0.005$) for ever smokers (Supplementary Fig. 14-16).

Subgroup and sensitivity analyses

In the analysis of smoking status and acute pancreatitis there were positive associations in nearly all subgroup analyses defined by sex, duration of follow-up, geographic location, number of cases, study quality and adjustment for confounding factors (including age, education, alcohol, BMI, physical activity) and potential intermediate factors (diabetes, gallstones, triglycerides) (Table 2). With meta-regression analyses there was between-subgroup heterogeneity only in the subgroup analysis by number of cases for current smoking and acute pancreatitis and there was a weaker association in the studies with a larger number of cases compared to those with a low number of cases (Table 1). Because of the limited number of studies for chronic pancreatitis and acute and chronic pancreatitis combined no further subgroup analyses were conducted.

Because of the limited number of studies in the dose-response analyses we repeated the analysis of current vs. never smokers restricted to the studies included in the dose-response analysis to see if there was a difference in the overall result which could be due to selective reporting. When the analysis of current vs. never smokers and acute pancreatitis was restricted to three studies that reported on cigarettes per day the summary RR was 1.86 (95% CI: 1.32–2.62), while it was 1.44 (95% CI: 1.15–1.81) when it was restricted to the four studies included in the analysis of pack-years in current smokers, and 1.57 (95% CI: 1.31–1.89) for the three studies included on pack-years in former smokers, which compared to 1.49 (95% CI: 1.29–1.72) for all the seven studies of current vs. never smokers and acute pancreatitis.

The results were similar when analyses of current vs. never smokers and chronic pancreatitis were restricted to the three and two studies that were included in the dose-response analyses of pack-years in current and former smokers with summary RRs of 1.94 (95% CI: 1.61–2.35) when restricted to the three studies of pack-years in current smokers, and 2.05 (95% CI: 1.65–2.54) for the two studies of pack-years in former smokers vs. 1.93 (95% CI: 1.60–2.32) for all the four studies of current vs. never smokers and chronic pancreatitis.

The mean (median) study quality scores were 7.2 (7.0) for the studies included in the analysis of smoking status and acute pancreatitis out of 9.0 possible (Supplementary Table 2).

Discussion

This meta-analysis of prospective studies found that current smoking was associated with 49%, 93% and 62% increases in the

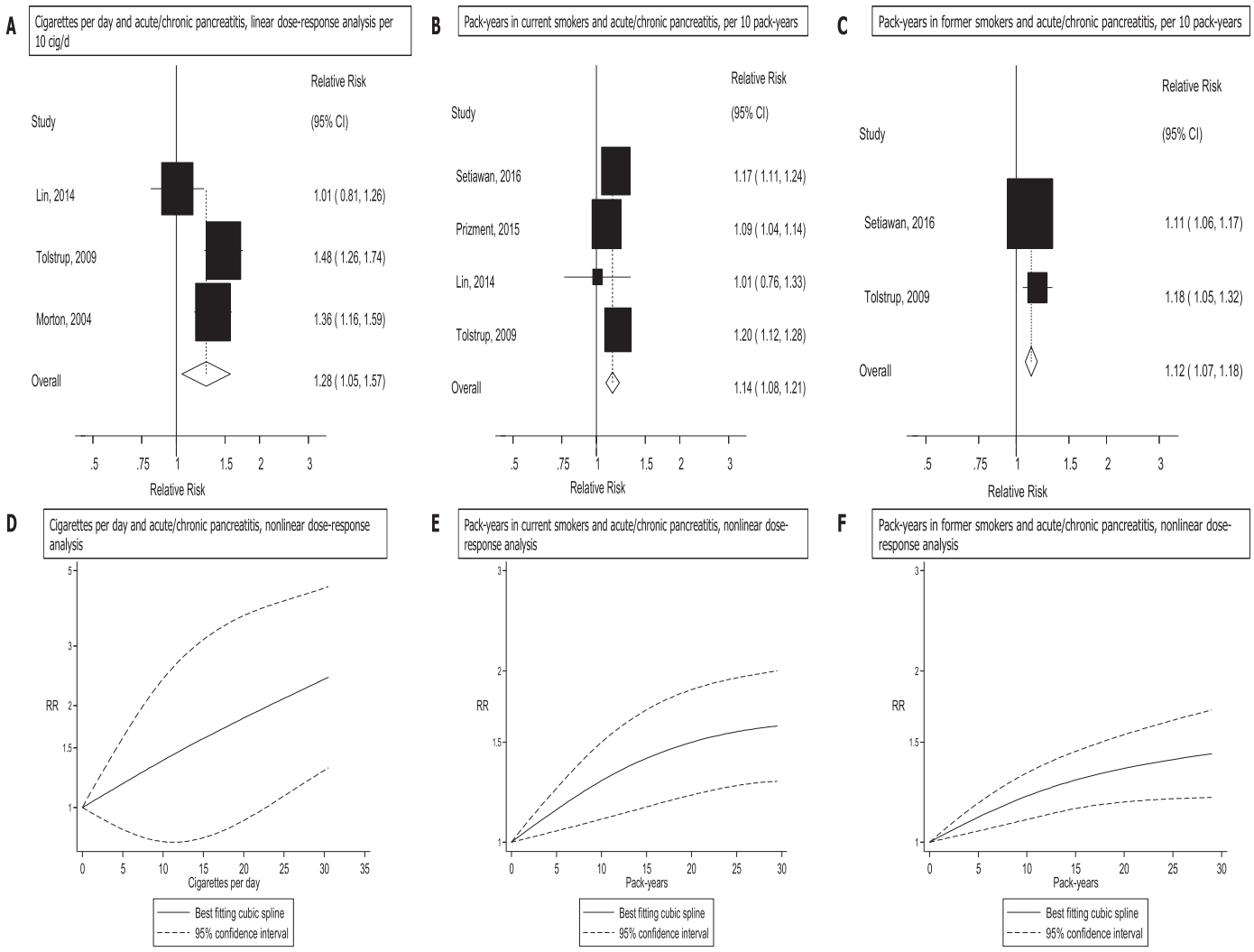

Fig. 5. Cigarettes per day and pack-years and risk of acute/chronic pancreatitis.

relative risk of acute pancreatitis, chronic pancreatitis and acute/chronic pancreatitis combined compared to never smokers, respectively, while the corresponding results for former smokers showed 24%, 30% and 29% increases in the relative risk compared to never smokers. In the dose-response analysis there was a 30% and 28% increase in the risk of acute pancreatitis and acute/chronic pancreatitis combined per 10 cigarettes smoked per day and 10–22% increases in the risk of acute, chronic or acute and chronic pancreatitis combined per 10 pack-years of smoking. There was no evidence of nonlinearity of the association for cigarettes per day, but some indication of nonlinearity for pack-years in current smokers and acute pancreatitis with a stronger association between 0 and 20 pack-years than above, however, the test for nonlinearity was not significant in the remaining analyses. The association between current smoking and pancreatitis was restricted to non-gallstone-related pancreatitis and not observed for gallstone-related pancreatitis, while for former smokers there was a weak association for gallstone-related pancreatitis, but a stronger association for non-gallstone-related pancreatitis. Only one study reported on alcohol-related pancreatitis and idiopathic pancreatitis and found smoking was associated with increased risk of both subtypes even after adjusting for alcohol consumption [11].

In subgroup analyses of smoking status and acute pancreatitis, positive associations were observed both in men and women and across geographic locations (Europe, US and Asia) and there was little evidence of heterogeneity overall and between different subgroups, however, in some subgroups there was a limited number of studies.

Like any meta-analysis of published studies the current analysis may have been affected by limitations including potential confounding, measurement errors in the assessment of tobacco smoking as well as publication bias. Although confounding by other risk factors is a possibility we found that the associations between smoking and acute pancreatitis persisted among subgroups of studies that adjusted for age, education, alcohol, BMI, and physical activity and the results also persisted among studies that adjusted for diabetes and gallstones, which might be considered intermediate risk factors. Residual confounding from other or non-established risk factors cannot be entirely excluded. Tobacco smoking is in general measured well by self-report, however, because of the prospective design of the include studies any measurement errors would most likely have led to attenuation of the true underlying association. Although publication bias can affect meta-analyses of published studies there was no evidence of

Table 2
Subgroup analyses of tobacco smoking and acute pancreatitis.

		Current smoking and acute pancreatitis					Former smoking and acute pancreatitis					Ever smoking and acute pancreatitis				
		n	RR (95% CI)	I^2 (%)	P_h^1	P_h^2	n	RR (95% CI)	I^2 (%)	P_h^1	P_h^2	*n*	RR (95% CI)	I^2 (%)	P_h^1	P_h^2
All studies		7	1.49 (1.29–1.72)	67.9	0.005		7	1.24 (1.15–1.34)	0	0.49		7	1.39 (1.25–1.54)	77.0	0.002	
Gender																
Men		1	1.44 (1.17–1.77)			0.30/0.67[3]	1	1.22 (1.04–1.42)			0.95/0.81[3]	1	1.29 (1.14–1.46)			0.30/0.80[3]
Women		2	1.27 (1.11–1.45)	81.5	0.02		2	1.26 (1.12–1.41)	0	0.96		2	1.26 (1.15–1.38)	61.4	0.11	
Men, women		5	1.54 (1.40–1.68)	50.4	0.09		5	1.23 (1.08–1.41)	26.6	0.24		5	1.43 (1.33–1.55)	65.8	0.02	
Follow-up																
<10 years		2	1.45 (1.29–1.63)	0	0.91	0.81	2	1.20 (0.98–1.48)	0	0.47	0.82	2	1.37 (1.20–1.57)	31.1	0.23	0.73
≥10 years		5	1.54 (1.23–1.92)	78.6	0.001		5	1.25 (1.12–1.39)	17.6	0.30		5	1.42 (1.22–1.67)	77.0	0.002	
Geographic location																
Europe		4	1.75 (1.40–2.18)	52.1	0.10	0.29	4	1.25 (1.01–1.56)	42.4	0.16	0.73	4	1.55 (1.24–1.93)	74.3	0.009	0.54
America		2	1.23 (0.88–1.72)	84.7	0.01		2	1.24 (1.13–1.36)	0	0.95		2	1.23 (1.06–1.43)	62.7	0.10	
Asia		1	1.45 (1.28–1.64)				1	1.34 (0.93–1.92)				1	1.44 (1.28–1.62)			
Number of cases																
Cases <250		2	2.23 (1.69–2.95)	0	0.73	0.04	2	1.56 (0.75–3.25)	72.9	0.06	0.62	2	1.97 (1.43–2.70)	50.4	0.16	0.08
Cases 250-<500		1	1.48 (1.06–2.06)				1	1.14 (0.89–1.47)				1	1.25 (1.03–1.53)			
Cases ≥500		4	1.37 (1.20–1.56)	64.5	0.04		4	1.24 (1.14–1.34)	0	0.95		4	1.32 (1.21–1.43)	49.3	0.12	
Study quality																
0–3 stars		0				0.83	0				0.91	0				0.71
4–6 stars		1	1.44 (1.26–1.64)				1	1.24 (1.12–1.37)				1	1.31 (1.21–1.42)			
7–9 stars		6	1.52 (1.26–1.84)	73.2	0.002		6	1.24 (1.09–1.41)	8.5	0.36		6	1.42 (1.23–1.64)	72.9	0.002	
Adjustment for confounding factors																
Age	Yes	6	1.52 (1.26–1.84)	73.2	0.002	0.83	6	1.24 (1.09–1.41)	8.5	0.36	0.91	6	1.42 (1.23–1.64)	72.9	0.002	0.71
	No	1	1.44 (1.26–1.64)				1	1.24 (1.12–1.37)				1	1.31 (1.21–1.42)			
Education	Yes	4	1.50 (1.35–1.68)	40.1	0.17	0.65	4	1.28 (1.11–1.49)	36.4	0.19	0.60	4	1.45 (1.27–1.65)	73.8	0.009	0.47
	No	3	1.45 (0.94–2.24)	83.3	0.003		3	1.18 (1.00–1.40)	0	0.83		3	1.29 (1.05–1.59)	64.5	0.06	
Alcohol	Yes	6	1.55 (1.39–1.73)	42.4	0.12	0.06	6	1.24 (1.13–1.36)	8.4	0.36	0.90	6	1.43 (1.28–1.60)	64.9	0.01	0.26
	No	1	1.02 (0.81–1.28)				1	1.25 (0.97–1.61)				1	1.12 (0.94–1.32)			
BMI	Yes	7	1.49 (1.29–1.72)	67.9	0.005	NC	7	1.24 (1.15–1.34)	0	0.49	NC	7	1.39 (1.25–1.54)	77.0	0.002	NC
	No	0					0					0				
Physical activity	Yes	2	1.45 (1.32–1.58)	0	0.94	0.74	2	1.25 (1.13–1.37)	0	0.69	0.91	2	1.36 (1.24–1.49)	41.0	0.19	0.81
	No	5	1.57 (1.20–2.07)	78.6	0.001		5	1.24 (1.06–1.44)	23.8	0.26		5	1.44 (1.18–1.75)	77.2	0.001	
Adjustment for potential intermediate factors																
Diabetes mellitus	Yes	4	1.46 (1.35–1.58)	0	0.99	0.66	4	1.23 (1.13–1.33)	0	0.88	0.48	4	1.34 (1.27–1.42)	0	0.52	0.44
	No	3	1.69 (0.94–3.04)	89.1	<0.0001		3	1.39 (0.97–2.01)	53.8	0.12		3	1.61 (1.04–2.51)	88.2	<0.0001	
Gallstones	Yes	2	1.45 (1.29–1.63)	0	0.91	0.81	2	1.20 (0.98–1.48)	0	0.47	0.82	2	1.37 (1.20–1.57)	31.1	0.23	0.73
	No	5	1.54 (1.23–1.92)	78.6	0.001		5	1.25 (1.12–1.39)	17.6	0.30		5	1.42 (1.22–1.67)	77.0	0.002	
Triglycerides	Yes	0				NC	0				NC	0				NC
	No	7	1.49 (1.29–1.72)	67.9	0.005		7	1.24 (1.15–1.34)	0	0.49		7	1.39 (1.25–1.54)	68.9	0.004	

n denotes the number of studies.
BMI, body mass index, NC, not calculable because no studies were present in one of the subgroups.
[1] P for heterogeneity within each subgroup.
[2] P for heterogeneity between subgroups with meta-regression analysis.
[3] P for heterogeneity between men and women (excluding studies with both sexes) with meta-regression analysis.

publication bias with the statistical tests used or by inspection of the funnel plots. Nevertheless, in several analyses the number of studies was too low to test meaningfully for publication bias. In sensitivity analyses we restricted the analyses of smoking status to the same studies that were included in the dose-response analyses of cigarettes per day and pack-years and when studies were restricted to the same studies as in the analysis of cigarettes per day the association was stronger than for all the studies combined, which might suggest possible overestimation of the association, however, when analyses of smoking status were restricted to the same studies as in the pack-years analysis there was little difference in the results. Further studies are therefore needed, particularly on cigarettes per day, but also on pack-years and years since smoking cessation.

A number of biological mechanisms could explain why tobacco smoking increases risk of pancreatitis. Tobacco smoking increases the risk of type 2 diabetes [8] and gallstones [9], which are established risk factors for pancreatitis [2]. However, in this analysis the association between smoking and pancreatitis persisted among studies that adjusted for both diabetes and gallstones and there was a stronger association between smoking and non-gallstone-related pancreatitis than with gallstone-related pancreatitis, thus it seems the association is independent of these risk factors. An experimental study in rats showed that exposure to tobacco smoke induced chronic pancreatic inflammatory processes with fibrosis and scarring of pancreatic acinar structures and concurrent increases in expression of pancreatitis-associated protein and trypsinogen and chymotrypsinogen gene expression as well as reduced pancreatic enzyme content were observed [28]. Although tobacco smoke contains more than 4000 chemical compounds experimental studies have mainly studied the role of nicotine and nicotine-derived nitrosamine ketone (NNK) in relation to pancreatitis. Animal studies have shown that exposure to nicotine resulted in nicotine accumulation in pancreas and intestines [29], and exposure to nicotine has been shown to induce pathological changes in exocrine pancreatic tissue including cytoplasmic swelling, vacuolization, formation of pyknotic nuclei and karyorrhexis [30–33], similar to what is seen in acute pancreatitis [30]. In addition, nicotine exposure reduces pancreatic amylase secretion, particularly after cholecystokinin stimulation and increases retention of pro-enzymes in the pancreas [31,33–37], and has been shown to alter circulating levels of gastrin and cholecystokinin [38], changes which are observed in pancreatitis [29,39]. NNK is one of the most toxic carcinogens found in tobacco smoke and has been shown to cause premature activation of digestive enzymes (trypsinogen and chymotrypsinogen) in acinar cells [40], a major initial step in the development of pancreatitis and to cause cellular injury (vacuolization, pyknotic nuclei, and edema) in the pancreas after a 2-week exposure period in rats [40].

With regard to the strengths of the current study we included prospective studies which are not affected by recall bias and are less likely to be affected by selection bias, and which also have a clear temporal relation between the exposure and the outcome. We conducted detailed subgroup and sensitivity analyses and in general the findings were similar across most subgroup analyses and they were robust in sensitivity analyses. The large sample size contributed to a robust estimate of the association between tobacco smoking and risk of pancreatitis, and there was little evidence of heterogeneity. There was also a dose-response relationship between increasing number of cigarettes smoked per day and pack-years of smoking and risk of pancreatitis. These findings provide further evidence that tobacco smoking increases pancreatitis risk and support recommendations and policies that promote smoking cessation among current smokers and smoking avoidance among non-smokers.

Conclusion

This meta-analysis found an increased risk of acute pancreatitis, chronic pancreatitis and acute/chronic pancreatitis combined among smokers and there is a lower risk among former smokers than among current smokers. There was a dose-response relationship between increasing number of cigarettes per day smoked and pack-years of smoking and pancreatitis risk. A positive association was observed between current smoking and non-gallstone-related pancreatitis, but not with gallstone-related pancreatitis. Any further studies should clarify the association between tobacco smoking, dose of smoking, years since smoking cessation and risk of pancreatitis subtypes.

Contribution

DA designed the research, conducted the literature search and analyses and wrote the first draft of the paper. DA and YMS conducted the literature screening. YMS checked the data extractions for accuracy. DA, YMS, TN, ER interpreted the data, revised the subsequent drafts for important intellectual content, read and approved the final manuscript. DA takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflicts of interest

The authors declare that there is no duality of interest associated with this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.09.004.

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