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ORIGINAL CONTRIBUTION

Inflammatory potential of diet and pancreatic cancer risk in the EPIC study

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Abstract

Purpose There is existing evidence on the potential role of chronic inflammation in the pathogenesis of pancreatic cancer (PC) and on how risk may be modulated by dietary factors. Pro-inflammatory diets are suggested to be associated with increased risk of PC but, so far, evidence remains not conclusive. We examined the association between the dietary inflammatory potential and PC risk within the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which includes 450,112 participants.

Methods After a 14-year follow-up, a total of 1239 incident PC cases were included in this study. The inflammatory potential of the diet was estimated using an Inflammatory Score of the Diet (ISD). Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between the ISD and PC were estimated using multivariable Cox regression models, adjusted for known risk factors for PC.

Results Participants with higher ISDs had a higher risk of developing PCs. In the fully adjusted multivariate model, the risk of PC increased by 11% (HR 1.11, 95% CI 1.02–1.22) for 1 point each standard deviation increase in the ISD score. Neither obesity nor any other known risk factor for PC showed statistically significant interactions.

Conclusion To the best of our knowledge, this is the first prospective study reporting a positive relationship between the inflammatory potential of diet and PC. Since early diagnosis and treatment of pancreatic cancer might be challenging, prevention remains the major hope for reducing the burden of this disease.

Keywords Inflammatory potential of diet · Pancreatic cancer · Prospective cohort · Epidemiology · Dietary patterns

Introduction

Pancreatic cancer (PC) is the twelfth most commonly occurring cancer and the eighth in the number of deaths worldwide [1]. One- and five-year survival rates are 29% and 7%, respectively [2]. The most determinant risk factors for PC are found amidst individuals with rare syndromes or mutations, including hereditary pancreatitis. More common strong risk factors for pancreatic cancer include certain pancreatic cysts, pancreatitis, tobacco smoking, diabetes mellitus, a family history of pancreatic cancer, obesity, high alcohol consumption and having a non-O blood group [3, 4].

Although the aetiology of PC is not yet clearly understood, chronic inflammation is known to play an important role in its carcinogenesis [3]. In addition to local inflammation of the pancreas, several lines of evidence point towards systemic, low-grade, chronic inflammation being involved in the pathogenesis. Other lifestyle factors such as physical

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inactivity, alcohol consumption and obesity have been related to low-grade inflammation [5, 6].

Several foods and food components have an impact on blood concentrations of inflammatory markers [7], indicating that diet plays a role in the regulation of chronic inflammation. Some epidemiological studies have shown an association between greater inflammatory potential of the diet and risk of gastrointestinal cancers [8, 9]. In relation to inflammatory dietary patterns and PC risk, results are heterogeneous [10–14], with cohort studies so far having shown negative results [13, 14].

The main objective of this study was to assess the association between dietary inflammatory potential and pancreatic cancer risk in a large multicenter European cohort study. In addition, we aimed to assess potential interactions with other important risk factors for PC.

Materials and methods

Study setting and population

The methodological details and rationale behind the EPIC study have been previously described [15, 16]. In brief, EPIC is a prospective cohort study that involves 23 centres from 10 different European countries. A total of 492,763 participants, ages 35–70 years, were recruited between 1992 and 1998. Prior to analysis, participants who had pre-baseline cancer (other than non-melanoma skin cancer) were excluded ($n=24{,}550$), as were those without complete follow-up information ($n=3137$), those with missing data on diet or lifestyle and those in the top or bottom 1% of the distribution of the ratio of energy intake to energy requirements. Greece did not take part in this research project ($n=14{,}964$). As a result, 450,112 participants were included in the final study population of this study. The ethical review boards from the International Agency for Research on Cancer and from all local centers approved the study.

Ascertainment of pancreatic cancer cases

Cancer incidence information was assessed through population cancer registries or through a combination of the following three methods: health insurance records, active follow-up or cancer and pathology registries. PC was classified as C25 (C25.0–C25.3 and C25.7–C25.9), based on the 10th revision of the ICD [17]. Fifty-three cases were censored due to them being: neuroendocrine pancreatic tumors ($n=35$), Islet cell carcinomas ($n=5$), glucagonoma ($n=1$), insulinoma ($n=1$), carcinoid tumours ($n=10$), malignant lymphoma (non Hodking) ($n=1$) or benign tumours ($n=1$).

Assessment of dietary variables

Dietary data were collected by means of country-specific validated questionnaires, either quantitative or semi-quantitative, recording usual diet over the previous 12 months [15]. A lifestyle questionnaire [16] was used to collect information about sociodemographic characteristics, lifestyle (including smoking habits) and medical history. Anthropometric measures and blood samples were also collected at recruitment.

Assessment of the inflammatory score of the diet (ISD) and calibration of intakes

A detailed description of the methodology used for the calculation of the ISD can be found in previous publications [8, 9]. In brief, the ISD was constructed upon the previously existing literature-based Dietary Inflammatory Index (DII) which is based on scoring forty-five food and nutrient parameters according to their inflammatory potential [18].

To calculate individual ISDs, each participant's intake of 28 available food parameters from EPIC questionnaires was first standardized using the mean and standard deviation of the study population. The absolute value of the ISD for a given individual is not an exact measure of the inflammatory effect of their diet. An ISD value of 0 implies that participants hold the mean intake of the 28 components which were used to calculate the ISD in the reference population. More detailed information on punctuation on the included components is presented in supplementary Table 1. The ISD is to be considered a 'relative' index which allows categorizing individuals' diets along a continuum, from maximally anti-inflammatory to maximally pro-inflammatory. Positive values indicate a more pro-inflammatory diet; and negative values correspond to anti-inflammatory diets.

First, to improve the comparability of dietary data across centres and to minimize measurement error, a linear regression calibration approach was applied by using data from the 24-h dietary recall (24hDR) subsample of participants [19]. Sex and country-specific calibration models were applied to obtain individual predicted values of dietary exposures. Measurements from the 24hDRs were regressed on dietary intake as per the questionnaires. The model included total energy intake, age at recruitment, centre, education level, smoking status, body mass index (BMI) and levels of physical activity. These models were then used to obtain predicted values on intake for all participants. The predicted (calibrated intake) values of each food component were used to calculate the ISD. A bootstrap sampling procedure (with a total of 400 repetitions) was used to compute the mean and standard deviation of the predicted (calibrated) intake of each food component of the ISD in our population [16].

Statistical analysis

To assess the association between the inflammatory potential of diet (measured by the ISD) and PC risk, hazard ratios (HRs) and 95% confidence intervals (CI) were estimated, using Cox proportional hazards models. Entry time was defined as age at recruitment, whereas exit time was the age at diagnosis (cases), death, or end of follow-up, whichever occurred first. All models were stratified by study centre and age-at- recruitment (in 1-year categories) and adjusted for sex and total energy intake (quartiles). Subsequently, multivariable models were further adjusted for the following potential confounders: smoking status and intensity (never a smoker; current, 1–15 cigarettes/day; current, 16–25 cigarettes/day; current > 25 cigarettes/day; former, quit ≤ 10 years; former, quit 11–20 years; former, quit > 20 years ago; occasional smokers, cigar and/or pipe; smokers with unknown status, and unknown); BMI (kg/m2 < 25, 25.0–29.9, ≥ 30); alcohol consumption (non-consumer or consumers of < 5 g /day, 5.0–14.9 g/day, 15.0–29.9 g/day, 30.0–59.9 g/day, ≥ 60 g/day); and history of diabetes (no, yes, unknown). The selection of confounders was done a priori based upon the known risk factors of pancreatic cancer available in EPIC and associated with the inflammatory potential of the diet. To avoid overfitting, a statistical criterion was applied, excluding variables (physical activity and educational level) that showed low significance in the univariate model ($p > 0.2$).

The ISD was analysed both as a categorical variable classified by quartiles (where the first quartile was used as the reference category) and as a continuous, standardized one, divided by its standard deviation. Trend tests across quartiles of the ISD were calculated by entering the categorical variable into the model as a continuous term. The non-linearity of the effect of the ISD on PC risk was assessed by adding a quadratic term to the model with the ISD as continuous variable, and using the likelihood ratio test to compare models with and without the quadratic term. A non-significant LR test was interpreted as indicative of a linear effect of the ISD on PC risk, even though this is not technically considered a formal proof of linearity. The LR test was also used to evaluate potential interactions between the ISD (as a continuous variable) and all other variables included in the fully adjusted model. A chi-squared test based upon the scaled Schoenfeld residuals was used to evaluate if the assumptions of proportional hazards were met. To determine potential reverse causality, a sensitivity analysis was conducted by excluding the first 2 years of follow-up.

Results

Among the 450,112 participants in the cohort, and for the average follow-up period of 14 years, a total of 1239 incident cases of pancreatic cancer were identified. The inflammatory potential of the diet in all participants, as measured by the ISD, had a mean value of 0.37 (SD 1.71). Values ranged from − 6.43 to + 5.67; the median and 25th and 75th percentiles were 0.50, − 0.77, and 1.64, respectively.

Table 1 shows the distribution of participants and ISD values according to the main characteristics of the studied population. The mean ISD was significantly higher in participants with higher BMIs, lower levels of alcohol consumption, in current smokers and physically inactive individuals.

The association between the inflammatory potential of diet and pancreatic cancer risk is presented in Table 2. A statistically significant (HR 1.24; 95% CI 1.12–1.35 for each SD score) increase in risk was found in the basic model. After adjusting for tobacco smoking, the risk was dramatically reduced. Nonetheless, the fully adjusted model remains significant (HR 1.11; 95% CI 1.02–1.22) for each 1 SD increase in the score.

Table 3 shows the association between ISD and risk of PC, stratified by inflammation-related lifestyle factors. The ISD was associated with an increased risk of PC in participants with high alcohol consumption, as well as physically inactive individuals, but there was no evidence of interaction with these separate subgroups. In terms of BMI categories, the increased risk of PC for each 1-point SD increase in ISD was only statistically significant amongst obese participants (HR 1.32, 95% CI 1.05, 1.65) (p for interaction = 0.84).

The association remained virtually the same after excluding subjects diagnosed in the first 2 years of follow-up (HR 1.12, 95% CI 1.02, 1.23 for each SD increase in the ISD) ($n = 82$) (data not shown).

Discussion

In this large European prospective study, we observed that participants with a higher ISD presented a higher risk of developing PC. Each 1-point increment in the score's SD increased PC risk by 11%. This is, to the best of our knowledge, the first prospective study reporting a positive relationship between the inflammatory potential of diet and PC.

Two case–control studies have used the Dietary Inflammatory Index (DII®) to assess the association between dietary inflammatory potential and PC risk. Both studies reported > twofold increased risk in the most pro-inflammatory diet group [10, 11]. A more recent cohort study including 328 pancreatic cancer cases showed that inflammatory dietary potential (as measured by DII®) was not associated with PC risk (HR Q5 *vs* Q1 0.94; 95% CI 0.66–1.35; p-trend = 0.43) [12]. A combined analysis including data from 5 different cohorts (1,268 cases) also reported a statistically positive association, overall comparable to our results (HR 1SD: 1.09, 95% CI 1.02–1.15). However, the results of each individual study were not statistically significant [13].

Table 1 Baseline characteristics of subjects across quartiles of the inflammatory score of the diet (ISD) in the EPIC study

				Inflammatory Score of the Diet (ISD)				
	All		PC	Quartile 1	Quartile 2	Quartile 3	Quartile 4	Mean (95% CI)[1]
ISD cutoffs				(− 6.44, − 0.77)	(− 0.77, 0.50)	(0.50, 1.64)	(1.64, 5.70)	
n	450,112	(100%)	1239	112,528	112,528	112,528	112,528	
Sex, *n* (%)								
Men	131,426	(29.2%)	531	55,564 (49.4%)	38,627 (34.3%)	24,307 (21.6%)	12,928 (11.5%)	0.37 (0.36,0.38)
Women	318,686	(70.8%)	708	56,964 (50.6%)	73,901 (65.7%)	88,221 (78.4%)	99,600 (88.5%)	0.36 (0.36,0.37)
Age, yr								
< 50	190,664	(42.4%)	169	57,633 (51.2%)	43,952 (39.1%)	43,120 (38.3%)	45,959 (40.8%)	0.28 (0.27,0.28)
50 to < 60	175,649	(39.0%)	618	37,877 (33.7%)	46,741 (41.5%)	46,945 (41.7%)	44,086 (39.2%)	0.46 (0.46,0.47)
≥ 60	83,799	(18.6%)	452	17,018 (15.1%)	21,835 (19.4%)	22,463 (20.0%)	22,483 (20.0%)	0.36 (0.36,0.37)
Energy, Kcal/day								
Mean (SD)	2081.8 (412.2)		1239	2330.6 (436.2)	2166.0 (395.5)	2006.9 (337.0)	1823.5 (279.1)	0.37 (0.36, 0.37)
Alcohol, gr/day								
< 5	125,586	(27.9%)	333	17,558 (15.6%)	24,587 (21.8%)	34,243 (30.4%)	49,198 (43.7%)	0.60 (0.59,0.61)
5 to < 15	172,301	(38.3%)	386	39,948 (35.5%)	44,026 (39.1%)	46,309 (41.2%)	42,018 (37.3%)	0.38 (0.37,0.38)
≥ 15	152,225	(33.8%)	520	55,022 (48.9%)	43,915 (39.0%)	31,976 (28.4%)	21,312 (18.9%)	0.16 (0.15,0.17)
Smoking status, *n* (%)								
Never	219,294	(48.7%)	471	58,454 (51.9%)	58,470 (52.0%)	57,822 (51.4%)	44,548 (39.6%)	0.09 (0.08,0.10)
Former	122,680	(27.3%)	338	36,928 (32.8%)	31,296 (27.8%)	28,171 (25.0%)	26,285 (23.4%)	0.25 (0.24,0.26)
Current	99,715	(22.2%)	415	16,419 (14.6%)	21,241 (18.9%)	24,035 (21.4%)	38,020 (33.8%)	1.03 (1.02,1.04)
Unknown	8423	(1.9%)	15	727 (0.6%)	1521 (1.4%)	2500 (2.2%)	3675 (3.3%)	1.35 (1.32,1.38)
BMI, Kg/m^2								
< 25	239,693	(53.3%)	528	63,020 (56.0%)	60,931 (54.1%)	62,333 (55.4%)	53,409 (47.5%)	0.30 (0.30,0.31)
25 to < 30	154,781	(34.4%)	509	38,045 (33.8%)	38,638 (34.3%)	36,614 (32.5%)	41,484 (36.9%)	0.43 (0.42,0.43)
≥ 30	55,638	(12.4%)	202	11,463 (10.2%)	12,959 (11.5%)	13,581 (12.1%)	17,635 (15.70%)	0.48 (0.47,0.49)
DM, *n* (%)								
No	400,452	(89.0%)	1039	100,231 (89.1%)	100,550 (89.4%)	100,114 (89.0%)	99,557 (88.5%)	0.40 (0.40,0.41)
Yes	10,738	(2.4%)	66	3142 (2.8%)	2802 (2.5%)	2530 (2.2%)	2264(2.0%)	0.00 (− 0.02,0.03)
NS	38,922	(8.6%)	134	9155 (8.1%)	9176 (8.2%)	9884 (8.8%)	10,707 (9.5%)	0.09 (0.08,0.11)
Physical activity, *n* (%)								
Inactive	88,032	(19.6%)	285	15,433 (13.7%)	19,536 (17.4%)	23,426 (20.8%)	29,637 (26.3%)	0.54 (0.53,0.55)
Moderately inactive	149,941	(33.3%)	406	37,680 (33.5%)	39,105 (34.8%)	38,349 (34.1%)	34,807 (30.9%)	0.31 (0.30,0.31)
Moderately active	120,199	(26.7%)	287	29,764 (26.5%)	29,860 (26.5%)	30,986 (27.5%)	29,589 (26.3%)	0.41 (0.40,0.42)
Active	83,116	(18.5%)	239	28,708 (25.5%)	22,429 (19.9%)	17,576 (15.6%)	14,403 (12.8%)	0.15 (0.14,0.16)
NS	8824	(2.0%)	22	943 (0.8%)	1598 (1.4%)	2191 (1.9%)	4092 (3.6%)	1.15 (1.12,1.18)
Education level, *n* (%)								
None	15,551	(3.5%)	50	5509 (4.9%)	3790 (3.4%)	3481 (3.1%)	2771 (2.5%)	− 0.23 (− 0.26,− 0.21)
Primary	111,064	(24.7%)	428	13,945 (12.4%)	21,856 (19.4%)	28,408 (25.2%)	46,855 (41.6%)	1.00 (0.99,1.01)
Tech./prof	103,783	(23.1%)	311	24,040 (21.4%)	25,077 (22.3%)	25,351 (22.5%)	29,315 (26.1%)	0.48 (0.47,0.49)
Secondary	93,910	(20.9%)	161	19,288 (17.1%)	25,795 (22.9%)	28,561 (25.4%)	20,266 (18.0%)	0.37 (0.36,0.38)
Longer educat	108,931	(24.2%)	230	44,027 (39.1%)	31,417 (27.9%)	22,675 (20.2%)	10,812 (9.6%)	− 0.17 (− 0.18,− 0.17)
NS	16,873	(3.7%)	59	5719 (5.1%)	4593 (4.1%)	4052 (3.6%)	2509 (2.2%)	− 0.49 (− 0.51,− 0.47)

[1]Adjusted means (95% CI) obtained from a linear regression model including all the variables in the table

Table 2 Association of Inflammatory Score of the Diet (ISD) and pancreatic cancer among the EPIC population

		HR	(95% CI)		*p* value	ISD continuous[1]
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	for trend	HR (95% CI)
cases, *n*	262	291	320	366		1239
Basic model[2]	[Reference]	1.13 (0.95, 1.35)	1.32 (1.09, 1.59)	1.55 (1.25, 1.91)	< 0.001	1.24 (1.14, 1.35)
Basic model plus tobacco[3]	[Reference]	1.05 (0.88, 1.25)	1.15 (0.95, 1.39)	1.21 (0.97, 1.52)	0.06	1.12 (1.02, 1.22)
Multivariate model[4]	[Reference]	1.04 (0.87, 1.24)	1.14 (0.95, 1.38)	1.20 (0.96, 1.50)	0.07	1.11 (1.02, 1.22)
Multivariate model[5]	[Reference]	1.09 (0.90, 1.31)	1.16 (0.95, 1.42)	1.23 (0.97, 1.54)	0.07	1.12 (1.02, 1.23)

[1]Hazard ratio (HR) per each increase in one standard deviation (SD) of the ISD

[2]Stratified by age and center, and adjusted for sex and energy intake (in quartiles)

[3]Basic model plus smoking intensity variable

[4]Multivariate model: basic model and further adjusted by smoking intensity (never, current 1–15, 16–25, or ≥ 26 cigarettes/day, former ≤ 10, 11– < 20, or ≥ 20 years, current pipe/cigar/occasional smoking, and current vs. former missing or unknown), body mass index (< 25, 25– < 30, or ≥ 30 kg/m2), alcohol consumption (non consumer, < 5, 5– < 15, 15– < 30, 30– < 60 or ≥ 60 gr/day), and diabetes mellitus (no, yes, and unknown)

[5]Multivariate model excluding subjects with two or less years of follow-up

A recent prospective study which included 850 women with pancreatic cancer and used an empirical inflammatory score found a non-significant positive association (HR, 1.26, 95% CI 0.98–1.63) for each 1SD increment of the score) [14].

The contrasting results between our study and previous cohort studies could be due to several reasons. These include potential differences in the dietary habits of subjects and possible differing ranges of intakes in the components used to estimate the inflammatory potential of the diet, as well as differences in the prevalence of inflammatory-related lifestyle factors. Most importantly, we used predicted (calibrated intake) values of each component to calculate ISD. Measurement error from Food Frequency Questionnaires used in previously reported cohort studies [11–13] could have led to substantial underestimations of relative risk and could partially explain the differences with our findings.

To date, the exact mechanism by which each dietary component has a pro- or anti-inflammatory effect remains unclear. This also applies to the extent to which the overall inflammatory potential of an individual's diet contributes to the hypothesized risk of pancreatic cancer. The inflammatory potential of diet may contribute to tumorigenesis of the pancreas by increasing blood levels of inflammatory cytokines, which can lead to excessive generation of reactive oxygen species as a normal immune response to cytotoxicity [20]. In turn, this may result in damage to the DNA, mutagenesis and, ultimately, tumorigenesis [20, 21].

The results of this study are in accordance with the evidence on other healthy dietary patterns, such as the Mediterranean diet and Healthy Lifestyle Index, which may be associated with a lower risk of PC [22, 23]. Our suggestive finding that the association could be more pronounced in obese individuals (non- large interaction) needs to be further investigated, ideally within larger cohort studies. A recent hypothesis is that obesity could be partially the consequence of previous chronic low-grade inflammation. If this were so, a bidirectional association between inflammation and obesity could exist [24]. Moreover, it has been shown that the abundance of inflammatory cells in excess adipose tissue contributes to a chronic low-grade inflammatory state [25]. Another potential biological mechanism might be the effect of diet on changes in the intestinal microbiota, which precede adiposity-promoted low-grade inflammation [26]. Stronger associations were also found in current smokers and physically active participants (test for interaction non significant). Both of these results are in accordance with previous EPIC findings assessing other healthy lifestyle patterns and PC risk [23].

Several methodological limitations relating to the construction of the ISD score should be considered when interpreting our findings. Due to the limited availability of dietary data in the EPIC database, the ISD in our study included 28 out of the original 45 items used in the DII. However, a previous publication found that seven key components have explained 91% of the inter-individual variance in the DII [27]. In fact, most articles published on PC risk which used DII or derived methodologies did not specify the detailed list of included items (availability ranged from 28 to 35). Systematic and random errors, inherent to dietary information based upon the individual's memory applied to the dietary data used to construct the ISD (derived from self-reported country-specific dietary questionnaires), are further limitations. The calibration we carried out in this study aimed to mitigate this limitation. We also lacked information on the use of anti-inflammatory drugs and supplements, as well as the history of chronic pancreatitis.

Our study has several important strengths, including its prospective design, long follow-up period and large sample size. We also adjusted for multiple potential confounding

Table 3 Adjusted hazard ratios (HRs) and 95% confidence intervals (CI) of PC and ISD (continuous) by subgroups of sex, age, smoking status, BMI, diabetes mellitus, alcohol consumption and physical activity, in relation to the inflammatory score of the diet (ISD) in the EPIC study

Subgroup	Cases, *n*	ISD continuous[1] HR (95% CI)	*p* value for interaction[2]
Sex			
Men	531	1.12 (0.98, 1.28)	0.67
Women	708	1.12 (0.99, 1.27)	
Age, yr			
< 50	169	1.26 (0.96, 1.64)	0.72
50 to < 60	618	1.12 (0.99, 1.27)	
≥ 60	452	1.07 (0.93, 1.23)	
Smoking status			
Never	471	1.13 (0.98, 1.32)	0.25
Former	338	1.12 (0.95, 1.31)	
Current	415	1.16 (1.00, 1.36)	
BMI, Kg/m^2			
< 25	528	1.09 (0.95, 1.25)	0.84
25 to < 30	509	1.06 (0.92, 1.21)	
≥ 30	202	1.32 (1.05, 1.65)	
DM			
No	1039	1.12 (1.02, 1.24)	0.94
Yes	66	0.94 (0.62, 1.42)	
Alcohol consumption, gr/day			
< 5	333	1.09 (0.91, 1.31)	0.47
5 to < 15	386	1.05 (0.89, 1.24)	
≥ 15	520	1.18 (1.03, 1.34)	
Physical activity			
Inactive	285	0.91 (0.75, 1.11)	0.83
Mod. Inactive	406	1.08 (0.92, 1.27)	
Mod. Active	287	1.23 (1.01, 1.49)	
Active	239	1.23 (1.02, 1.49)	

[1]Hazard ratio (HR) per each increase in one standard deviation (SD) of the ISD. Cox proportional hazards models are stratified by age at recruitment and centre, and adjusted for sex, alcohol consumption and total energy intakes, BMI, smoking intensity and diabetes mellitus

[2]Significance level for the interaction between participant's characteristics and the Inflammatory Score of the Diet (ISD)

factors and controlled for the possibility of reverse causality by excluding the first two years of follow-up.

In conclusion, our results show that a more pro-inflammatory diet is associated with increased pancreatic cancer risk. Prevention remains the key goal for reducing the burden of the disease. Further studies combining complementary methodologies to the estimated inflammatory potential of the diet with large sample sizes are needed to confirm these findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00394-022-02809-y.

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Data availability Author elects to not share data.

Declarations

Conflict of interest The authors have declared no conflicts of interest.

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