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Research Article

Coffee Consumption and Risk of Pancreatic Cancer: An Updated Meta-analysis of Cohort Studies

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Abstract

Objective: To review the association between coffee consumption and risk of pancreatic cancer in a meta-analysis of cohort studies and evaluate their dose–response relationship.

Methods: We searched PubMed and EMBASE for cohort studies of coffee consumption and pancreatic cancer risk up to 5 January 2020. A fixed-effects model was used for pooling overall relative risk (RR) and corresponding 95% confidence interval (CI) for the highest versus lowest coffee consumption category, while the analysis was also stratified by sex, region and coffee type. Egger's and Begg's test was adopted to exam the publication bias. The dose-response analysis was performed as well.

Results: A total of 21 high-quality studies from 18 publications were selected, including 2,859,065 participants and 11,023 pancreatic cancer cases. The pooled relative risk of 21 studies for highest versus lowest category of coffee consumption was 0.95 (95% CI 0.87-1.02, I^2 = 43.4%, P for heterogeneity = 0.018). Subgroup analysis showed that coffee consumption was associated with a reduced pancreatic cancer risk in males (RR 0.72, 95%CI 0.53-0.91) but not in females (RR 0.89, 95% CI

0.73-1.05). For dose-response analysis, the overall RR for increment of one cup/day of coffee consumption was 1.00 (95%CI, 0.99-1.02) of 15 studies, without statistically significant.

Conclusions: This meta-analysis indicates non-significant association between coffee consumption and pancreatic cancer risk. No evidence of publication bias was found.

Keywords: Coffee, Pancreatic cancer, Meta-analysis

Introduction

Pancreatic cancer is a highly malignant tumor of the digestive system. In recent years, the prognosis of patients is improving but is still poor with an overall five-year survival rate of 8% [1]. According to the most recent data from the American Cancer Society, pancreatic cancer is the fourth leading cause of cancer deaths, and estimates that 23,800 and 21,950 deaths (in men and women, respectively) due to pancreatic cancer are projected to occur in the United States in 2019 [2]. In China, though pancreas cancer is not among the top five causes of cancer-related deaths, its mortality rate has increased by 9% in the past 10 years [3]. Therefore, pancreatic cancer has become a major public health problem threatening human life and health and has attracted more and more attention [1].

Coffee is one of the most commonly consumed beverages all over the world [4], and has been consumed for more than 1000 years. It is a complex mixture of numerous chemical compounds, which may have either beneficial or detrimental effects on human health [5]. Therefore, the relationship between coffee consumption and health has been studied widely, including in a recent umbrella analysis [6] that indicated consistent benefits of coffee consumption for all-cause mortality, liver disease, type-2 diabetes, and some cancers, a finding which was also replicated elsewhere [7]. However, there is conflicting evidence about the effect of coffee consumption pancreatic cancer, with one meta-analysis concluding that coffee consumption was related with the increasing risk of pancreatic cancer [8], and others showing a beneficial effect on pancreatic cancer risk [9,10]. Finally, another meta-analysis indicated no clear trend between coffee consumption and risk of pancreatic cancer [11]. The most recent meta-analysis [12] of 13 cohort studies (up to 1 February 2018), including 959,992 study participants and 3,831 pancreatic cancer cases, included a limited number of studies, which could weaken the power of review. In addition, in the past two years, several new large cohort studies referring to coffee intake and pancreatic cancer [13-15] have emerged, covering more 1.4 million participants and 7,000 cases of pancreatic cancer. Thus, we sought to perform an updated meta-analysis including a large number of high-quality studies to explore the association between coffee consumption and risk of pancreatic cancer.

Methods

Literature search

On 5 January 2020, we searched two electronic databases (PubMed and EMBASE), with the following search terms: (coffee OR caffeine OR intake OR consumption OR diet OR dietary OR beverages OR drinks OR drinking) AND (pancreas OR pancreatic) AND (neoplasia OR neoplasm OR cancer OR tumor OR adenocarcinomas OR malignancy OR malignancies). To obtain more data ensuring the power of evaluation, we did not have a limit on starting date. Furthermore, we limited our search to human studies which were written in English. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement) guidelines to report this study.

Inclusion and exclusion criteria

Two authors (Mingzhu Zhou and Na Zhang) selected studies independently, studies were included if they met the following criteria: (1) cohort study; (2) the exposure was coffee consumption, including total coffee, caffeinated coffee or decaffeinated coffee, filtered coffee or boiled coffee; (3) the outcome was pancreatic cancer; and (4) provided the relative risk (RR) or hazard ratio (HR) adjusted for smoking and their 95% confidence intervals

(CI) of pancreatic cancer for every category of coffee consumption. Studies were excluded if they were as follows: (1) information was insufficient, including the number of participants and cases, RR or HR, and the dose of coffee consumption in each exposure category; (2) duplicate reports.

Data extraction and quality assessment

Date extraction and quality assessment of included publications were conducted independently by two researchers (Mingzhu Zhou and Na Zhang) and disagreements were resolved by discussion. For each study, the following information was extracted: the first author's name and year of publication, country, period of follow-up, age at baseline, number of cases, number of subjects, categories of coffee consumption, RR or HR of pancreatic cancer and corresponding 95% CIs for every category of coffee consumption, and variates adjusted in the statistical analysis. The quality of each publication was evaluated with Newcastle-Ottawa Quality Assessment Scale (NOS), the scale ranges from 0 to 9 points, if scale ≥7 points, the study was considered high quality.

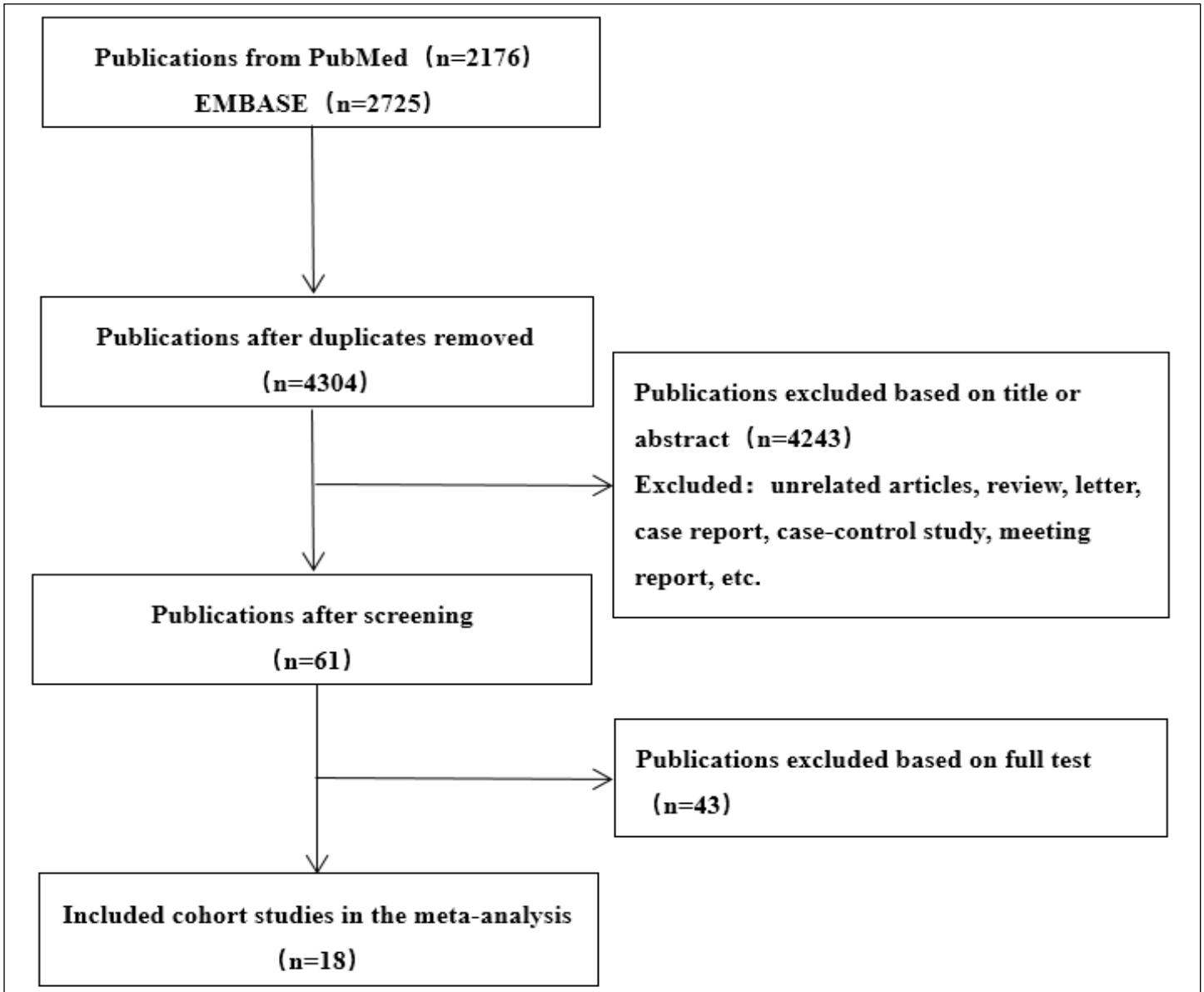

Figure 1: Flow chart of study selection (search until 5 January 2020).

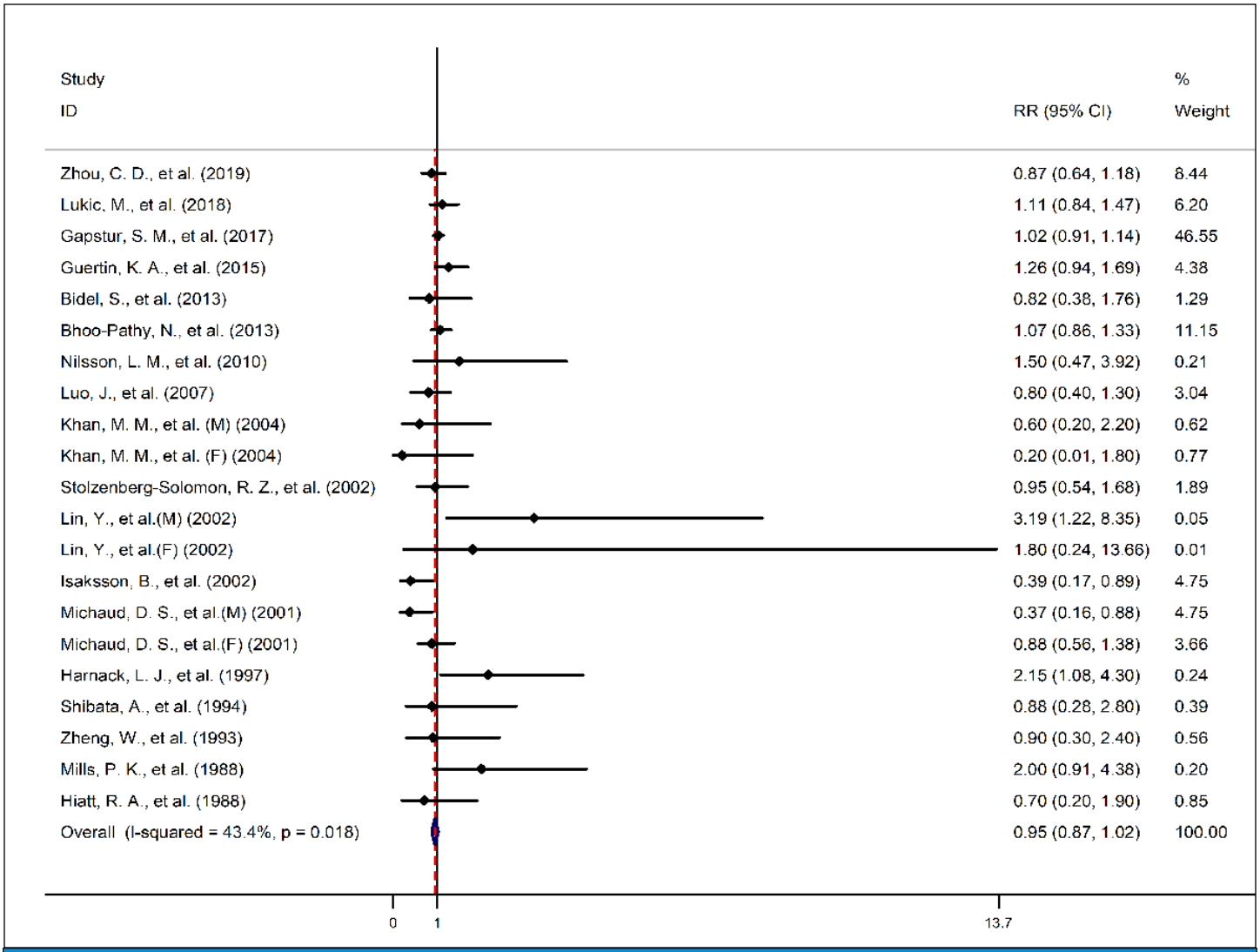

Figure 2: Forest plot of overall RRs (fixed effects model) of coffee consumption (highest versus lowest category) and pancreatic cancer risk. The pooled relative risk indicates non-significant association between coffee consumption and pancreatic cancer risk.

Statistical analysis

If a study reported RR for both sexes (males and females) separately, but did not have an overall result, the results for each sex were treated as a separate study. For all the included cohort studies, we computed overall RRs with 95% CIs for the highest versus lowest category of coffee consumption. The heterogeneity was measured by I^2 statistics and the chi-square test, if I^2>50% or P<0.10 was observed, results were defined as heterogeneous, and then the random effect model was used as the pooling method. If not, the fixed effect model was adopted. Besides, Egger's test, Begg's test and a funnel plot were used to evaluate a potential publication bias and P<0.05 suggested the presence of publication bias. A sensitivity analysis was conducted by dropping each study for each time to see whether the significant heterogeneity was driven by one specific study. Subgroup analysis was performed for sex, region and coffee type. For the dose–response analysis, we used the method proposed by Greenland, et al. [16] to evaluate linear trends from the correlated natural logs of the RRs through categories of coffee consumption and only included studies that reported at least three exposure categories. For every study, the midpoint of the range was assigned as the average exposure

value in each category, and the open-ended upper category was assumed to have the same amplitude as the adjacent category. All statistical analyses were conducted with Stata/SE12.0 software (Stata Corp, College Station, TX).

Results

Search results and the quality of included publications

A total of 4,748 records were found from PubMed and EMBASE, while 61 publications were selected for further assessment after removing duplicates and screening titles or abstracts. Finally, 18 cohort studies [13-15, 17-31] were identified based on full test, including 2,859,065 participants and 11,023 cases of pancreatic cancer. Among these 18 cohorts, three of them reported 2 separate outcomes (males and females) [22,24,26], therefore, a total of 21 studies were included in this meta-analysis. The process of selecting studies is summarized in Figure 1. The main characteristics of included studies are shown in Table 1. Of the 18 cohorts, 7 were located in Europe (1 in UK, 1 in Norway and Sweden, 2 in Finland, 2 in Sweden and 1 in multiple European countries), 3 in Asia (Japan) and 8 in North America (United States). All of the included studies had a relatively high quality (NOS score ≥7) and the assessment is reported in supplemental material (Supplementary data).

Coffee consumption and risk of pancreatic cancer

The overall RR of pancreatic cancer risk for the highest versus the lowest category of coffee consumption are shown in Figure 2. The summary RR for the 18 cohorts (21 studies) included in the meta-analysis was 0.95 (95% CI 0.87-1.02, I^2 = 43.4%, P for heterogeneity =0.018). Neither Egger's test (P for bias =0.450) nor Begg' test (P for bias = 0.634) indicated a significant publication bias. The funnel plot is shown in Figure 3. And sensitivity analysis confirmed the stability of our results.

Subgroup analysis

Subgroup analysis was performed according to sex, region and coffee type. For sex, nine studies were conducted in females, and analysis of these studies showed that there was no association between coffee consumption and pancreatic cancer risk (RR 0.89, 95% CI 0.73-1.05, I^2 = 0.0%, P for heterogeneity =0.521). On the contrary, when nine studies conducted in males were pooled, coffee consumption was associated with a reduced pancreatic cancer risk (RR 0.72, 95%CI 0.53-0.91, I^2 = 28.0%, P for heterogeneity =0.196). We also divided selected studies into

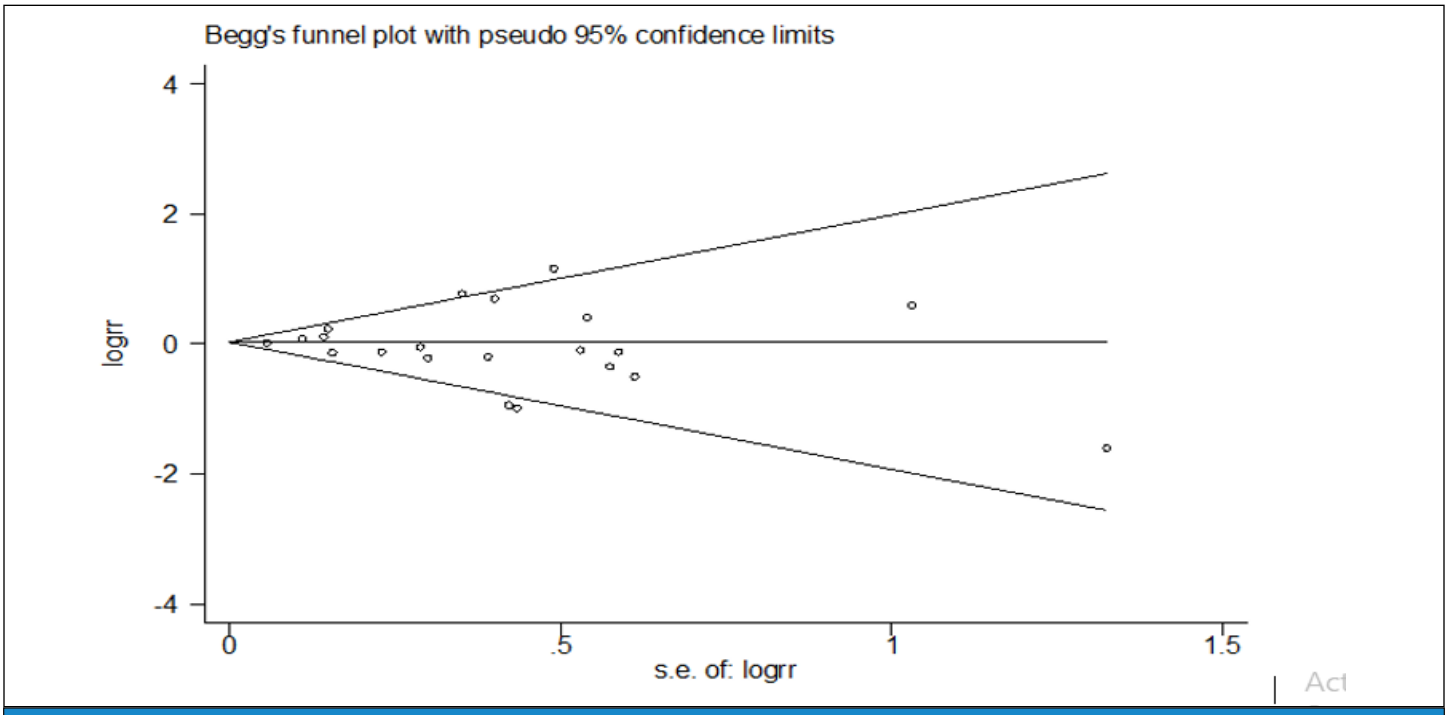

Figure 3: Begg's funnel plot for publication bias. No evidence of publication bias was found.

Table 1: Characteristics of included studies.

Study	Country	Follow-up period	Age	Cases	Subjects	Coffee consumption	RR/HR(95%CI)	Adjustments	NOS score
Zhou, C. D., et al. (2019)[13]	UK	1996-2001	59.5	962	309,797 women	0	1.00 (reference)	smoking, dietary energy intake, type of meat consumed, height, BMI, social deprivation, alcohol intake, educational qualifications, region	8
						1-2 cups/day	1.02 (0.83, 1.26)		
						3-4 cups/day	0.96 (0.76, 1.22)		
						≥5 cups/day	0.87 (0.64, 1.18)		
Lukic, M., et al. (2018)[14]	Norway	1991-2014	30-70 (NOWACS)	491	193,439	≤1 cup/day	1.00 (reference)	smoking status, BMI, sex, self-reported history of diabetes	8
	Sweden		25-74 (NSHDS)			1-4 cups/day	1.05 (0.80, 1.38)		
						≥4 cups/day	1.11 (0.84, 1.47)		
Gapstur, S. M., et al. (2017) [15]	U.S., Columbia, and Puerto Rico	1982-2012	28–94	5612	922,896	Never	1.00 (reference)	age, sex, smoking variables, race, marital status, education, alcohol consumption, body mass index, physical activity, family history of cancer, red and processed meat/ vegetable intake, and current tea drinking	8
						≤1 cup/day	1.01 (0.92, 1.10)		
						2-3 cups/day	1.03 (0.94, 1.11)		

						4-5 cups/day	1.04 (0.94, 1.15)		
						≥6 cups/day	1.02 (0.91, 1.14)		
						Per 2 cups/day	1.00 (0.97, 1.02)		
Guertin, K. A., et al. (2015)[17]	US	1995-2006	62(50-71)	1541	457,366	None	1.00 (reference)	Age, sex, smoking, diabetes, race/ethnicity, BMI, highest level of education, alcohol consumption, health status, use of nutritional supplements, physical activity, history of cardiovascular disease, family history of cancer, total energy intake, the nutrient density-adjusted intakes	8
						<1 cup/day	1.05 (0.85, 1.30)		
						1 cup/day	1.06 (0.86, 1.31)		
						2-3 cups/day	1.03 (0.85, 1.26)		
						4-5 cups/day	1.01 (0.80, 1.27)		
						≥6 cups/day	1.26 (0.94, 1.69)		
Bidel, S., et al. (2013)[18]	Finland	1972-2006	26–74	235	60,041	0	1.00 (reference)	age, study year, education, cigarette smoking, alcohol consumption, leisure time physical activity, history of diabetes, tea consumption, and body mass index	8
						1-2 cups/day	0.86 (0.42, 1.74)		

						3-4 cups/day	0.86 (0.45, 1.64)		
						5-6 cups/day	0.78 (0.41, 1.47)		
						7-9 cups/day	0.92 (0.46, 1.83)		
						≥10 cups/day	0.82 (0.38, 1.76)		
Bhoo-Pathy, N., et al. (2013) [19]	Europe	1992-2000	51.2	865	477,312	No intake	1.09 (0.80, 1.50)	sex, center, and age at diagnosis in 1-year categories, and adjusted for height, weight, smoking status, history of diabetes, highest attained education, physical activity, energy intake, as well as red meat, processed meat, alcohol, tea, soft drink, fruit, and vegetable intake	8
						Low	1.00 (reference)		
						Moderately low	1.11 (0.92, 1.34)		
						Moderately high	0.99 (0.81, 1.21)		
						High intake	1.07 (0.86, 1.33)		
						Per 100 mL	1.00 (0.97, 1.02)		
Nilsson, L. M., et al. (2010) [20]	Sweden	1992– 2007	50	74	64,603	<1 cup/day	1.00 (reference)	age, sex, BMI, smoking, education, and recreational physical activity	7
						1-3 cups/day	1.18 (0.47, 3.02)		
						4 cups/day	1.50 (0.57, 3.92)		
Luo, J., et al. (2007)[21]	Japan	1990-2003	40-69	233	102,137	Rarely	1.00 (reference)	body mass index, leisure-time physical activity in terms of frequency of sports, smoking status, alcohol intake, history of diabetes , history of cholelithiasis, study area and age	7

						1–2 cups/week	1.0 (0.7, 1.4)		
						3–4 cups/week	1.1 (0.7, 1.7)		
						1–2 cups/day	0.9 (0.6, 1.3)		
						3 or more cups/ day	0.8 (0.4, 1.3)		
Khan, M. M., et al. (2004)[22]	Japan	1984-2002	58	25	3,158	Men nondrinkers	1.0 (reference)	age and smoking	7
				12 men	1,524 men	Men drinkers	0.6 (0.2, 2.2)	age, health status, health education, health screening & smoking	
				13 women	1,634 women	Women nondrinkers	1.0 (reference)		
						Women drinkers	0.2 (0.01, 1.8)		
Stolzenberg-Solomon, R. Z., et al. (2002) [23]	Finland	1985-1997	58(50–69)	163	27,111 male smokers	≤321.4 g/day	1.00 (reference)	age and years of smoking	7
						321.4-450.0 g/ day	1.48 (0.89, 2.46)		
						450.0-624.9 g/ day	1.12 (0.61, 2.03)		
						624.9-878.6 g/ day	1.72 (1.01, 2.86)		
						>878.6 g/day	0.95 (0.54, 1.68)		
Lin, Y., et al. (2002)[24]	Japan	1988–1990	57.3(40–79)	90 M	99,527	Males		age and cigarette smoking in pack-years	8
				62 F	44,646 men and 54,881 women	Nondrinkers	1.00 (reference)		
						1–2 cups/month	0.74 (0.37, 1.49)		
						1–4 cups/week	0.58 (0.32, 1.08)		
						1 cup/day	0.59 (0.26, 1.33)		

						2–3 cups/day	0.75 (0.36, 1.59)		
						≥4 cups/day	3.19 (1.22, 8.35)		
						Females			
						Nondrinkers	1.00 (reference)		
						1–2 cups/month	1.27 (0.64, 2.54)		
						1–4 cups/week	0.74 (0.36, 1.50)		
						1 cup/day	0.94 (0.44, 2.01)		
						2–3 cups/day	0.31 (0.07, 1.33)		
						≥4 cups/day	1.80 (0.24, 13.66)		
Isaksson, B., et al. (2002)[25]	Sweden	1969-1997	56	131	21,884	0–2 cups/day	1.00 (reference)	sex, age and cigarette smoking	7
						3–6 cups/day	0.91 (0.60, 1.38)		
						≥7 cups/day	0.39 (0.17, 0.89)		
Michaud, D. S., et al. (2001) [26]	United States	1986-1998	40-75 (HPFS)	288	136,593 (HPFS 47,794 men; NHS 88,799 women)	Men (HPSF)		age in 5-year categories, pack-years of smoking, BMI, history of diabetes mellitus, history of cholecystectomy, energy intake, period	7
		1980-1996	30–55(NHS)			None	1.00 (reference)		
						<1 cup /day	1.04 (0.67, 1.61)		
						1 cup /day	0.48 (0.24, 0.95)		
						2–3 cups /day	0.89 (0.56, 1.40)		
						>3 cups /day	0.37 (0.16, 0.88)		
						Women (NHS)			
						None	1.00 (reference)		
						<1 cup /day	0.72 (0.36, 1.44)		
						1 cup /day	0.71 (0.38, 1.30)		
						2–3 cups /day	0.88 (0.58, 1.34)		
						>3 cups /day	0.88 (0.56, 1.38)		

Harnack, L. J., et al. (1997) [27]	Iowa	1986-1994	≥55	66	33,976 women	≤7 cups /week	1.00 (reference)	age, smoking status, and pack-years of smoking	7
						8-17.5 cups / week	1.91 (0.92, 4.00)		
						17.5 cups / week	2.15 (1.08, 4.30)		
Shibata, A., et al. (1994)[28]	United States	1981-1990	65-85	65	13,976	< 1 cup/day	1.00 (reference)	sex, age and cigarette smoking	7
						1 cup/day	1.82 (0.75, 4.43)		
						2-3 cups/day	1.67 (0.74, 3.77)		
						≥4 cups/day	0.88 (0.28, 2.80)		
Zheng, W., et al. (1993)[29]	United States	1966-1986	≥35	56	17,633 White men	< 3 cups/day	1.0 (reference)	age, smoking index, and alcohol index	7
						3-4 cups/day	0.6 (0.3, 1.2)		
						5-6 cups/day	0.7 (0.4, 1.6)		
						7 cups/day	0.9 (0.3, 2.4)		
Mills, P. K., et al. (1988)[30]	United States	1976-1983	≥25	40	34,000	Never	1.00 (reference)	age, sex, cigarettes	7
						<Daily	1.41 (0.56, 3.58)		
						>Daily	2.00 (0.91, 4.38)		
Hiatt, R. A., et al. (1988)[31]	United States	1978-1984	40.8	49	122,894	Nondrinkers	1.0 (reference)	age, sex, ethnic origin, blood glucose level, treatment for diabetes, smoking, and consumption of alcohol	7
						< 1cup/day	0.8 (0.3, 2.6)		
						1-3 cups/day	0.9 (0.4, 2.1)		
						>4 cups/day	0.7 (0.2, 1.9)		

three group according to region (Europe, Asia, America). Seven studies conducted in Europe and no differences were identified in the association between coffee intake and pancreatic cancer risk (RR 0.92, 95%CI 0.78-1.05, I^2 = 49.8%, P for heterogeneity =0.063), and similar result was found in the five studies in Asia (RR 0.70, 95%CI 0.33-1.07, I^2 = 0.0%, P for heterogeneity =0.493) and nine studies in America (RR 0.93, 95%CI 0.68-1.19, I^2 = 54.8%, P for heterogeneity =0.024). After we tested for coffee type, the pooled RR was 0.75 (95% CI 0.57, 0.93), 0.90 (95% CI 0.60, 1.20), 1.07 (95% CI 0.87, 1.27), 1.01 (95% CI 0.76, 1.25) for filtered coffee, boiled coffee, caffeinated coffee and decaffeinated coffee, respectively. Results of subgroup analysis are shown in Table 2.

Dose–response analysis

A total of 15 outcomes from 13 publications [13-15,17,18,20,21,24,26-30] were included in the dose-response analysis for the relationship between coffee consumption and pancreatic cancer risk. The pooled RR for an increment of one cup/day of coffee consumption was 1.00 (95%CI, 0.99-1.02), and was not statistically significant. The Goodness-of-fit indicated no significant heterogeneity among these studies (Q = 19.32, P = 0.153).

Table 2: Results of subgroup analysis.

Subgroup	Number of studies	RR (95% CI)	I^2	P
Sex				
Male	9	0.72 (0.53, 0.91)	28.00%	0.196
Female	9	0.89 (0.73, 1.05)	0.00%	0.521
Region				
Europe	7	0.92 (0.78, 1.05)	49.80%	0.063
Asia	5	0.70 (0.33, 1.07)	0.00%	0.493
America	9	0.93 (0.68, 1.19)	54.80%	0.024
Coffee type				
Filtered	2	0.75 (0.57, 0.93)	0.00%	0.69
Boiled	2	0.90 (0.60, 1.20)	53.30%	0.143
Caffeinated	2	1.07 (0.87, 1.27)	0.00%	1
Decaffeinated	2	1.01 (0.76, 1.25)	0.00%	0.825

Discussion

Coffee may impact the etiology of cancer of various sites along multiple pathways, such as regulation of DNA repair [32] and induction of apoptosis [33]. There exists a possibility that caffeine could reduce insulin sensitivity [34] and induce pancreatic cancer. In the past few decades, many investigations have been carried out on coffee intake and pancreatic cancer but with inconsistent results [8-12]. Thus, this meta-analysis was conducted to examine the association between coffee consumption and pancreatic cancer risk with 21 high-quality studies from 18 cohorts and to evaluate dose-response trends with 15 studies described in 13 publications. Findings suggested that there was no association between coffee consumption and pancreatic cancer risk (RR 0.95, 95% CI 0.87-1.02), which was similar to the results of a meta-analysis based on 37 case-control and 17 cohort studies (RR 1.13, 95% CI 0.99-1.29) [12]. Subgroup analysis showed significant differences when stratified by sex. The results suggested that there was no association between coffee consumption and pancreatic cancer risk (RR 0.89, 95% CI 0.73-1.05) when studies conducted in females were pooled but coffee consumption was associated with a reduced pancreatic cancer risk (RR 0.72, 95%CI 0.53-0.91) among studies with males, which were similar to the result of a meta-analysis with fourteen cohort studies [35]. Given the impact of cultural, dietary and lifestyle factors, the biological make-up of the subjects in different region [36,37], we tested for region, no significant association between coffee consumption and the risk of pancreatic cancer was observed in Europe (RR 0.92, 95%CI 0.78-1.05), Asia (RR 0.70, 95%CI 0.33-1.07) and America (RR 0.93, 95%CI 0.68-1.19), respectively. The coffee type [38] and brewing method [39,40] can vary from country to country, which may have an effect on the results of study. Just as studies showed that the compounds retained in coffee was dependent on the preparation method [41]. So we tested for coffee type, we noted that the filtered coffee might play a positive role on pancreatic cancer (RR 0.75, 95% CI 0.57-0.93), but not for boiled coffee, caffeinated coffee and decaffeinated coffee, it is possible that because a small number of studies which described coffee type were included.

Certain strengths of this meta-analysis should be acknowledged. Firstly, this meta-analysis included cohort studies which were considered high quality, with a larger sample size than meta-analysis performed ever before, which could provide enough power to find association. Additionally, recall bias was greatly minimized with prospective design. Since there are no human experimental studies, these cohort studies could be the best epidemiological evidence available [42]. Secondly, study selection, data extraction and quality assessment of selected studies were performed by two authors independently and discrepancies were resolved by discussion. Furthermore, subgroup analysis was performed to explore if there were any differences among different gender, region and coffee type. Finally, sensitivity analysis confirmed that

our result was robust.

There were also several limitations to this study. Firstly, the data of coffee consumption in most studies was obtained by dietary frequency questionnaire, which is often based on the participants' self-reporting. And it's possible that some participates have changed their coffee consumption habits after the baseline assessment. But evidence has emerged about reproducibility and validity of information on coffee consumption [43]. Secondly, the assessment of exposure was defined by cups in the selected studies, however, no study told us the information about cup size. The sizes of cups can be different between different countries, for example, standard coffee cups are larger in the United States than in Europe or Japan [44]. Finally, not all included studies adjusted potentially confounding factors, like race, sex, and alcohol intake.

As described in introduction, previous meta-analyses have shown different results between coffee consumption and pancreatic cancer. Li T, et al. [12] showed that the risk of pancreatic cancer was increased with the increment of coffee intake (RR 1.06, 95% CI 1.05-1.07). While Ran H, et al. [9] showed the opposite (RR 0.75, 95% CI 0.63-0.86). And Turati F, et al. [11] concluded no relationship between them (RR 1.13, 95% CI 0.99-1.29). Some researchers [8] put forward that it was possible that any relationship between coffee and pancreatic cancer wasn't causal but explainable through something between them such as biological, social and environmental factors. For instance, some epidemiological studies [45,46] have shown that the risk of pancreatic cancer is related to blood type. Person whose blood type were A, AB and B have a significantly higher risk of pancreatic cancer than those with type O. In addition, the onset of pancreatic cancer was associated with smoking [47], alcohol [48], obesity [49], dietary [50], age [51], ethnicity, family history and genetic history, infection [52] and so on.

All in all, the results of this study indicated no significant association between coffee consumption and the risk of pancreatic cancer. Of course, there must be many factors affect the relationship between coffee consumption and the risk of pancreatic cancer, and more exploration is needed in future research.

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