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ORIGINAL ARTICLE

High Body Mass Index and Central Adiposity Is Associated with Increased Risk of Acute Pancreatitis: A Meta-Analysis

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Abstract

Background Higher body mass index and waist circumference have been associated with increased risk of pancreatitis in several prospective studies; however, the results have not been entirely consistent.

Aims We conducted a systematic review and dose-response meta-analysis of prospective studies on adiposity and risk of pancreatitis to clarify this association.

Methods PubMed and Embase databases were searched for studies on adiposity and pancreatitis up to January 27, 2020. Prospective studies reporting adjusted relative risk (RR) estimates and 95% confidence intervals (CIs) for the association between adiposity and risk of pancreatitis were included, and summary RRs (95% CIs) were calculated using a random effects model.

Results Ten prospective studies with 5129 cases and 1,693,657 participants were included. The summary RR (95% CI) of acute pancreatitis was 1.18 (95% CI: 1.03–1.35, $I^2 = 91\%$, $n = 10$ studies) per 5 kg/m^2 increase in BMI and 1.36 (95% CI: 1.29–1.43, $I^2 = 0\%$, $n = 3$) per 10 cm increase in waist circumference. There was evidence of a nonlinear association between BMI and acute pancreatitis, $p_{\text{nonlinearity}} < 0.0001$, with a steeper association at higher levels of BMI, but not for waist circumference, $p_{\text{nonlinearity}} = 0.19$. Comparing a BMI of 35 with a BMI of 22, there was a 58% increase in the RR and there was a four-fold increase in the RR comparing a waist circumference of 110 cm with 69 cm. There was no evidence of publication bias.

Conclusions This meta-analysis suggests that both increasing BMI and waist circumference are associated with a dose-response-related increase in the risk of acute pancreatitis.

Keywords Body mass index · Central adiposity · Waist circumference · Pancreatitis · Systematic review · Meta-analysis

Introduction

Pancreatitis is an inflammatory disorder of the pancreas characterized by symptoms such as severe abdominal pain, nausea and vomiting [1]. Pancreatitis develops when digestive enzymes produced by the pancreas are activated in the

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pancreas instead of in the small intestine, causing inflammation and fibrosis [2]. Pancreatitis is an important risk factor for pancreatic cancer (relative risk of 8) [3, 4] as well as for all-cause and cause-specific mortality [4, 5]. Incidence rates of pancreatitis vary from 4 up to > 100 cases per 100,000 persons per year globally, with higher rates in America for acute pancreatitis, and in Europe for chronic pancreatitis, while the lowest rates are observed in Southeast Asia [6]. In addition, the incidence of the disease has been increasing substantially over the last decades in secular trend studies in the USA and Europe [7–13]. The wide variation in the incidence of pancreatitis internationally combined with the rapid changes in the incidence of the disease over time within countries suggests that modifiable risk factors may be of major importance in the etiology of the disease. High alcohol intake [4, 14], smoking [4, 15], diabetes mellitus [4] and a history of gallstones [4, 14] are among the established or suspected risk factors for pancreatitis.

Overweight and obesity as measured by body mass index (BMI, kg/m^2) is an established risk factor for type 2 diabetes [16] and gallstone or gallbladder disease [17], which are risk factors for pancreatitis [4], and adiposity is also an established risk factor for pancreatic cancer [18], for which pancreatitis is a risk factor [4]. High BMI has also been directly associated with increased risk of acute pancreatitis in some prospective studies [4, 19–21]; however, the results are not entirely consistent as several other studies found no clear association [22–24] and one study suggested a U-shaped association [25]. In addition, higher waist circumference has been consistently associated with increased risk of acute pancreatitis [4, 24]. Whether the association differs by subtype of pancreatitis (e.g., gallstone-related or alcohol-related pancreatitis) is not clear, and whether the association between BMI and pancreatitis is independent of diabetes or gallbladder disease is also not clear. Two Swedish studies [24] and a Chinese study [4] suggested a stronger association between waist circumference and pancreatitis than for BMI, particularly when mutually adjusted, and this finding might suggest insulin resistance may be an important contributor to pancreatitis. Although two previous meta-analyses found a 34–43% increase in risk of pancreatitis or acute pancreatitis with obesity [26, 27], they both had several limitations including the low number of studies ($n = 5$ and $n = 2$) which led to the combination of patient-based studies (type 2 diabetes, hypertension), one study on recurrent pancreatitis among pancreatitis patients, one case-control study and a population-based cohort study in one meta-analysis [26], while only two cohort studies were included in a second meta-analysis [27]. In addition, no results were reported for overweight and no dose-response analyses were conducted; thus, it is not clear if there is a dose-response relationship between increasing adiposity and pancreatitis or if there are any threshold levels. Given that several population-based cohort studies on adiposity and the risk of incident pancreatitis now have been published [4, 19–25], we therefore conducted a systematic review and dose-response meta-analysis of the available prospective studies to better define the strength and shape of the dose-response relationship between adiposity and risk of pancreatitis.

Materials and Methods

Search Strategy and Inclusion Criteria

Pubmed and Embase databases were searched for eligible studies up to January 27, 2020, as part of a larger project on risk factors for pancreatitis. The search terms used are provided in the supplementary text. We followed PRISMA criteria for reporting meta-analyses [28]. The reference lists of the identified publications were also searched for further studies.

Study Selection

We included published retrospective and prospective cohort studies and nested case-control studies within cohorts that reported adjusted relative risk (RR) estimates and 95% confidence intervals (CIs) for the association between any measure of adiposity (BMI, waist circumference, waist-to-hip ratio, weight gain, body fat) and the risk of pancreatitis. A list of the excluded studies and the exclusion reasons can be found in Supplementary Table 1. DA and YMS conducted the screening of the literature search.

Data Extraction

The following data were extracted from each study: The first author's last name, publication year, country where the study was conducted, the name of the study, study period and duration of follow-up, sample size, sex, number of cases, measure of adiposity, subgroup, RRs and 95% CIs 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 per 5 kg/m^2 increase in BMI and per 10 cm of waist circumference (the two adiposity measures which had enough studies to be analyzed) [29]. The average of the natural logarithm of the RRs was estimated, and the RR from each study was weighted using random effects weights. We used the method of Greenland and Longnecker to estimate linear trends across categories of BMI and waist circumference [30]. For studies which reported

adiposity measures by ranges, we estimated the midpoint for each category. When extreme categories were open-ended, we estimated an upper and lower cutoff value using the width of the adjacent category; however, when the WHO categories of BMI were used we used 18.5 as a lower cutoff if the upper cutoff was < 25. For studies in which the lowest category was not the reference category, we used the method of Hamling to convert the risk estimates so the lowest category became the reference category. We also conducted sensitivity analyses simply excluding the categories below the reference category. Fractional polynomial models were used to investigate a potential nonlinear association between BMI and waist circumference and risk of pancreatitis [31, 32]. The best-fitting second-order fractional polynomial regression model, defined as the one with the lowest deviance, was determined. A likelihood ratio test was used to assess the difference between the nonlinear and linear models to test for nonlinearity [31].

Heterogeneity between studies was evaluated using Q and I^2 statistics [33]. 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% indicate 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 [34].

Publication bias was assessed using Egger's test [35] and Begg-Mazumdar's test [36] and by inspection of funnel plots. The statistical analyses were conducted using the software package Stata, version 13.0 software (StataCorp, Texas, USA).

Results

We identified ten population-based prospective studies (eight publications, nine risk estimates) [4, 19–25] that were included in the meta-analysis of adiposity and risk of pancreatitis risk (Fig. 1, Table 1). Two publications included results from two studies each; the Swedish Mammography Cohort and the Cohort of Swedish Men [24] and the Copenhagen City Heart Study and the Copenhagen General Population Study [21]. Two studies were conducted in women, one in men and seven studies in men and women combined. Six studies were from Europe, two studies were from the USA and two studies were from Asia (Table 1).

Ten prospective studies (eight publications, nine risk estimates) [4, 19–25] with 1,693,657 participants and 5129

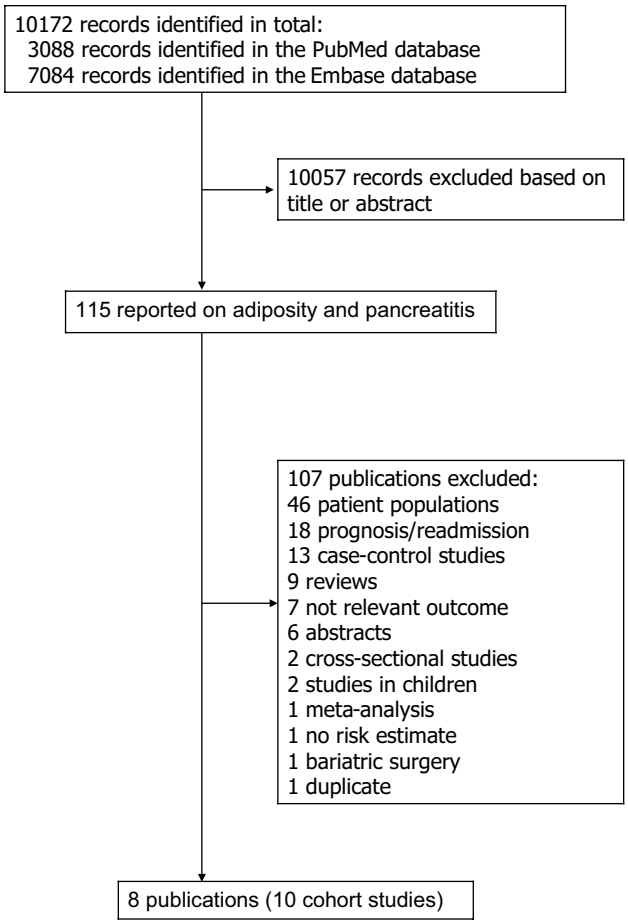

Fig. 1 Flowchart of study selection

cases were included in the analysis of BMI and the risk of acute pancreatitis. The summary RR was 1.18 (95% CI: 1.03–1.35, $I^2 = 91.1\%$, $p_{\text{heterogeneity}} < 0.0001$) per 5 kg/m^2 increase in BMI (Fig. 2a). There was no evidence of publication bias with Egger's test ($p = 0.93$) or with Begg's test ($p = 0.35$) (Supplementary Figure 1). The summary RR ranged from 1.14 (95% CI: 1.00–1.30) when excluding the study by Pang et al. [4] to 1.24 (95% CI: 1.12–1.37) when excluding the study by Choi et al. [25] (Supplementary Figure 2, Supplementary Figure 3a). One large Korean study found a L-shaped or U-shaped association between BMI and pancreatitis, which was more pronounced in ever smokers, and alcohol drinkers than in never smokers and nondrinkers, which could suggest potential residual confounding [25]. When data for never smokers were used instead of the total population for this study, the summary RR was 1.21 (95% CI: 1.09–1.34, $I^2 = 81.5\%$, $p_{\text{heterogeneity}} < 0.0001$) per 5 kg/m^2 increase in BMI (Supplementary Figure 4). Alternatively, when excluding the categories below the reference category when the lowest category was not the reference category, the summary RR was

Table 1 Prospective studies of body fatness and pancreatitis

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Assessment of anthropometric measures	Adiposity measure, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
Morton et al. [19], USA	Kaiser Permanente Medical Care Program	1978–1985–1998, ~16.5 years follow-up	128934 men and women: 439 pancreatitis cases	Measured	BMI, gallstone-related pancreatitis	Per 1 kg/m^2	1.08 (1.05–1.11)	Age, sex, race, education, alcohol
			168/125/110 gallstone/ alcohol/ idiopathic pancreatitis cases		BMI, alcohol-related pancreatitis	Per 1 kg/m^2	0.96 (0.92–1.01)	
					BMI, idiopathic pancreatitis	Per 1 kg/m^2	1.04 (0.98–1.06)	
Lindkvist et al. [22], 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	Measured	BMI	< 20	1.02 (0.56–1.88)	Age, sex, Malmo Modification of the Michigan Alcoholism Screening Test, smoking status, cigarettes per day
						20–25	1.00	
						25–30	1.15 (0.83–1.60)	
						> 30	1.45 (0.85–2.48)	
						Per 1 kg/m^2	1.05 (1.01–1.09)	
Gonzalez-Perez et al. [23], 2010, United Kingdom	The Health Improvement Network	1996–2006, 4.0 years follow-up	285525 men and women, age 20–79 years: 395 acute pancreatitis cases 4552 controls	Measured	BMI	< 20	1.13 (0.63–2.02)	Age, sex, Townsend index, ischemic heart disease, exposure to antibiotics, H_2 blockers, proton pump inhibitors, NSAIDs (aspirin and coxibs), antihypertensive drugs, smoking, alcohol, diabetes, antidiabetic drugs, gastrointestinal disease (gallstones, biliary tract disease, cholecystitis, gastroenteritis, abdominal pain, and others), paracetamol, ACE inhibitors
						20–24	1.00	
						25–29	0.99 (0.75–1.31)	
						≥ 30	0.92 (0.68–1.24)	

Table 1 (continued)

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Assessment of anthropometric measures	Adiposity measure, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
Sadr-Azodi et al. [24], Sweden	Swedish Mammography Cohort and the Cohort of Swedish Men	1997–2009, 12 years follow-up	68158 men and women, age 46–84 years: 424 acute pancreatitis	Self-reported (validated)	Waist circumference, total	72 cm	0.55 (0.33–0.92)	Age, sex, education, diabetes, known gallstone disease, monthly alcohol consumption, smoking, fruit and vegetables, mutual adjustment between BMI and waist circumference
						81	1.00	
						90	1.31 (0.97–1.78)	
						100	1.50 (1.04–2.16)	
						110	2.37 (1.50–3.74)	
						Per 10 cm	1.35 (1.19–1.53)	
					BMI	23.0 kg/m^2	1.00	
						26.8	1.18 (0.92–1.51)	
						31.6	1.02 (0.68–1.53)	
					Waist circumference, non-gallstone related acute pancreatitis	72 cm	0.62 (0.30–1.30)	
						81	1.00	
						90	1.44 (0.95–2.21)	
						100	1.39 (0.83–2.32)	
						110	2.12 (1.13–4.00)	
						Per 10 cm	1.22 (1.03–1.45)	
					BMI	23.0 kg/m^2	1.00	
						26.8	1.24 (0.89–1.73)	
						31.6	0.74 (0.40–1.38)	
					Waist circumference, gallstone related acute pancreatitis	72 cm	0.49 (0.23–1.00)	
						81	1.00	
						90	1.16 (0.75–1.79)	
						100	1.63 (0.96–2.75)	
						110	2.79 (1.45–5.38)	
						Per 10 cm	1.56 (1.29–1.90)	
					BMI	23.0 kg/m^2	1.00	
						26.8	1.12 (0.77–1.62)	
						31.6	1.27 (0.73–2.24)	
					Waist circumference, total, non-severe acute pancreatitis	72 cm	0.46 (0.25–0.84)	
						81	1.00	
						90	1.28 (0.92–1.78)	
						100	1.54 (1.03–2.29)	
						110	2.28 (1.37–3.78)	
						Per 10 cm	1.38 (1.20–1.59)	

Table 1 (continued)

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Assessment of anthropometric measures	Adiposity measure, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
					Waist circumference, non-gallstone related non-severe acute pancreatitis	72 cm	0.62 (0.27–1.42)	
						81	1.00	
						90	1.42 (0.88–2.29)	
						100	1.45 (0.82–2.56)	
						110	2.13 (1.05–4.33)	
						Per 10 cm	1.28 (1.06–1.55)	
					Waist circumference, gallstone related non-severe acute pancreatitis	72 cm	0.35 (0.15–0.83)	
						81	1.00	
						90	1.14 (0.71–1.81)	
						100	1.64 (0.94–2.89)	
						110	2.54 (1.23–5.23)	
						Per 10 cm	1.53 (1.24–1.90)	
					Waist circumference, total, severe acute pancreatitis	72 cm	1.08 (0.37–3.11)	
						81	1.00	
						90	1.53 (0.72–3.23)	
						100	1.34 (0.53–3.36)	
						110	2.88 (0.98–8.47)	
						Per 10 cm	1.24 (0.93–1.66)	
					Waist circumference, non-gallstone related severe acute pancreatitis	72 cm	0.66 (0.14–3.16)	
						81	1.00	
						90	1.52 (0.60–3.83)	
						100	1.13 (0.35–3.64)	
						110	2.06 (0.49–8.60)	
						Per 10 cm	1.02 (0.70–1.48)	
					Waist circumference, gallstone related severe acute pancreatitis	72 cm	2.06 (0.44–9.57)	
						81	1.00	
						90	1.45 (0.40–5.27)	
						100	1.70 (0.38–7.58)	
						110	4.48 (0.83–24.12)	
						Per 10 cm	1.73 (1.08–2.80)	

Table 1 (continued)

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Assessment of anthropometric measures	Adiposity measure, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
					Waist circumference, total acute pancreatitis, men	72 cm	0.82 (0.11–6.21)	
						81	1.00	
						90	1.31 (0.74–2.30)	
						100	1.55 (0.85–2.82)	
						110	2.25 (1.15–4.41)	
						Per 10 cm	1.32 (1.11–1.58)	
					Waist circumference, non-gallstone related acute pancreatitis	72 cm	1.13 (0.15–8.78)	
						81	1.00	
						90	1.22 (0.63–2.37)	
						100	1.18 (0.57–2.42)	
						110	1.70 (0.74–3.91)	
						Per 10 cm	1.19 (0.95–1.48)	
					Waist circumference, gallstone related acute pancreatitis	72 cm	–	
						81	1.00	
						90	1.52 (0.52–4.47)	
						100	2.60 (0.86–7.87)	
						110	3.80 (1.14–12.69)	
						Per 10 cm	1.63 (1.20–2.24)	
					Waist circumference, total acute pancreatitis, women	72 cm	0.55 (0.32–0.94)	
						81	1.00	
						90	1.31 (0.90–1.92)	
						100	1.37 (0.80–2.37)	
						110	3.02 (1.43–6.37)	
						Per 10 cm	1.40 (1.16–1.68)	

Table 1 (continued)

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Assessment of anthropometric measures	Adiposity measure, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
					Waist circumference, non-gallstone related acute pancreatitis	72 cm	0.68 (0.30–1.52)	
						81	1.00	
						90	1.42 (0.80–2.51)	
						100	1.54 (0.70–3.42)	
						110	3.67 (1.19–11.33)	
						Per 10 cm	1.27 (0.96–1.67)	
					Waist circumference, gallstone related acute pancreatitis	72 cm	0.47 (0.22–0.98)	
						81	1.00	
						90	1.24 (0.74–2.07)	
						100	1.24 (0.58–2.62)	
						110	2.63 (0.97–7.11)	
						Per 10 cm	1.53 (1.19–1.96)	
Prizment et al. [20], USA	Iowa Women's Health Study	1986–2004, ~18 years follow-up	36436 women, age ≥65 years: 511 acute pancreatitis cases 149 chronic pancreatitis cases	Self-reported (validated)	BMI, acute pancreatitis	< 25.0	1.00	Age, time of Medicare enrolment, smoking status, pack-years of smoking
						25.0–29.9	1.29 (1.05–1.60)	
						≥ 30.0	1.35 (1.07–1.70)	
					BMI, chronic pancreatitis	< 25.0	1.00	
						25.0–29.9	0.67 (0.46–0.97)	
						≥ 30.0	0.59 (0.37–0.94)	

Table 1 (continued)

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Assessment of anthropometric measures	Adiposity measure, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
Pang et al. [4], China	China Kadoorie Biobank Study	2004–2008–2015, 9.2 years follow-up	510314 men and women, age 30–79 years: 1079 acute pancreatitis cases 683 other pancreatitis cases 113 chronic pancreatitis cases	Measured	BMI, acute pancreatitis	< 20.0	0.91 (0.75–1.10)	Age, sex, region, education, smoking, alcohol, medication (aspirin, ACE-I, beta blockers, statins, diuretics, Calcium antagonists, metformin, insulin), diabetes, physical inactivity, gallbladder disease
						20.0–< 22.5	1.00 (0.87–1.14)	
						22.5–< 25.0	1.27 (1.13–1.42)	
						25.0–< 27.0	1.61 (1.41–1.85)	
						≥ 27.0	1.96 (1.72–2.24)	
						Per 3.4 kg/m^2	1.31 (1.24–1.39)	
						Per 3.4 kg/m^2	1.09 (0.97–1.27)	Waist circumference
					Waist circumference	< 71.7 cm	0.73 (0.62–0.87)	
						71.7–< 77.0	1.00 (0.86–1.16)	
						77.0–< 82.2	1.17 (1.02–1.33)	
						82.2–< 88.5	1.33 (1.17–1.51)	
						≥ 88.5	1.87 (1.66–2.11)	
						Per 9.8 cm	1.35 (1.27–1.43)	
						Per 9.8 cm	1.25 (1.11–1.41)	+BMI
					BMI, other pancreatitis	Per 3.4 kg/m^2	1.24 (1.15–1.34)	+waist circumference
					Waist circumference	Per 9.8 cm	1.30 (1.20–1.40)	+BMI
					BMI, chronic pancreatitis	Per 3.4 kg/m^2	0.86 (0.70–1.06)	
					Waist circumference	Per 9.8 cm	1.00 (0.82–1.22)	

Table 1 (continued)

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Assessment of anthropometric measures	Adiposity measure, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
Choi et al. [25], Korea	Korean National Screening Cohort	2002–2003–2013, 10.5 years follow-up	512928 men and women, age 40–79 years: 1656 acute pancreatitis cases	Measured	BMI, acute pancreatitis	12.0–18.4	1.72 (1.32–2.23)	Age, sex, smoking status, alcohol use, physical activity, comorbid diabetes, comorbid gallstone disease at baseline
						18.5–20.9	1.44 (1.23–1.68)	
						21.0–22.9	1.16 (1.01–1.34)	
						23.0–24.9	1.00	
						25.0–27.4	1.00 (0.87–1.16)	
						27.5–29.9	1.23 (1.02–1.49)	
						30.0–50.0	1.55 (1.18–2.04)	
						Per 5 kg/m^2	0.89 (0.82–0.97)	
					BMI, severe acute pancreatitis	12.0–18.4	2.24 (1.32–3.80)	
						18.5–20.9	1.69 (1.20–2.40)	
						21.0–22.9	1.51 (1.10–2.08)	
						23.0–24.9	1.00	
						25.0–27.4	1.26 (0.91–1.75)	
						27.5–29.9	1.51 (0.99–2.31)	
						30.0–50.0	1.98 (1.09–3.59)	
						Per 5 kg/m^2	0.86 (0.72–1.04)	
					BMI, non-severe acute pancreatitis	12.0–18.4	1.60 (1.18–3.59)	
						18.5–20.9	1.39 (1.17–1.65)	
						21.0–22.9	1.09 (0.93–1.27)	
						23.0–24.9	1.00	
						25.0–27.4	0.95 (0.81–1.12)	
						27.5–29.9	1.17 (0.94–1.45)	
						30.0–50.0	1.46 (1.07–1.99)	
						Per 5 kg/m^2	0.90 (0.82–0.99)	
					BMI, gallstone-related acute pancreatitis	12.0–18.4	0.90 (0.43–1.88)	
						18.5–20.9	1.01 (0.69–1.47)	
						21.0–22.9	1.04 (0.75–1.43)	
						23.0–24.9	1.00	
						25.0–27.4	1.11 (0.82–1.52)	
						27.5–29.9	1.63 (1.12–2.37)	
						30.0–50.0	2.04 (1.21–3.46)	
						Per 5 kg/m^2	1.38 (1.16–1.66)	

Table 1 (continued)

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Assessment of anthropometric measures	Adiposity measure, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
					BMI, non-gallstone-related acute pancreatitis	12.0–18.4	1.95 (1.48–2.59)	
						18.5–20.9	1.56 (1.31–1.85)	
						21.0–22.9	1.20 (1.02–1.40)	
						23.0–24.9	1.00	
						25.0–27.4	0.97 (0.83–1.15)	
						27.5–29.9	1.12 (0.90–1.40)	
						30.0–50.0	1.41 (1.02–1.95)	
						Per 5 kg/m^2	0.79 (0.72–0.87)	
					BMI and acute pancreatitis, men	Per 5 kg/m^2	0.77 (0.69–0.86)	
					BMI and gallstone-related acute pancreatitis	Per 5 kg/m^2	1.31 (1.02–1.68)	
					BMI and non-gallstone-related acute pancreatitis	Per 5 kg/m^2	0.69 (0.61–0.77)	
					BMI and acute pancreatitis, women	Per 5 kg/m^2	1.12 (0.97–1.28)	
					BMI and gallstone-related acute pancreatitis	Per 5 kg/m^2	1.47 (1.14–1.91)	
					BMI and non-gallstone-related acute pancreatitis	Per 5 kg/m^2	1.01 (0.85–1.18)	
					BMI and acute pancreatitis, current drinker	Per 5 kg/m^2	0.74 (0.65–0.83)	
					BMI and gallstone-related acute pancreatitis	Per 5 kg/m^2	1.30 (0.97–1.74)	
					BMI and non-gallstone-related acute pancreatitis	Per 5 kg/m^2	0.66 (0.57–0.75)	
					BMI and acute pancreatitis, non-drinkers	Per 5 kg/m^2	1.03 (0.91–1.16)	

Table 1 (continued)

First author, publication year, country	Study name or description	Study period	Number of participants, number of cases	Assessment of anthropometric measures	Adiposity measure, subgroup	Comparison	Relative risk (95% confidence interval)	Adjustment for confounders
					BMI and gallstone-related acute pancreatitis	Per 5 kg/m^2	1.38 (1.09–1.74)	
					BMI and non-gallstone-related acute pancreatitis	Per 5 kg/m^2	0.93 (0.81–1.07)	
					BMI and acute pancreatitis, ever smokers	Per 5 kg/m^2	0.67 (0.59–0.76)	
					BMI and gallstone-related acute pancreatitis	Per 5 kg/m^2	1.42 (1.04–1.95)	
					BMI and non-gallstone-related acute pancreatitis	Per 5 kg/m^2	0.57 (0.50–0.66)	
					BMI and acute pancreatitis, never smokers	Per 5 kg/m^2	1.04 (0.93–1.17)	
					BMI and gallstone-related acute pancreatitis	Per 5 kg/m^2	1.29 (1.02–1.63)	
					BMI and non-gallstone-related acute pancreatitis	Per 5 kg/m^2	0.97 (0.85–1.11)	
Hansen et al. [21], Denmark	Copenhagen City Heart Study and Copenhagen General Population Study	1994–1994–2001–2003–2017	117531 men and women, age 20–≥ 100 years: 458 acute pancreatitis cases	Measured	BMI	< 18.5	1.6 (0.6–4.2)	Age, sex, smoking, alcohol, lipid-lowering therapy, physical activity, diabetes, gallstone disease
						18.5–24.9	1.0	
						25.0–29.9	1.4 (1.1–1.8)	
						30.0–34.9	2.1 (1.6–2.9)	
						≥ 35.0	2.8 (1.8–4.3)	
		2003–2015–2017, 8 years follow-up			BMI, men	Per 1 kg/m^2	1.09 (1.05–1.12)	
					BMI, women	Per 1 kg/m^2	1.05 (1.03–1.09)	
					BMI, CCHS	Per 1 kg/m^2	1.05 (1.01–1.10)	
					BMI, CGPS	Per 1 kg/m^2	1.07 (1.05–1.10)	

ACE angiotensin converting enzyme-inhibitor, *BMI* Body mass index, *NSAID* non-steroidal anti-inflammatory drugs

1.25 (95% CI: 1.12–1.40, $I^2 = 85.2\%$, $p_{heterogeneity} < 0.0001$) per 5 kg/m^2 increase in BMI (Supplementary Figure 5).

There was evidence of a nonlinear association between BMI and acute pancreatitis ($p_{nonlinearity} < 0.0001$), and there was a steeper association at higher levels of BMI than at lower levels (Fig. 2b, Supplementary Table 2). Exclusion of the Korean study led to a more linear dose-response relationship between BMI and acute pancreatitis, although the test for nonlinearity was still significant ($p_{nonlinearity} = 0.001$) (Supplementary Figure 3b, Supplementary Table 2).

Only four studies (three publications, three risk estimates) were included in the analysis of BMI and gallstone-related pancreatitis [19, 24, 25] and non-gallstone-related pancreatitis [19, 24, 25], and two studies were included in the analysis of BMI and chronic pancreatitis [4, 20], and the summary RRs were 1.34 (95% CI: 1.16–1.56, $I^2 = 52\%$, $p_{heterogeneity} = 0.13$) (Supplementary Figure 6), 0.93 (95% CI: 0.76–1.14, $I^2 = 82\%$, $p_{heterogeneity} = 0.004$) (Supplementary Figure 7), and 0.78 (95% CI: 0.65–0.92, $I^2 = 0\%$, $p_{heterogeneity} = 0.80$) (Supplementary Figure 8), respectively.

Three cohort studies (two publications) [4, 24] were included in the analysis of waist circumference and risk of acute pancreatitis (1503 cases, 578,472 participants). The summary RR was 1.36 (95% CI: 1.29–1.43, $I^2 = 0\%$, $p_{heterogeneity} = 0.90$) per 10 cm increase in waist circumference (Fig. 3a). There was no evidence of a nonlinear association between waist circumference and risk of acute pancreatitis ($p_{nonlinearity} = 0.19$), and there was a fourfold increase in risk when comparing a waist circumference of 110 cm with one of 69 cm (Fig. 3b, Supplementary Table 3).

Subgroup and Sensitivity Analyses

There was a positive association between BMI and acute pancreatitis in most subgroup analyses stratified by sex, duration of follow-up, number of cases and adjustment for confounding factors (including age, education, alcohol, smoking, waist circumference and physical activity) or potentially mediating factors (diabetes mellitus, gallstones/gallbladder disease and triglycerides), although in some subgroups the association was not statistically significant (Table 2). With meta-regression analyses, there was no evidence that the results differed between these subgroups; however, within-subgroup heterogeneity was lower among studies in women ($I^2 = 0\%$) and among the American studies ($I^2 = 0.8\%$) (Table 2). The mean (median) study quality score was 8.4 (8.0) out of 9.0.

Discussion

This meta-analysis of ten prospective studies suggests that a 5 kg/m^2 increase in BMI is associated with an 18% increase in the relative risk of acute pancreatitis, and a 10 cm increase in waist circumference is associated with a 36% increase in the relative risk. There was some evidence of nonlinearity in the analysis of BMI, with a steeper increase in risk at higher levels of BMI than at lower levels and with the increased risk being most pronounced in the obese and severely obese range. When comparing a BMI of 30, 35 and 40 with a BMI of 22, there was a 34%, 102% and 235% increase in the relative risk of acute pancreatitis. There was no evidence of nonlinearity in the analysis of waist circumference and acute pancreatitis, and there was a fourfold increase in risk when comparing the highest vs. the lowest level of waist circumference. There was a positive association between BMI and gallstone-related pancreatitis, but not with non-gallstone-related pancreatitis, while an inverse association was observed between BMI and chronic pancreatitis; however, these results were based on only 2–4 studies; thus, caution is needed in the interpretation of these findings and further studies are needed before firm conclusions can be drawn. Only two studies investigated waist circumference and different types of pancreatitis and found a slightly stronger association with gallstone-related pancreatitis, than for non-gallstone-related pancreatitis [24]; however, there was still a strong and significant association even for the latter. The current findings are consistent with a previous meta-analysis on BMI and acute pancreatitis which found a 43% increase in the RR among obese compared to normal weight subjects [27]; however, only three studies (two publications) with 603 cases and 101,369 participants were included in the analysis [27], while the current analysis included > 5000 cases and > 1.69 million participants and therefore provides a more comprehensive assessment of the available evidence.

Several biological pathways could explain why higher BMI or waist circumference is associated with increased risk of pancreatitis. Excess weight is a strong risk factor for type 2 diabetes [37], gallstones [17] and elevated levels of triglycerides [38], which again are strongly associated with increased risk of pancreatitis [14, 39–42]. The observation in the current analysis that there was a positive association between BMI and gallstone-related pancreatitis, but not for non-gallstone-related pancreatitis (RR = 1.34 vs. 0.93 per 5 kg/m^2) might suggest that increased risk of gallstones may account for much of the increased risk of pancreatitis with overweight and obesity as measured by BMI; however, given that there were only four studies in each of these analyses, further studies are needed before firm conclusions can be made. In contrast, the association between waist circumference and pancreatitis was strong both for gallstone-related pancreatitis (RR = 2.5) and for non-gallstone-related pancreatitis (RR = 2.1) in two Swedish cohorts even after adjustment for BMI [24], suggesting that other mechanisms could contribute as well. A combined analysis of two Danish studies suggested recently that elevated triglycerides appeared to mediate 22% of the excess risk of the association between

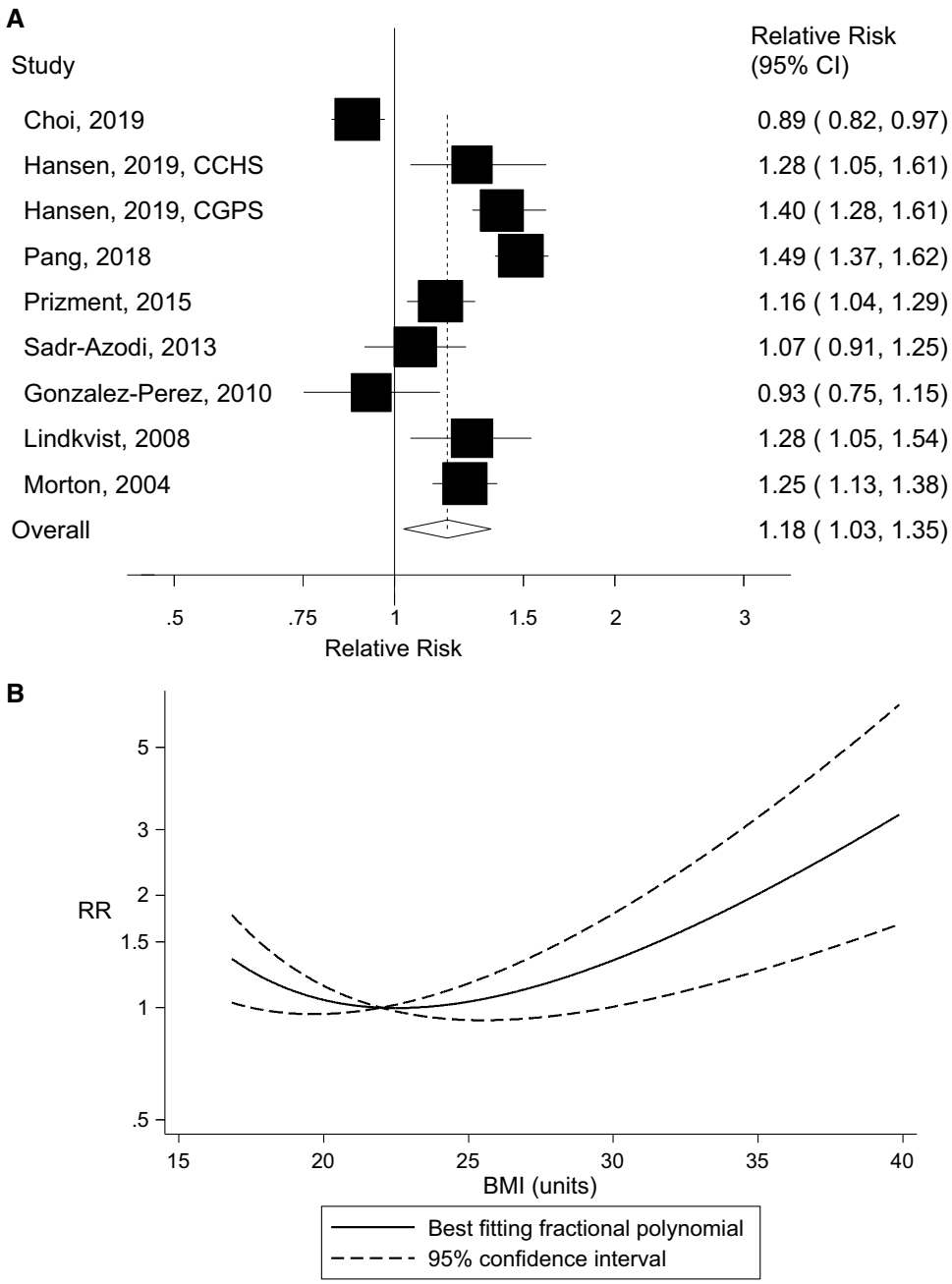

Fig. 2 Body mass index and acute pancreatitis, linear dose-response analysis per 5 kg/m^2 (**a**) and nonlinear dose-response analysis (**b**)

BMI and acute pancreatitis [21]. Higher BMI is associated with more adipocytes within the pancreas which are dispersed adjacent to the exocrine pancreatic acinar cells [43]. In acute pancreatitis, these adipocytes are damaged by the release of lipases which hydrolyze their triglycerides into unsaturated fatty acids, which in turn cause necrosis of the acinar cells [43]. In chronic pancreatitis, adipocyte mass is unrelated to BMI, and adipocytes are surrounded by fibrosis, which prevents the lipolytic flux between the two compartments [43]. This could be part of the explanation for the difference in the results for BMI and acute and chronic pancreatitis. Adiposity could also impact pancreatitis indirectly because certain obesity treatments such as bariatric surgery, duodeno-jejunal bypass liner and gastric balloons in some cases can cause acute pancreatitis; however, this would most likely explain only a small percentage of cases [43]. Adiposity is associated with low-grade inflammation and with lower levels of adiponectin, a cytokine with anti-inflammatory properties and which reduces insulin resistance [44]. It has been shown that adiponectin reduced the development of acute pancreatitis in mice fed a high-fat diet [45].

Limitations that may have affected the results of the current meta-analysis include potential confounding, heterogeneity, measurement errors in the assessment of

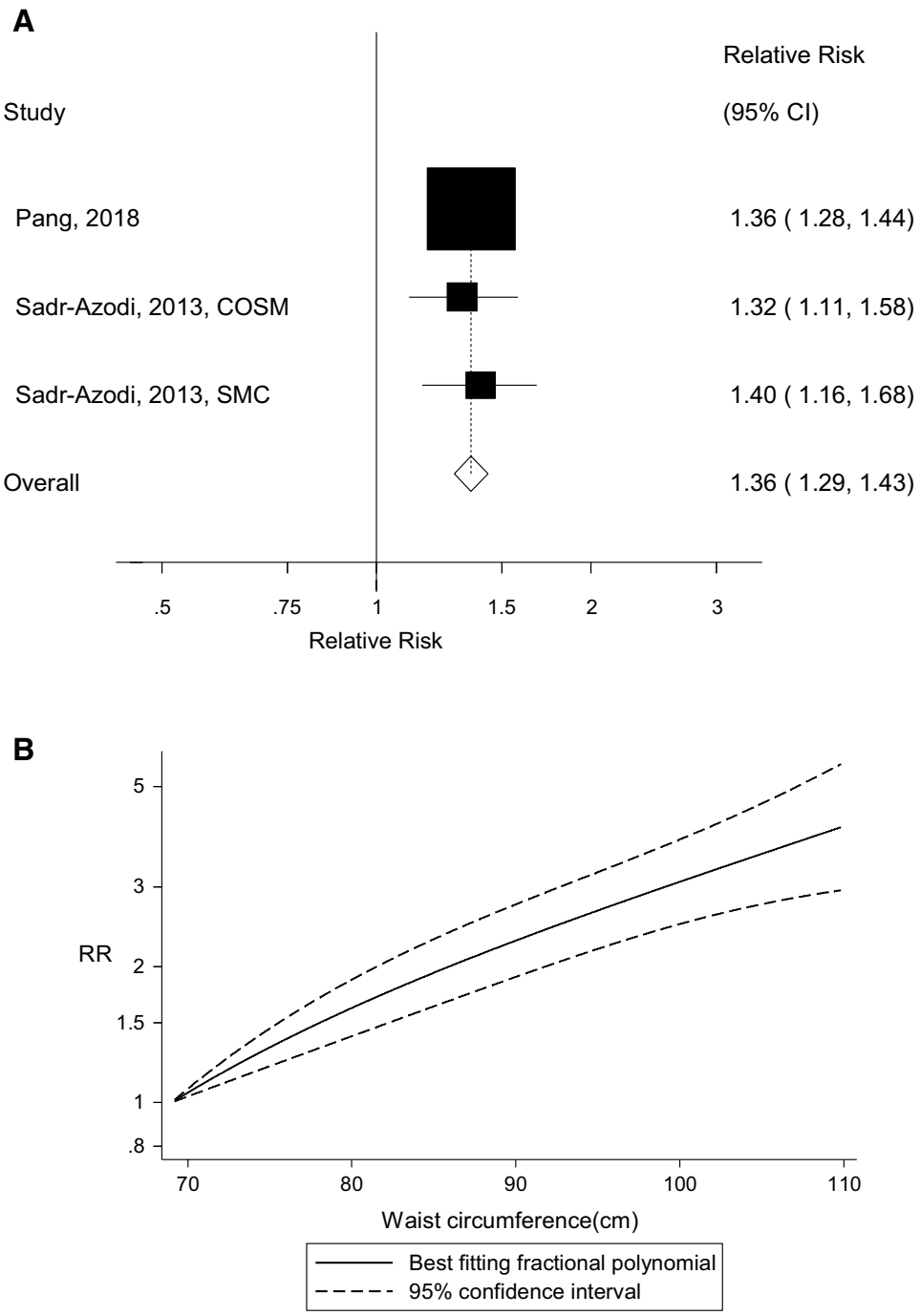

Fig. 3 Waist circumference and acute pancreatitis, linear dose-response analysis per 10 cm (**a**) and nonlinear dose-response analysis (**b**)

anthropometric measures and publication bias. We cannot exclude the possibility of residual confounding as persons with overweight and obesity tend to have a generally less healthy lifestyle including lower physical activity, unhealthier diets and higher rates of type 2 diabetes compared to normal weight individuals, while persons with a low BMI more often are smokers than persons with a high BMI. Several of the studies adjusted for a range of confounding factors and the results persisted across most subgroups with adjustment for confounding factors. In addition, there was little evidence of heterogeneity between these subgroup analyses. However, one study from Korea suggested an L-shaped or U-shaped association between BMI and acute pancreatitis, with an inverse association overall and among men, ever smokers and alcohol drinkers when the association was analyzed on a continuous scale, but not among women, never smokers and nondrinkers [25]. This might suggest that confounding by smoking and alcohol could have affected the results of that study and is also likely to explain the difference in the association by sex as smoking prevalence is much higher

Table 2 Subgroup analyses of body mass index and acute pancreatitis

	Body mass index and acute pancreatitis				
	n	Relative risk (95% CI)	I^2 (%)	P_h^1	P_h^2
All studies	9	1.18 (1.03–1.35)	91.1	< 0.0001	
Sex					
Men	2	1.09 (0.55–2.14)	97.9	< 0.0001	0.60/0.75[3]
Women	3	1.18 (1.09–1.27)	0	0.40	
Men, women	5	1.20 (1.03–1.41)	84.5	< 0.0001	
Follow-up					
< 10 years	4	1.28 (1.09–1.52)	82.0	0.001	0.26
≥ 10 years	5	1.11 (0.96–1.29)	87.7	< 0.0001	
Assessment of weight/height					
Measured	7	1.20 (1.01–1.43)	93.1	< 0.0001	0.63
Self-reported (validated)	2	1.13 (1.03–1.23)	0	0.41	
Geographic location					
Europe	5	1.19 (1.02–1.38)	72.9	0.005	0.88
America	2	1.20 (1.12–1.30)	0.8	0.32	
Asia	2	1.15 (0.70–1.90)	98.6	< 0.0001	
Number of cases					
Cases < 250	2	1.28 (1.11–1.47)	0	0.99	0.62
Cases 250– < 500	4	1.17 (1.00–1.36)	79.4	0.002	
Cases ≥ 500	3	1.15 (0.84–1.58)	97.2	< 0.0001	
Study quality					
0–3 stars	0				NC
4–6 stars	0				
7–9 stars	9	1.18 (1.03–1.35)	91.1	< 0.0001	
Adjustment for confounding factors					
Age					
Yes	9	1.18 (1.03–1.35)	91.1	< 0.0001	NC
No	0				
Education					
Yes	3	1.27 (1.06–1.52)	87.2	< 0.0001	0.43
No	6	1.14 (0.96–1.35)	89.7	< 0.0001	
Alcohol					
Yes	8	1.18 (1.01–1.39)	92.2	< 0.0001	0.91
No	1	1.16 (1.04–1.29)			
Smoking					
Yes	8	1.17 (1.00–1.37)	92.1	< 0.0001	0.76
No	1	1.25 (1.13–1.38)			
Waist circumference					
Yes	1	1.07 (0.91–1.25)			0.59
No	8	1.19 (1.03–1.39)	92.0	< 0.0001	
Physical activity					
Yes	4	1.24 (0.93–1.64)	96.3	< 0.0001	0.52
No	5	1.15 (1.05–1.26)	50.3	0.09	
Adjustment for potential intermediate factors					
Diabetes					
Yes	6	1.16 (0.93–1.43)	94.3	< 0.0001	0.70
No	3	1.21 (1.13–1.30)	0	0.52	
Gallstones or gallbladder disease					
Yes	6	1.16 (0.93–1.43)	94.3	< 0.0001	0.70
No	3	1.21 (1.13–1.30)	0	0.52	

Table 2 (continued)

	Body mass index and acute pancreatitis				
	n	Relative risk (95% CI)	I^2 (%)	P_h^1	P_h^2
Triglycerides					
Yes	0				NC
No	9	1.18 (1.03–1.35)	91.1	< 0.0001	

n denotes the number of risk estimates (one publication reported the results for two studies combined)

[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 of men and women combined

NC, not calculable because no studies were present in one of the subgroups

in males than among females in this population [46]. Any further studies could conduct analyses stratified by other risk factors to further explore the impact of residual confounding by smoking and alcohol or other factors. We also cannot exclude residual confounding from non-established risk factors such as diet or other unknown factors. There was high heterogeneity in the overall analysis of BMI and acute pancreatitis; however, heterogeneity was low among studies in women and among the American studies.

There was little differences in the results when subgroups were stratified by adjustment for various confounding factors including alcohol, smoking and physical activity. There was also little heterogeneity between subgroups of studies that adjusted for potential intermediate risk factors including diabetes and gallstones. We can also not exclude the possibility of residual confounding by other potential risk factors, and few studies have adjusted for dietary risk factors to date. However, the confounder would have to be relatively strong to fully account for the threefold–fourfold difference in risk observed for extremes in BMI and waist circumference.

Anthropometry was assessed by self-report in a few studies and this may have led to measurement errors in the exposure assessment; however, this was the case for only three studies which also validated the self-reports. Several studies have shown relatively high correlations between measured and self-reported anthropometric variables with correlation coefficients of around 0.95–0.97, suggesting that self-report of adiposity is relatively accurate [47–49]. Because of the prospective design of the included studies, any measurement errors in the assessment of anthropometric measures would most likely have biased the results toward the null. In addition, the positive associations between BMI and acute pancreatitis persisted both among the seven studies that used measured weight and height for the anthropometric assessment and among the three studies with self-reported weight and height. Although there was no between subgroup heterogeneity the association was slightly stronger in the studies that measured weight and height compared with those that used self-reported anthropometric measures (RR = 1.20 vs. 1.13). In the China Kadoorie Biobank Study, more or less similar associations were observed between different adiposity measures such as BMI, waist circumference, waist-to-hip ratio, hip circumference, body fat percentage, height-adjusted weight and weight change and risk of acute pancreatitis [4]. Because anthropometric variables usually were measured only at baseline, it was not possible to take into account changes in adiposity in this analysis and it is therefore possible that weight gain over time may account for part of the association observed between adiposity and the risk of developing pancreatitis. The China Kadoorie Biobank Study found a positive association between both BMI at age 25 and weight change between age 25 and baseline and the risk of acute pancreatitis [4]. Because of limited data on adiposity and severity of pancreatitis, we were not able to analyze this association; however, some previous studies suggested obesity increases the risk of severe pancreatitis, complications and mortality in pancreatitis patients [50–52].

Although publication bias can affect the results of meta-analyses of published studies, we found no evidence of publication bias in the analysis of BMI and acute pancreatitis. There were too few studies to conduct subgroup analyses or test for publication bias in the analysis of waist circumference and acute pancreatitis.

This meta-analysis has several strengths including 1) the prospective design of the included studies which avoids problems with recall bias and reduces the potential for selection bias, 2) the robustness of the findings in multiple subgroup and sensitivity analyses and 3) with > 5,100 cases and ~ 1.7 million participants, we had sufficient statistical power to detect even a moderate association between adiposity and acute pancreatitis. Our findings have important clinical and public health implications as the number of persons who are overweight and obese has increased considerably over the last decades in all areas of the world [53]. If this trend continues it may contribute to additional cases of pancreatitis and related consequences such as increased incidence of pancreatic cancer and premature mortality, but it could be halted with widespread adoption of healthier diets and increased levels of physical activity [54].

Conclusion

This meta-analysis suggests that higher BMI and waist circumference are associated with increased risk of acute pancreatitis. Further studies are needed on different measures of adiposity and the risk of different subtypes of pancreatitis (acute vs. chronic and gallstone-related vs. non-gallstone-related) and to clarify the underlying mechanisms, but the findings underscore the importance of weight control for the prevention of acute pancreatitis.

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Author's contributions 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. DA, YMS, TN and 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.

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Compliance with ethical standards

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

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