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Review

Dietary Factors and Pancreatic Cancer Risk: An Umbrella Review of Meta-Analyses of Prospective Observational Studies

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A B S T R A C T

Dietary factors may be associated with the occurrence of pancreatic cancer. This umbrella review aimed to review and grade the evidence for the associations between dietary factors and pancreatic cancer risk. We searched PubMed, EMBASE, Web of Science, Scopus, Cochrane Database of Systematic Reviews, and CINAHL for eligible literature. We included meta-analyses of randomized controlled trials (RCTs) or prospective observational studies. We used AMSTAR-2, a measurement tool to assess systematic reviews, to evaluate the methodological quality of the included meta-analyses. For each association, we calculated the summary effect size, 95% CI, heterogeneity, number of cases, 95% prediction interval, small-study effect, and excess significance bias. The protocol for this review was registered in the PROSPERO database (CRD42022333669). We included 41 meta-analyses of prospective observational studies describing 59 associations between dietary factors and pancreatic cancer risk. None of the retrieved meta-analyses included RCTs. No association was supported by convincing or highly suggestive evidence; however, there was suggestive evidence of a positive association between fructose intake and pancreatic cancer risk. There was weak evidence for an inverse association of nuts intake or adherence to the Mediterranean diet with pancreatic cancer incidence, and for positive associations between a higher intake of red meat or heavy alcohol intake and pancreatic cancer incidence. The remaining 54 associations were nonsignificant. Consistent with the American Institute for Cancer Research review, this umbrella review found that regular consumption of nuts and reduced intake of fructose, red meat, and alcohol were associated with a lower risk of pancreatic cancer. Emerging weak evidence supported an inverse association between adherence to the Mediterranean diet and pancreatic cancer risk. As some associations were rated as weak and most were considered nonsignificant, further prospective studies are needed to investigate the role of dietary factors and risk of pancreatic cancer.

Keywords: diet, pancreatic cancer, evidence, meta-analyses, umbrella review

Statement of Significance

This umbrella review goes beyond prior literature in several ways. The expert report published by World Cancer Research Fund and the American Institute for Cancer Research (AICR) in 2018 included data derived from prospective and retrospective studies, with a search strategy until September 2011. However, a considerable number of relevant meta-analyses have been published since 2011, which are included in our review. Of the 41 meta-analyses included in this review, 40 were published after the last AICR review, and 37 had search strategy cutoff dates beyond the previous AICR review. Additionally, we used only prospective studies, which are prone to less confounding than retrospective studies, to assess the robustness of the evidence. Consistent with the AICR review, the results of this review highlight that regular nuts consumption and reduced intake of fructose, red meat, and alcohol were associated with a lower risk of pancreatic cancer. There was an inverse association between adherence to the Mediterranean diet and pancreatic cancer risk, but this association is supported by weak evidence.

Abbreviations used: CUP, Continuing Update Project; E, expected; O, observed; PI, prediction interval; RCT, randomized controlled trial; WCRF/AICR, World Cancer Research Fund and the American Institute for Cancer Research.

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Introduction

Owing to its poor prognosis, pancreatic cancer leads to almost as many deaths (466,000) as the number of confirmed cases (496,000) and is the seventh leading cause of cancer death in both men and women worldwide [1]. Pancreatic cancer is expected to be the third leading cause of cancer death in Europe by 2025 [2] and the second-leading cause of cancer death in the United States by 2030 [3]. Most pancreatic cancer patients present at an advanced stage with nonspecific symptoms and are unsuitable for radical surgery [4]. Given that there are few early signs and symptoms of pancreatic cancer, and the response to treatment is currently very limited, the survival rates for people with this condition are poor, with the 5-y survival rate approaching 10% for the first time in 2020 in the United States [4]. Unfortunately, the burden of pancreatic cancer is estimated to increase significantly in the coming decades, partly because of a lack of established screening or early detection methods [5]. Therefore, identifying and understanding potentially modifiable risk factors and establishing interventions to address these may be the most effective way to reduce the burden of this deadly disease until new treatments are found.

Prior literature suggests that the occurrence of pancreatic cancer is associated with multiple factors, with <10% of cases attributed to genetic variation and the remaining 90% linked with environmental conditions or unhealthy lifestyles [6–8]. However, except for smoking, diabetes, and obesity, relatively few modifiable risk factors have been identified [9–11]. In recent years, numerous studies have focused on the role of dietary factors in pancreatic cancer, which may be modifiable risk factors for this disease. Most of these studies have been summarized by systematic reviews and meta-analyses. However, some meta-analyses were derived from retrospective studies (e.g., case-control studies), which are likely to report inaccurate dietary consumption measures and suffer from several biases, including recall bias, thereby reducing the strength of the pooled scientific evidence [12,13]. Therefore, additional evidence should be gathered and assessed to inform public health policy.

In 2018, the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) released their third expert report examining the relationship between diet, nutrition, physical activity, and cancer risk, including risk of pancreatic cancer. The literature search was limited to Medline and included randomized controlled trials (RCTs), prospective cohort studies, and retrospective case-control studies, with the search for pancreatic cancer up to September 2011 [14]. However, because the AICR review included case-control studies, selection bias is likely to occur and is a potential weakness of the work. Furthermore, since 2011, many large-scale prospective cohort studies investigating the association between dietary intake and pancreatic cancer risk have been completed and summarized through meta-analysis [15–17]. Therefore, we conducted this umbrella review of meta-analyses to evaluate the evidence of the associations between dietary factors and risk of pancreatic cancer.

Methods

Protocol registration

We have prospectively registered the protocol of this umbrella review in the PROSPERO database (https://www.crd.york.ac.uk/PROSPERO, CRD42022333669). This umbrella review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [18].

Search strategy

We conducted a comprehensive literature search to identify meta-analyses of RCTs or prospective observational studies that examined the association between dietary factors and pancreatic cancer risk. We searched PubMed, EMBASE, Web of Science, Scopus, Cochrane Database of Systematic Reviews, and CINAHL up to 3 June, 2022. The following search terms were used: (diet* OR drink* OR eating OR food* OR nutrition* OR consumption* OR intake*) AND (pancreatic OR pancreas) AND (adenocarcinoma* OR cancer* OR carcino* OR malign* OR neoplas* OR tumo*) AND (meta-analys* OR systematic review* OR systematic overview*). No filter or restriction was applied. The search strategy is presented in Supplemental Table 1. In addition, the references of the included full-text articles were reviewed for additional relevant articles.

Eligibility criteria

Two authors (XP-Q and JC) independently screened the titles and abstracts to identify potentially eligible articles and then reviewed the full text of all eligible articles. Any disagreements were resolved through discussion and consultation with a third author (GQ-J).

Studies were included on the basis of the following criteria: *1*) meta-analyses of RCTs or prospective observational studies exploring the association between dietary factors and pancreatic cancer risk; *2*) availability of summary risk estimates and 95% CIs; and *3*) published in English. If the meta-analyses data were derived from cohort studies and case-control studies, only results from cohort studies were included. If an article reported separate meta-analyses of multiple eligible dietary factors, all factors were assessed separately. If the associations between dietary factors and pancreatic cancer risk were evaluated by dose-response analysis and highest compared with lowest intake, we only included the dose-response analysis [19]. If >1 meta-analysis focused on the same association, we selected the most recent 1 with the largest number of cases.

Studies were excluded according to the following criteria: *1*) retrospective observational studies (case-control or cross-sectional studies); *2*) associations between dietary factors and pancreatic cancer that reported other outcomes but not incidence (e.g., mortality); *3*) systematic reviews that did not include quantitative analysis; *4*) animal studies and/or in vitro studies; *5*) not a full-text article (conference abstracts, letter, note, protocol); and *6*) publication in a language other than English.

The Population, Intervention, Comparison, Outcomes, and Study framework of eligibility criteria is presented in Supplemental Table 2.

Data extraction

Two authors (XP-Q and JC) independently extracted data using an Excel spreadsheet, and all disagreements were resolved by consulting a third author (GQ-J). We extracted the following data from each eligible meta-analysis: *1*) name of the first author; *2*) year of publication; *3*) dietary factors; *4*) number of cohort studies or case-cohort studies; *5*) number of case-control studies; *6*) meta-analysis metrics (OR, RR, and HR); and *7*) pooled effect

size and 95% CI. In addition, we extracted data from the original studies included in the eligible meta-analysis: *1*) name of the first author; *2*) year of publication; *3*) number of cases and the total number of participants; *4*) meta-analysis metrics (OR, RR, and HR); *5*) effect size and corresponding 95% CI; and *6*) data comparison form (dose-response analysis; highest compared with lowest intake).

Assessment of methodological quality

AMSTAR-2, a measurement tool to assess systematic reviews, is a tool for assessing the methodological quality of systematic reviews and meta-analyses and contains 16 distinct domains [20]. Seven of these domains are considered critical [20]: (item 2) registration of the protocol before the start of the review; (item 4) adequate and comprehensive literature search; (item 7) providing a list of excluded literature and reasons for exclusion; (item 9) using appropriate tools to assess risk of bias of included individual studies; (item 11) using appropriate statistical methods for meta-analysis; (item 13) consideration of risk of bias in the included studies when interpreting the results of the review; and (item 15) assessing publication bias and the possible impact on the results. Two authors (XP-Q and JC) used AMSTAR-2 independently to evaluate the methodological quality of the included meta-analyses. Disagreements were resolved through discussion with a third author (ZY). The methodological quality of the meta-analyses was rated as high, moderate, low, or critically low.

Statistical analysis

Data extracted from the original studies from the eligible meta-analysis were recalculated to obtain additional results to assess the level of evidence for the reported associations [21]. The random-effects model was used to calculate the combined effect size and corresponding 95% CI [22]. We also calculated the effect size of the largest data study for each association. The I^2 statistic was calculated to check for statistical heterogeneity. An I^2 value below 25% or 50% indicated low or moderate heterogeneity in the data, whereas an I^2 value above 50% or 75% indicated significant or considerable heterogeneity, respectively [23]. In addition, we assessed the 95% prediction interval (PI), which further explains the heterogeneity between studies and examines uncertainty in the expected effect size for new studies with the same association [24,25].

We also assessed the small-study effect, commonly referred to as publication bias, to determine whether such studies tended to provide a greater estimated risk than larger studies [26]. An Egger P value < 0.10 was considered statistical evidence for small-study effects [27]. In addition, we applied the excess significance test to assess whether the number of statistically significant studies observed (O) in the meta-analysis exceeded the expected (E) number [28]. In agreement with published umbrella reviews [29,30], the excess significance bias was set at $P < 0.10$. All analyses were performed using R software (version 4.1.2, R Core Team, 2021), using the meta package (version 5.2.0, Guido Schwarzer, 2022) and the metafor package (version 3.0.2, Viechtbauer, 2021).

Evaluation of the quality of evidence

None of the retrieved meta-analyses included RCTs, so we only assessed the epidemiologic credibility of observational studies. Using the grading scheme applied in previously published umbrella reviews [29,30], statistically significant ($P < 0.05$) associations between dietary factors and pancreatic cancer incidence were divided into 4 classes according to the level of evidence. P value ≥ 0.05 suggested no statistically significant association.

The criteria for determining the level of evidence were as follows:

Convincing evidence (class I): statistical significance with $P < 10^{-6}$; the number of cases >1000; statistical significance of the largest data study ($P < 0.05$); 95% PI excluded the null; $I^2 < 50\%$; no small-study effects ($P > 0.10$); and no excess significance bias ($P > 0.10$). Highly suggestive evidence (class II): statistical significance with $P < 10^{-6}$; the number of cases >1000; statistical significance of the largest data study ($P < 0.05$); and class I criteria not met. Suggestive evidence (class III): statistical significance with $P < 10^{-3}$; the number of cases >1000; and class I–II criteria not met. Weak evidence (class IV): statistical significance with $P < 0.05$ and class I–III criteria not met. Nonsignificant statistical associations were set at $P \geq 0.05$.

Results

Literature identification and selection

As shown in Figure 1, we retrieved 1896 records from 6 electronic databases (PubMed, EMBASE, Web of Science, Scopus, Cochrane Database of Systematic Reviews, and CINAHL) through a comprehensive search using the search terms included in Supplemental Table 1. A total of 894 records were excluded because of duplication using EndNote software (version X9.3.3, Clarivate Analytics, 2022). Scanning of the titles and abstracts according to the eligibility criteria excluded 827 records. A total of 175 full-text articles were identified for further evaluation, of which 134 were further excluded on the basis of the eligibility criteria, with the reasons for exclusion shown in Figure 1. Finally, 41 meta-analyses were included in this umbrella review [15–17,31–68]. Details of the 134 excluded full-text articles are mentioned in Supplemental Table 3.

Characteristics of included meta-analyses

The eligible 41 meta-analyses described 59 associations, including 384 studies, that estimated pancreatic cancer incidence associated with dietary exposure. The search for pancreatic cancer risk in relation to dietary factors in the third expert report published by the WCRF/AICR [14] was conducted up to September 2011. The meta-analyses included in this umbrella review were published from 2009 to 2022, 40 of which were published after the publication of the AICR review (September 2011), with 37 having a search strategy that extended beyond this date. To assess the methodological quality of individual studies, 1 meta-analysis [15] used the Strengthening The Reporting of Observational Studies in Epidemiology statement; 1 [65] used the Critical Appraisal Skills Program; 3 [31,44,63] used Risk of Bias In Nonrandomized Studies assessment tool; and 25 [16,17,34–40,42,49–54,56–58,60–62,64,66,68] used the Newcastle-Ottawa Quality Assessment Scale (Table 1). The remaining 11 [32,33,41,43,45–48,55,59,67] did not conduct any formal quality assessment. None of the meta-analyses included RCTs; 58 associations between pancreatic cancer risk

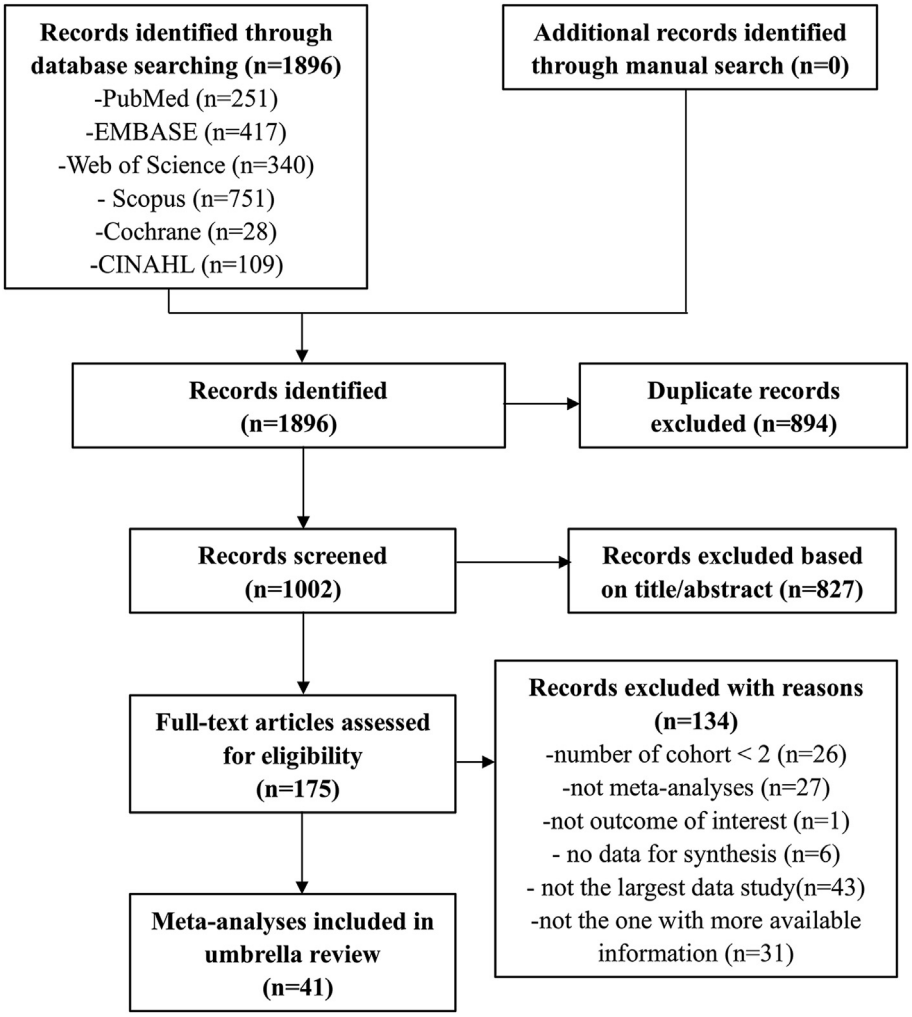

FIGURE 1. Flowchart of the literature selection process.

and dietary exposures were assessed using cohort studies, and 1 association was evaluated using cohort and case-cohort studies. The number of cohort studies for each association ranged from 2 to 21. The number of participants ranged from 32,251 to 4,180,303, and the number of cases ranged from 213 to 8092, with 43 associations having >1000 cases.

The included meta-analyses reported pooled estimates of the association between dietary factors and pancreatic cancer risk. Dietary factors included: dietary patterns (3 associations including unfavorable data-driven dietary patterns, favorable data-driven dietary patterns, and adherence to the Mediterranean diet) [15]; food items or food groups (13 associations including fruits, vegetables, eggs, red meat, processed meat, fish, poultry, cheese, and yogurt intake) [16,17,31–37]; beverages (10 associations including milk, tea, green tea, coffee, soft drinks, sweetened beverages, and alcohol intake) [37–44]; macronutrients (13 associations including carbohydrates, fat, protein, trans-FAs, SFAs, unsaturated FAs, cholesterol, and fiber intake) [45–53]; micronutrients (16 associations including magnesium, selenium, zinc, vitamins, acrylamide, flavan-3-ols, and nitrate intake) [54–65]; and other (4 associations including dietary inflammatory index, GI, GL, and EI) [66–68].

Assessing the methodological quality using AMSTAR-2 indicated that 6 meta-analyses [16,31,39,53,66,68] were of high quality, 19 [17,34–36,38,40,49–52,54,56–58,61–65] were of moderate quality, 10 [15,32,37,44,47,48,55,59,60,67] were of low quality, and the remaining 6 [33,41–43,45,46] were rated as critically low quality (Table 1). The detailed assessment of methodological quality is presented in Supplemental Table 4.

Summary of associations between pancreatic cancer and dietary factors

As shown in Table 2, 59 associations from 41 meta-analyses were recalculated using random-effects models to assess the level of evidence. A total of 5 associations yielded nominal statistical significance at $P < 0.05$. Of these, only 1 reached statistical significance at $P < 10^{-3}$, but none reached statistical significance at $P < 10^{-6}$. Two of the 5 associations, including adherence to the Mediterranean diet (RR: 0.87; 95% CI: 0.80, 0.96) and higher intake of nuts (RR: 0.89; 95% CI: 0.82, 0.97), suggested a lower risk of pancreatic cancer. The remaining 3 associations, including red meat (RR: 1.14; 95% CI: 1.01, 1.28), fructose (RR: 1.22; 95% CI: 1.09, 1.37), and heavy alcohol intake (RR: 1.15; 95% CI: 1.04, 1.27), suggested a higher risk of pancreatic cancer.

After calculating the effect size of the largest data study for each association, only 2 of the 59 associations (fructose and

TABLE 1
The methodological quality of included meta-analyses that evaluate dietary factors and pancreatic cancer risk

Study (Ref)	Dietary factor	Original article retrieval time	Cohort study, *n*	Cases, *n*	Participants, *n*	Quality assessment	AMSTAR-2
Zheng 2017 [15]	Unfavorable data-driven dietary patterns	15 June, 2016	3	622	159,314	STROBE	Low
	Favorable data-driven dietary patterns		10	1749	767,805		
	Adherence to Mediterranean diet		4	1149	527,567		
Zhao 2018 [16]	Fruit	March, 2017	8	2868	1,207,165	NOS	High
	Vegetable		8	2963	1,228,537		
	Cruciferous vegetable		6	1973	903,294		
Zhang 2020 [17]	Nuts	August, 2019	3	2098	672,692	NOS	Moderate
Darooghegi Mofrad 2021 [31]	Potato	August, 2020	3	2496	928,461	ROBINS-E	High
Bae 2009 [32]	Citrus fruit	December, 2007	5	4783	1,478,929	NA	Low
Paluszkiewicz 2012 [33]	Eggs	December, 2010	7	1645	539,706	NA	Critically low
Jiang 2019 [34]	Fish	30 March, 2019	12	4937	1,776,968	NOS	Moderate
Zhao 2017 [35]	Red meat	February, 2016	15	8572	3,108,104	NOS	Moderate
	Processed meat		14	8092	2,898,736		
Gao 2022 [36]	Poultry	28 February, 2020	11	3474	1,258,913	NOS	Moderate
Arafa 2021 [37]	Cheese	31 March, 2021	2	2410	922,454	NOS	Low
	Yogurt		5	2435	935,319		
	Milk		6	2497	951,240		
Chen 2014 [38]	Tea	29 August, 2013	12	5881	853,419	NOS	Moderate
Filippini 2020 [39]	Green tea	January, 2019	7	855	319,741	NOS	High
Wang 2016 [40]	Light alcohol	August, 2015	17	>2115	2,325,677	NOS	Moderate
	Moderate alcohol		20	>1881	4,180,303		
	Heavy alcohol		18	>1549	4,153,388		
Gallus 2011 [41]	Soft drinks containing sugar and caffeine	June, 2010	6	1219	929,709	NA	Critically low
Nie 2016 [42]	Coffee	November, 2015	21	4395	1,869,416	NOS	Critically low
Zhou 2019 [43]	Coffee among never-smokers	December, 2017	4	725	856,794	NA	Critically low
Llaha 2021 [44]	Sweet beverages	31 June, 2020	6	3207	1,991,179	ROBINS-E	Low
Aune 2012 [45]	Carbohydrates	September, 2011	9	3202	1,112,404	NA	Critically low
	Sucrose		8	2801	1,092,616		
	Fructose		6	2430	1,031,605		
Shen 2015 [46]	Fat	February, 2014	6	3063	1,064,123	NA	Critically low
Zhang 2022 [47]	Protein	1 October, 2019	2	217	77,156	NA	Low
Chen 2015 [48]	Cholesterol	April, 2014	4	1173	427,310	NA	Low
Michels 2021 [49]	Trans-FAs	22 March, 2022	7	2463	683,363	NOS	Moderate
Wang 2020 [50]	N-3 PUFAs	31 December, 2019	2	600	148,640	NOS	Moderate
Kim 2020 [51]	N-6 PUFAs	March, 2020	4	2028	762,238	NOS	Moderate
Yao 2015 [52]	SFAs	June, 2014	6	1031	1,064,199	NOS	Moderate
	MUFAs		5	913	873,654		
	PUFAs		6	1044	940,270		
Nucci 2021 [53]	Fiber	11 July, 2021	3	1579	332,690	NOS	High
Ko 2014 [54]	Magnesium	November, 2012	3	1165	525,095	NOS	Moderate
Wang 2016 [55]	Selenium	July, 2016	3	411	128,215	NA	Low
Li 2017 [56]	Zinc	31 January, 2017	2	211	101,104	NOS	Moderate
Huang 2016 [57]	β-carotene	30 December, 2015	4	811	115,124	NOS	Moderate
	Lycopene		3	748	101,148		
Wei 2020 [58]	Vitamin B-6	April, 2020	3	575	190,782	NOS	Moderate
	Vitamin B-12		2	428	108,860		
	Methionine		4	901	316,262		
Hua 2016 [59]	Vitamin C	31 May, 2015	6	1140	278,000	NA	Low
Liu 2018 [60]	Vitamin D	30 March, 2015	3	1103	267,906	NOS	Low

(*continued on next page*)

TABLE 1 (*continued*)

Study (Ref)	Dietary factor	Original article retrieval time	Cohort study, *n*	Cases, *n*	Participants, *n*	Quality assessment	AMSTAR-2
	Vitamin E		6	1371	305,677		
Fu 2021 [61]	Folate	25 November, 2019	7	2383	1,002,034	NOS	Moderate
Chen 2016 [62]	Lutein and zeaxanthin	December, 2014	2	585	198,298	NOS	Moderate
Filippini 2022 [63]	Acrylamide	7 March, 2022	4[1]	1982	598,934	ROBINS-E	Moderate
Lei 2016 [64]	Flavan-3-ols	January, 2016	3	2815	598,866	NOS	Moderate
Picetti 2022 [65]	Nitrate	28 February, 2021	2	213	32,251	CASP	Moderate
Guo 2021 [66]	Dietary inflammatory index	22 November, 2020	2	3152	634,705	NOS	High
Yu 2012 [67]	EI	May, 2012	3	NA	141,903	NA	Low
Cai 2019 [68]	GI	June 2018	10	2663	1,091,232	NOS	High
	GL		12	3277	1,342,184		

CASP, Critical Appraisal Skills Program; NA, not available; NOS, Newcastle-Ottawa Quality Assessment Scale; ROBINS-E, Risk of Bias In Nonrandomized Studies; STROBE, Strengthening The Reporting of Observational Studies in Epidemiology.

[1] 4 studies = 3 cohort studies + 1 case-cohort study.

heavy alcohol intake) showed statistical significance. The minimum number of studies testing for 95% PI was 3. After estimating the 95% PI, 58 of the 59 associations were excluded because their 95% PI contained null values or fewer than 3 studies.

Most associations (46/59) showed low or moderate heterogeneity ($I^2 < 50\%$), 12 associations had significant heterogeneity estimates ($50\% < I^2 \leq 75\%$), and only 1 association had a considerable heterogeneity estimate ($I^2 > 75\%$). The minimum number of studies to assess small-study effects was 10, and 12 associations contained a sufficient number of original studies to provide statistical power for the Egger test, with evidence of small-study effects found for 2 associations (red meat and heavy alcohol intake). No excess significance bias was found for any of the associations.

As noted above, using data from cohort studies, 5 associations yielded nominal statistical significance at $P < 0.05$. Because data included in the previous AICR review [14] were obtained from prospective cohort studies and retrospective case-control studies, in the interest of allowing comparison with their results, we calculated pooled effect sizes using data from case-control studies only and case-control studies plus cohort studies, yielding statistically significant associations of 19 and 18, respectively. Detailed results of the analyses for cohort, case-control studies, and cohort plus case-control studies are shown in Supplemental Table 5.

Grading the quality of evidence

We graded the quality of evidence as convincing evidence (class I), highly suggestive evidence (class II), suggested evidence (class III), and weak evidence (class IV).

No association was supported by convincing or highly suggestive evidence after calculating the random-effects summary effect size, 95% CI, *P* value, heterogeneity, 95% PI, evidence of small-study effects, and evidence for excess significance bias. There was 1 positive association between a higher intake of fructose and pancreatic cancer risk by suggestive evidence [45]. Evidence for 4 associations (Mediterranean diet, higher intake of nuts, red meat, and heavy alcohol intake) was weak. Two associations (Mediterranean diet and higher intake of nuts) were inversely associated with pancreatic cancer risk [15,17]. The remaining 2 associations (red meat and heavy alcohol intake) were positively associated with risk of pancreatic cancer [35,40].

The remaining 54 associations were nonsignificant. The results of all the detailed analyses on which the evidence grading was based are shown in Table 2.

Discussion

This umbrella review included 41 published meta-analyses containing 59 pooled risk estimates of the association between dietary factors and the incidence of pancreatic cancer. We found 5 statistically significant associations; however, none of these was supported by convincing or highly suggestive evidence. There was suggestive evidence of a positive association between fructose intake and pancreatic cancer risk. The evidence for an inverse association of regular consumption of nuts and adherence to the Mediterranean diet with pancreatic cancer risk was weak. There was also weak evidence of positive associations

TABLE 2
Quality of evidence of associations between dietary factors and pancreatic cancer risk

Study (Ref)	Dietary factor	Comparison	MA metric	Random effect size (95% CI)	*P*	I^2, %	Largest study 95% CI	95% Prediction interval	Egger *P*	Excess significance test		Evidence class[1]
										O/E	*P*	
Zheng 2017 [15]	Unfavorable data-driven dietary patterns	Highest vs. lowest	RR	0.81 (0.59, 1.12)	0.2	0	0.48–1.14	0.10–6.42	NA	0/0.3	NP	No
	Favorable data-driven dietary patterns	Highest vs. lowest	RR	1.01 (0.89, 1.14)	0.91	3.7	0.64–1.13	0.87–1.17	0.91	1/0.5	0.4	No
	Adherence to Mediterranean diet	Highest vs. lowest	RR	0.87 (0.80, 0.96)	0.004	0	0.76–1.05	0.71–1.07	NA	2/1.2	0.35	IV
Zhao 2018 [16]	Fruit	Per 100 g/d increment	RR	1.01 (0.96, 1.06)	0.82	0	0.87–1.04	0.91–1.11	NA	1/0.7	0.54	No
	Vegetable	Per 100 g/d increment	RR	1.00 (0.96, 1.04)	0.94	7.3	0.97–1.07	0.92–1.08	NA	0/0.7	NP	No
	Cruciferous vegetable	Highest vs. lowest	RR	0.89 (0.75, 1.06)	0.19	13.8	0.69–1.30	0.63–1.27	NA	0/0.7	NP	No
Zhang 2020 [17]	Nuts	Highest vs. lowest	RR	0.89 (0.82, 0.97)	0.01	31.5	0.84–1.02	0.41–1.93	NA	1/1.2	NP	IV
Darooghegi Mofrad 2021 [31]	Potato	Highest vs. lowest	RR	1.03 (0.95, 1.11)	0.46	0	0.95–1.11	0.63–1.69	NA	0/0.2	NP	No
Bae 2009 [32]	Citrus fruit	Highest vs. lowest	RR	0.97 (0.86, 1.10)	0.65	0	0.82–1.11	0.80–1.18	NA	0/0.3	NP	No
Paluszkiewicz 2012 [33]	Eggs	Highest vs. lowest	RR	0.95 (0.89, 1.02)	0.16	0	0.78–1.13	0.88–1.04	NA	0/0.6	NP	No
Jiang 2019 [34]	Fish	Per 50 g/d increment	RR	1.03 (0.94, 1.12)	0.49	24.2	0.85–1.80	0.85–1.25	0.49	1/1.3	NP	No
Zhao 2017 [35]	Red meat	Highest vs. lowest	RR	1.14 (1.01, 1.28)	0.03	54.3	0.90–1.34	0.83–1.56	0.03	5/2.9	0.13	IV
	Processed meat	Highest vs. lowest	RR	1.09 (0.96, 1.23)	0.19	50.5	0.93–1.28	0.74–1.59	0.19	1/2.9	NP	No
Gao 2022 [36]	Poultry	Highest vs. lowest	RR	1.13 (1.00–1.27)	0.06	30.2	1.04–1.55	0.92–1.38	0.16	2/1.3	0.37	No
Arafa 2021 [37]	Cheese	Highest vs. lowest	RR	1.16 (0.87, 1.55)	0.3	0	0.91–1.75	NE	NA	0/0.2	NP	No
	Yogurt	Highest vs. lowest	RR	0.91 (0.79, 1.05)	0.19	0	0.81–1.07	0.73–1.14	NA	0/0.5	NP	No
	Milk	Highest vs. lowest	RR	0.95 (0.82, 1.11)	0.54	0	0.82–1.18	0.77–1.18	NA	0/0.3	NP	No
Chen 2014 [38]	Tea	Highest vs. lowest	RR	1.05 (0.88, 1.25)	0.57	18.3	0.52–1.63	0.81–1.37	0.26	0/0.8	NP	No
Filippini 2020 [39]	Green tea	Highest vs. lowest	RR	1.05 (0.85, 1.29)	0.65	8.5	0.84–1.80	0.80–1.38	NA	0/0.4	NP	No
Wang 2016 [40]	Light alcohol	Light vs. lowest	RR	0.97 (0.89, 1.05)	0.39	0	0.80–1.20	0.88–1.05	0.39	0/0.9	NP	No
	Moderate alcohol	Moderate vs. lowest	RR	0.96 (0.89, 1.04)	0.3	0	0.96–1.09	0.84–1.10	0.3	1/1.6	NP	No
	Heavy alcohol	Heavy vs. lowest	RR	1.15 (1.04, 1.27)	0.005	14.5	1.11–1.30	0.93–1.43	0.005	3/3	0.64	IV
Gallus 2011 [41]			RR	1.05 (0.94, 1.16)	0.4	39.1	0.85–1.04	0.81–1.35	NA		NP	No

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TABLE 2 (*continued*)

Study (Ref)	Dietary factor	Comparison	MA metric	Random effect size (95% CI)	*P*	I^2, %	Largest study 95% CI	95% Prediction interval	Egger *P*	Excess significance test		Evidence class[1]
										O/E	*P*	
	Soft drinks contain sugar and caffeine	Highest vs. lowest								0/0.9		
Nie 2016 [42]	Coffee	Highest vs. lowest	RR	0.98 (0.79, 1.23)	0.89	47.9	0.94–1.69	0.46–2.09	0.89	5/3.6	0.21	No
Zhou 2019 [43]	Coffee among never-smokers	Yes vs. no	RR	1.00 (0.86, 1.17)	0.99	0	0.79–1.20	0.71–1.41	NA	0/0.2	NP	No
Llaha 2021 [44]	Sweet beverages	Highest vs. lowest	RR	1.18 (0.96, 1.44)	0.11	54.6	0.86–1.33	0.65–2.13	NA	2/1.7	0.56	No
Aune 2012 [45]	Carbohydrates	Per 100 g/d increment	RR	0.97 (0.81, 1.16)	0.71	34.2	0.90–1.53	0.63–1.49	NA	1/1	0.67	No
	Sucrose	Per 25 g/d increment	RR	1.05 (0.92, 1.19)	0.49	52.1	0.92–1.16	0.75–1.45	NA	0/1.4	NP	No
	Fructose	Per 25 g/d increment	RR	1.22 (1.09, 1.37)	0.0008	0	1.09–1.55	1.03–1.44	NA	1/1.6	0.88	III
Shen 2015 [46]	Fat	Highest vs. lowest	RR	1.05 (0.85, 1.30)	0.67	66.7	1.03–1.46	0.54–2.03	NA	3/1.6	0.2	No
Zhang 2022 [47]	Protein	Highest vs. lowest	RR	0.98 (0.63, 1.54)	0.94	0	0.61–1.70	NE	NA	0/0.1	NP	No
Chen 2015 [48]	Cholesterol	Highest vs. lowest	RR	1.02 (0.86, 1.20)	0.81	0	0.90–1.33	0.69–1.50	NA	0/0.2	NP	No
Michels 2021 [49]	Trans-FAs	Highest vs. lowest	OR	0.99 (0.78, 1.26)	0.97	60.9	0.83–1.18	0.48–2.05	NA	1/1.7	NP	No
Wang 2020 [50]	N-3 PUFAs	Highest vs. lowest	RR	0.82 (0.51, 1.33)	0.42	70.6	0.77–1.35	NE	NA	1/0.8	0.63	No
Kim 2020 [51]	N-6 PUFAs	Highest vs. lowest	RR	0.99 (0.86, 1.14)	0.93	0	0.84–1.17	0.73–1.35	NA	0/0.2	NP	No
Yao 2015 [52]	SFAs	Highest vs. lowest	RR	1.04 (0.81, 1.35)	0.74	74.2	1.14–1.62	0.46–2.37	NA	2/1.9	0.61	No
	MUFAs	Highest vs. lowest	RR	1.07 (0.89, 1.29)	0.47	5.8	1.02–1.46	0.68–1.69	NA	1/0.6	0.49	No
	PUFAs	Highest vs. lowest	RR	0.91 (0.79, 1.05)	0.2	12.6	0.84–1.19	0.70–1.19	NA	1/0.7	0.52	No
Nucci 2021 [53]	Fiber	Highest vs. lowest	RR	0.99 (0.87, 1.11)	0.81	0	0.87–1.14	0.44–2.19	NA	0/0.2	NP	No
Ko 2014 [54]	Magnesium	Highest vs. lowest	RR	0.93 (0.76, 1.14)	0.47	0	0.72–1.42	0.25–3.49	NA	0/0.2	NP	No
Wang 2016 [55]	Selenium	Highest vs. lowest	RR	0.82 (0.62, 1.07)	0.14	0	0.52–1.59	0.14–4.69	NA	0/0.4	NP	No
Li 2017 [56]	Zinc	Highest vs. lowest	RR	0.89 (0.56, 1.44)	0.65	0	0.52–1.70	NE	NA	0/0.1	NP	No
Huang 2016 [57]	β-carotene	Highest vs. lowest	OR	0.89 (0.67, 1.18)	0.42	35.1	0.83–1.57	0.32–2.44	NA	1/0.6	0.51	No
	Lycopene	Highest vs. lowest	OR	0.98 (0.78, 1.23)	0.84	0	0.76–1.43	0.22–4.29	NA	0/0.2	NP	No
Wei 2020 [58]	Vitamin B-6		RR	0.92 (0.50, 1.69)	0.79	82.8	0.36–0.75	0.0006–1353.07	NA		NP	No

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TABLE 2 (*continued*)

Study (Ref)	Dietary factor	Comparison	MA metric	Random effect size (95% CI)	*P*	I^2, %	Largest study 95% CI	95% Prediction interval	Egger *P*	Excess significance test		Evidence class[1]
										O/E	*P*	
		Highest vs. lowest								1/1.2		
	Vitamin B-12	Highest vs. lowest	RR	0.88 (0.66, 1.17)	0.38	0	0.62–1.24	NE	NA	0/0.2	NP	No
	Methionine	Highest vs. lowest	RR	0.78 (0.57, 1.08)	0.14	56.2	0.68–1.29	0.22–2.80	NA	1/1.3	NP	No
Hua 2016 [59]	Vitamin C	Highest vs. lowest	RR	0.93 (0.78, 1.11)	0.43	0	0.75–1.34	0.72–1.20	NA	0/0.4	NP	No
Liu 2018 [60]	Vitamin D	Highest vs. lowest	RR	0.77 (0.53, 1.10)	0.15	58.3	0.56–1.04	0.02–39.0	NA	1/1.1	0.75	No
	Vitamin E	Highest vs. lowest	RR	0.91 (0.76, 1.09)	0.3	0	0.64–1.30	0.70–1.18	NA	0/0.4	NP	No
Fu 2021 [61]	Folate	Highest vs. lowest	RR	0.79 (0.58, 1.09)	0.15	67.8	0.51–1.30	0.29–2.14	NA	2/2.4	NP	No
Chen 2016 [62]	Lutein and zeaxanthin	Highest vs. lowest	RR	0.92 (0.64, 1.33)	0.65	46.5	0.78–1.50	NE	NA	0/0.4	NP	No
Filippini 2022 [63]	Acrylamide	Highest vs. lowest	RR	0.85 (0.73–1.00)	0.05	0	0.58–1.03	0.61–1.20	NA	0/0.7	NP	No
Lei 2016 [64]	Flavan-3-ols	Highest vs. lowest	RR	0.99 (0.87, 1.13)	0.91	0	0.91–1.17	0.39–2.53	NA	0/0.2	NP	No
Picetti 2022 [65]	Nitrate	Highest vs. lowest	RR	0.99 (0.80, 1.22)	0.92	0	0.82–1.29	NE	NA	0/0.1	NP	No
Guo 2021 [66]	Dietary inflammatory index	Highest vs. lowest	RR	1.03 (0.80–1.34)	0.81	39.3	0.85–1.08	NE	NA	0/0.5	NP	No
Yu 2012 [67]	EI	Per 1 MJ/d increment	RR	0.95 (0.87, 1.05)	0.33	59.2	NA	0.34–2.66	NA	1/1	0.76	No
Cai 2019 [68]	GI	Highest vs. lowest	RR	1.04 (0.92, 1.17)	0.58	0	0.92–1.54	0.90–1.20	0.58	0/0.5	NP	No
	GL	Highest vs. lowest	RR	0.93 (0.79, 1.10)	0.41	41.7	0.42–1.07	0.59–1.47	0.41	1/1.7	NP	No

MA, meta-analyses; NA, not applicable because the number of studies (<10) too small to test for small-study effects; NE, not estimated because the number of studies (<3) too small to test for 95% prediction interval; NP, not pertinent because the estimated number is larger than observed; O/E, observed/expected number of studies with significant results.

[1] Evidence class, class I (convincing): statistical significance at $P < 10^{-6}$, >1000 cases, the largest component study with a significant effect ($P < 0.05$), the 95% prediction interval excluded the null, no significant or considerable heterogeneity ($I^2 < 50\%$), no small-study effects ($P > 0.10$), and no excess significance bias ($P > 0.10$); class II (highly suggestive): significance at $P < 10^{-6}$, >1000 cases, and the largest component study with a significant effect ($P < 0.05$); class III (suggestive): statistical significance at $P < 10^{-3}$ and >1000 cases; class IV (weak): the remaining significant associations at $P < 0.05$; No, nonsignificant association $P \geq 0.05$.

between a higher intake of red meat and heavy alcohol consumption and pancreatic cancer incidence.

Meta-analysis is an important research design that evaluates the evidence and guides medical practice and health policy by combining data from individual studies [69]. However, meta-analyses highlighting only a few comparisons for 1 specific outcome may be misleading. To address this limitation, in 2009, Ioannidis et al. [70] introduced the umbrella review concept, a review designed to provide conclusive evidence by integrating evidence from multiple meta-analyses.

In 2018, the WCRF/AICR's Continuing Update Project (CUP) on pancreatic cancer concluded that the association of red meat, processed meat, heavy alcoholic beverages, foods and beverages containing fructose, and foods containing SFAs with pancreatic cancer risk was "limited-suggestive," whereas the conclusion was "limited-no conclusion" for the association of many other dietary factors with pancreatic cancer risk [14]. To further examine the associations between dietary factors and risk of pancreatic cancer and update recommendations in health policy or nutritional guidelines, we assessed the robustness of the meta-analytic evidence from prospective studies in this umbrella review. Compared with the expert report published by WCRF/AICR in 2018 [14], in which report data were derived from prospective cohort studies and retrospective case-control studies and only up until September 2011, our umbrella review has 2 strengths. First, as shown in Table 1, many relevant meta-analyses have been published since 2011; therefore, our umbrella review reflects an updated literature search. Of the 41 meta-analyses included in this review, 40 were published after the last AICR review, and 37 had search strategy cutoff dates beyond the previous AICR review. Second, we only included prospective cohort studies because case-control studies are inevitably subject to confounding factors and biases, especially recall bias. Compared with case-control studies, prospective cohort studies are better controlled for confounders, have less recall bias, and typically report null but report more robust associations. We used only cohort studies in this review and highlighted only 5 statistically significant associations. However, this number increased to 18 when both cohort and case-control studies were used.

We would especially like to thank the reviewers during the peer review process for informing us of a similar article recently published by Vincenza Gianfredi et al. [71]. This article assessed the strength of evidence for the association of dietary patterns and food items with pancreatic cancer risk by including prospective cohort and retrospective case-cohort studies. Our review differs from it in several ways. First, we included only cohort studies. Second, we assessed dietary factors that included both dietary patterns and food items, as well as beverages (including alcohol), macronutrients, and micronutrients. We did not further compare the similarities and differences in the results of the 2 articles because the design of the reviews differed markedly, especially concerning the types of studies included.

Based on 6 cohort studies, which included 2430 cases and 1,031,605 participants, this umbrella review found a positive association between higher intake of fructose and pancreatic cancer risk by suggestive evidence, which is consistent with results from the WCRF/AICR CUP report [14]. The specific mechanisms underlying this association remain speculative. Multiple lines of evidence suggest that insulin resistance may play a role in the etiology of pancreatic cancer. Established or possible risk factors for pancreatic cancer, including low physical activity, obesity, and type 2 diabetes, have also been associated with insulin resistance [72–74]. Several epidemiological and experimental studies suggest that high fructose intake may increase risk of insulin resistance, obesity, and type 2 diabetes. Therefore, it is possible that fructose's role in pancreatic cancer is linked to these risk factors [75–77]. Considering that the 95% PI for this association did not include a null value, heterogeneity was <25%, no small-study effect or excess significance bias existed, and the number of cases exceeded 1000, the evidence appears robust.

We found weak evidence for a positive association between red meat intake and pancreatic cancer risk, in agreement with the WCRF/AICR CUP report [14]. Several potential mechanisms could explain this association. First, cooking red meat at high temperatures, such as grilling, barbecuing, or frying, produces heterocyclic aromatic amines and polycyclic aromatic hydrocarbons, both of which are thought to increase cancer risk in humans [78,79]. Second, heme iron in red meat has been found to cause cytotoxicity, promote the proliferation of epithelial cells, induce lipid peroxidation, form free radicals and DNA adducts, and catalyze the formation of N-nitroso compounds, thereby promoting carcinogenesis [80,81]. Third, animal-derived proteins rich in branched-chain and aromatic amino acids have been found to increase risk of insulin resistance, which may play a role in the etiology of pancreatic cancer [74,82,83]. The association between red meat intake and cancer risk has also been highlighted in other umbrella reviews [84,85]. Veettil et al. [85] found convincing evidence of an association between higher intake of red meat and risk of colorectal cancer, and Qin et al. [84] found weak evidence for the association between red meat consumption and incidence of esophageal cancer.

In agreement with the WCRF/AICR CUP report [14], we found no significant effect of low to moderate alcohol intake on pancreatic cancer risk. However, there was weak evidence for a positive association between heavy alcohol intake and pancreatic cancer incidence. There are several possible explanations for the carcinogenic effects of alcohol consumption. First, the primary carcinogenic mechanism is related to the alcohol metabolite acetaldehyde, which has been identified as a carcinogen in several in vitro, human, and animal studies [86–88]. Second, chronic alcoholic pancreatitis can be caused by long-term heavy consumption of alcohol, which may, at least in part, underlie the association between alcohol consumption and pancreatic cancer risk [89]. Third, the carcinogenic effect might depend on the type of alcoholic beverage, and the association between alcohol intake and pancreatic cancer risk may also be because of a dose effect, given that the alcohol concentration in a glass of liquor is substantially higher than that in a glass of beer or wine; these associations should be adjective of the number of consumed alcohol units [90–92].

This review highlighted an inverse association between the high consumption of nuts and risk of pancreatic cancer, although the evidence for this association was weak. Nuts are rich in nutrients such as protein, MUFAs and PUFAs, fiber, antioxidants, and other bioactive compounds shown to confer health benefits [93,94]. Consumption of nuts may be linked with lower cancer risk by altering lipid metabolism and lowering low-density

lipoprotein and cholesterol concentrations, thereby reducing the storage of cholesterol ether in cancer cells and inhibiting the proliferation of tumor cells [95]. Additionally, it has been shown that a higher intake of nuts may reduce lipid peroxidation and insulin resistance, which are involved in cancer development and progression [74,96,97].

We found that adherence to the Mediterranean diet, which was not assessed in the WCRF/AICR CUP review, was inversely associated with pancreatic cancer risk by weak evidence. Dietary pattern analysis has emerged as an alternative method for assessing the relationship between diet and disease risk. Because this approach does not examine individual foods or nutrients but considers the diet as a whole, representing a broader range of food and nutrient consumption, it may be a better predictor of disease risk than individual foods or nutrients [98]. The Mediterranean diet is characterized by a high intake of fresh fruits, vegetables, legumes, nuts, nonrefined grains, and olive oil; moderate consumption of dairy products, fish, and alcohol (mainly red wine with the main meal); and low intake of red meat [99]. Owing to the combination of foods rich in antioxidants and anti-inflammatory nutrients, which may help reduce cellular oxidation and inflammatory processes, DNA damage, cell proliferation, and angiogenesis, the Mediterranean diet could be an effective and manageable strategy to decrease cancer incidence [100]. The associations between both unfavorable and favorable dietary patterns and pancreatic cancer risk were nonsignificant. Unfavorable dietary patterns were defined as including a large number of foods and components that are commonly considered harmful to health, such as red and processed meats, French fries, animal protein, and cholesterol, whereas favorable dietary patterns included a large number of healthy foods, such as fruits and vegetables, fiber, and whole grains [15]. However, considering that there is no clear consensus on the definitions of favorable, unfavorable, healthy, and unhealthy diets, it is possible that the definitions used in the original studies may differ, leading to inevitable heterogeneity among studies and thus affecting the interpretation of the results. Therefore, new prospective studies are needed to explore the relationship between different dietary patterns and pancreatic cancer risk.

This umbrella review also has several limitations that should be considered. First, we included studies from published meta-analyses and may have missed individual studies if they had not been evaluated in these meta-analyses. Second, the methodological quality of the overall meta-analyses, assessed by AMSTAR-2, may need to be revised for small subgroups. Third, we did not perform subgroup analysis (e.g., by sex, age group, or smoking status) because of the lack of subgroup data to grade the quality of the evidence for most exposures. Given that only 5 associations yielded nominal statistical significance at $P < 0.05$, we did not separately discuss differences in results between meta-analyses of moderate-high methodological quality compared with low quality. Fourth, this umbrella review only included data from observational studies, which may suffer from selection and recall bias, affecting the results of this review. Although we can describe and assess associations, we cannot determine causality or accurately provide recommendations for individual daily dietary intake standards. Fifth, the reliability of the umbrella review depends directly on the included meta-analyses and indirectly on the original studies. We could not control for bias in the original studies.

Given these limitations, further prospective studies are needed to draw definitive conclusions and provide public health recommendations.

In conclusion, the results of this umbrella review, which are consistent with those reported by the WCRF/AICR review, highlight the association between regular consumption of nuts and reduced intake of fructose, red meat, and alcohol with a lower risk of pancreatic cancer. Emerging weak evidence supported an inverse association between adherence to the Mediterranean diet and pancreatic cancer risk. As some associations were rated as weak and most were considered nonsignificant, further prospective studies are needed to investigate the role of dietary factors and risk of pancreatic cancer.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.advnut.2023.02.004.

Data Availability

Data described in the manuscript, code book, and analytic code will be available upon request.

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