British Journal of Nutrition (2022), 127, 1878–1887 doi:10.1017/S0007114521002907

Association of dietary inflammatory potential with risk of overall and cause-specific mortality

Xiude Li[1,2,3,4†], Bo Chen[5†], Jiawei Zhang[5†], Meiling Li[1], Zhuang Zhang[1], Yu Zhu[1], Xu-Fen Zeng[1], Hairong Li[1], Yingying Wang[1], Su-Fang Wang[1], Anla Hu[1], Qihong Zhao[1] and Wanshui Yang[1,2,3,4*]

[1]*Department of Nutrition, School of Public Health, Anhui Medical University, Hefei, Anhui, People's Republic of China*
[2]*Key Laboratory of Population Health Across Life Cycle, Anhui Medical University, Ministry of Education of the People's Republic of China, Anhui, People's Republic of China*
[3]*NHC Key Laboratory of Study on Abnormal Gametes and Reproductive Tract, Anhui, People's Republic of China*
[4]*Anhui Provincial Key Laboratory of Population Health and Aristogenics, Key Laboratory of Environmental Toxicology of Anhui Higher Education Institutes, Anhui Medical University, Anhui, People's Republic of China*
[5]*Department of Gastrointestinal Surgery, the First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, People's Republic of China*

(Submitted 28 April 2021 – Final revision received 6 July 2021 – Accepted 27 July 2021 – First published online 2 August 2021)

Abstract

Inflammation is a central mechanism in metabolic disorders associated with morbidity and mortality and dietary factors can modulate inflammation. We aimed to prospectively investigate the association between an empirically developed, food-based dietary inflammatory pattern (EDIP) score and the risk of overall and cause-specific mortality, using data from the US National Health and Nutrition Examination Survey from 1999 to 2014. EDIP score was derived by entering thirty-nine predefined commonly consumed food groups into the reduced rank regression models followed by stepwise linear regression, which was most predictive of two plasma inflammation biomarkers including C-reactive protein and leucocyte count among 25 500 US adults. This score was further validated in a testing set of 9466 adults. Deaths from baseline until 31 December 2015 were identified through record linkage to the National Death Index. During a median follow-up of 7·8 years among 40 074 participants, we documented 4904 deaths. Compared with participants in the lowest quintile of EDIP score, those in the highest quintile had a higher risk of overall death (hazard ratio (HR) = 1·19, 95 % CI 1·08, 1·32, P_{trend} = 0·002), and deaths from cancer (HR = 1·41, 95 % CI 1·14, 1·74, P_{trend} = 0·017) and CVD (HR = 1·22, 95 % CI 0·98, 1·53, P_{trend} = 0·211). When stratified by age, the association of EDIP with overall mortality was stronger among individuals under 65 years of age ($P_{interaction}$ = 0·001). Diets with a higher inflammatory potential were associated with increased risk of overall and cancer-specific mortality. Interventions to reduce the adverse effect of pro-inflammatory diets may potentially promote health and longevity.

Key words: **Diet: Inflammation: Cohort study: Mortality: Cancer prevention**

Chronic inflammation has been demonstrated as a central mechanism in metabolic disorders associated with morbidity and mortality[1–4]. Circulating concentrations of multiple inflammation biomarkers, such as C-reactive protein (CRP), IL-6 and TNF-α receptor 2, have been prospectively associated with risk of mortality[5–7]. Diet is a major modifiable risk factor for chronic diseases and has been shown to modulate inflammation[8,9]. However, it remains uncertain whether the pro-inflammatory potential of habitual diet is associated with increased risk of all and cause-specific mortality.

Dietary analysis approaches that directly measure the inflammation potential of diet represent the most efficient tools for large-scale observational studies of the role of diet quality regarding its potential to influence both inflammation and health outcomes. Recently, an empirically derived dietary inflammatory pattern (EDIP) score was developed to summarise the association between dietary factors and inflammation biomarkers (CRP, IL-6 and TNF-α receptor 2) using reduced rank regression (RRR) and was further validated to have a high ability to predict inflammation biomarkers in three Harvard cohorts[10]. Previous

Abbreviations: CRP, C-reactive protein; DII, dietary inflammatory index; EDIP, empirical dietary inflammatory pattern; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein; NHANES, National Health and Nutrition Examination Survey; RRR, reduced rank regression.

* **Corresponding author:** Wanshui Yang, email wanshuiyang@gmail.com

† These authors contributed equally as co-first authors for this article.

studies including research from our group showed that the EDIP score was associated with high risk of development of several chronic diseases including CVD[11], cancers[12–14] and type 2 diabetes[15]. However, there have been no epidemiological studies regarding the association between EDIP and mortality risk, though some studies[16–26] have investigated the risk of mortality in relation to a literature-derived dietary inflammatory index (DII). DII is an *a priori* dietary pattern (i.e. its development is based on the peer-reviewed articles on the association between dietary factors and inflammation), which is mainly nutrient-based (i.e. thirty-eight of its forty-five components are nutrients)[27]. In contrast, EDIP is an *a posteriori* dietary pattern (i.e. its development is data-driven and focused on identifying a dietary pattern predictive of inflammation biomarkers), which is based exclusively on food groups to closely reflect a real-life setting. Also, the EDIP score[10] was derived based on the populations under study, which are comprised mostly of European-American health professionals.

Therefore, we (1) re-developed and validated EDIP score in a large nationally representative sample from the US National Health and Nutrition Examination Survey (NHANES) and (2) prospectively investigated the association between adherence to EDIP and risk of overall and cause-specific deaths among US adults.

Methods

Study population

This is a longitudinal study using data from the NHANES. The NHANES is a survey executed by the Centers for Disease Control and Prevention and the National Centers for Health Statistics to monitor the health of a representative sample of about 5000 persons in the USA every year and available to the public. Details on NHANES study design, study protocol and data collection methods have been described elsewhere[28]. Participants included in the study aged 18 years or older who at least completed one 24-h dietary recall during the eight cycles of NHANES from 1999 to 2014. We excluded individuals with implausible energy intake (< 2510 or > 14 644 kcal/d for women; < 3347 or > 17 573 kcal/d for men, *n* 2507) or without linked mortality data (*n* 52). A total of 40 074 participants (20 984 women and 19 090 men) were included in the final analysis.

Assessments of diet, inflammatory markers and empirical dietary inflammatory pattern score

In NHANES, diet was assessed using 24-h recalls by a trained interviewer, with the use of a computer-assisted dietary interview system (i.e. the Multiple-Pass Method)[29]. From 1999 to 2002, only a single dietary recall was performed in-person in the NHANES Mobile Examination Center. Since 2003, participants had two 24-h dietary interviews, with the second one being conducted by telephone 3–10 d after the first recall in the Mobile Examination Center, to obtain a more complete picture of the usual dietary habits. Considering the dietary interview-specific non-response and day of the week for dietary recalls, a multistage, unequal probability of selection design (i.e. dietary sampling weights) was applied. Details on other quality control on dietary interview were described elsewhere[29,30].

CRP, high-sensitivity CRP (hs-CRP) and leucocyte count were available in most cycles of NHANES survey, and all have been considered as reliable biomarkers of chronic inflammation in large-scale epidemiological studies[10,31,32]. Besides, the leucocyte count was shown to be significantly positively associated with DII score in the NHANES[33]. Therefore, we used these markers for the development of EDIP in the present study. Other biomarkers including IL-1β, IL-4, IL-6, IL-10 and TNF-α receptor 2, which were used for the development of EDIP[10] and DII[27] previously, were not available in the NHANES. Laboratory methods of assessing fasting concentrations of glucose, CRP, hs-CRP and leucocyte count were reported in detail elsewhere[28,34].

To develop EDIP score, we used NHANES data from 1999 to 2010 as a training set, and data from 2015 to 2018 as a validation set. Participants were excluded if they were younger than 18 years, or had missing data on diet and inflammation biomarkers (hs-CRP or CRP, and leucocyte count), or had circulating CRP concentrations > 10 mg/l, which may have been due to infection or medication use. A total of 25 500 and 9466 participants were included in the training and validation set, respectively (online Supplementary Fig. S1). To reduce departures from the normal distribution, all inflammation biomarker levels were natural logarithm (loge) transformed.

We used RRR to derive EDIP predictive of two inflammatory biomarkers: CRP and leucocyte count, by entering thirty-nine predefined commonly consumed foods in the USA (online Supplementary Table S1), which were similar to those in Tabung's version of EDIP[10]. RRR can identify linear functions of predictors (i.e. food groups) that simultaneously explain as much response variation of inflammation biomarkers as possible. The first factor (i.e. the RRR dietary pattern) identified by RRR then underwent further data reduction by stepwise linear regression to identify the most important component food groups of the RRR dietary pattern, with the RRR dietary pattern as the dependent variable, the thirty-nine food groups as independent variables, and a significance level of $P = 0{\cdot}01$ for entry into, and retention in the model. We used regression coefficients from the final step of the regression as component weights. Higher EDIP scores (more positive) indicate more pro-inflammatory potential while lower (more negative) scores indicate anti-inflammatory potential of diets.

We also conducted several sensitivity analyses to test the robustness of the current EDIP score, and created three alternative versions of the EDIP (see online Supplementary Materials). The first alternative version was derived using 2003–2010 NHANES data, in which most participants (89·6 %) with two valid 24-h dietary recalls. In the second version, allowing for possibly different health effect of caffeinated and decaffeinated coffee, total coffee consumption was classified as caffeinated and decaffeinated coffee, and was separately entered into the model. The third version also distinguished caffeinated and decaffeinated coffee, but was developed using data from 2003–2010 NHANES with most individuals completed two 24-h dietary interviews.

British Journal of Nutrition

In the validation phase, the correlations between the derived EDIP scores and the construct validators of the EDIP (hs-CRP and leucocyte count) were calculated. We also tested the ability of the dietary indices to predict inflammatory markers in the validation set; we modelled age-adjusted and multivariable-adjusted (i.e. adjusted for age, sex, race/ethnicity, physical activity, smoking and some inflammation-related chronic diseases such as diabetes, cancer and CHD) linear regression to calculate relative concentrations of biomarkers (i.e. the relative differences in plasma concentration of hs-CRP and leucocyte count between higher index quintiles and the lowest quintile as reference).

Ascertainments of covariates

Standardised questionnaires were administrated through household interview to collect demographic and lifestyle factors, including age, sex, race/ethnicity, educational level, income, smoking and physical activity. Alcohol intake, body weight and height were obtained from participants who received physical examinations in the NHANES Mobile Examination Center. BMI was calculated as weight in kilograms divided by the square of the height in metres (kg/m^2). Family income was measured as the ratio of family income to poverty. Physical activity was calculated by summarising activities every week and was expressed in metabolic equivalent tasks-hours/week. Histories of cancer and diabetes were defined if individuals reported that they had ever been told by a health care professional that they had such diseases and/or to take prescribed medications due to the diseases. Additionally, patients with diabetes were identified if they had a fasting plasma glucose level ≥ 126 mg/dl.

Ascertainments of deaths

Deaths and causes of death were identified via record linkage to the National Death Index through 31 December 2015. In this analysis, cause-specific mortality was defined using the 10th revision of the International Classification of Diseases (ICD-10). Deaths from major CVD include deaths from diseases of heart (ICD-10 codes I00-I09, I11, I13, I20-I51) and cerebrovascular diseases (I60–169). Death from cancer was defined as code C00-97.

Ethics approval

The National Centers for Health Statistics approved the NHANES study protocol, and the written informed consent was obtained from all participants. The Institutional Review Board at Anhui Medical University determined that this analysis used public dataset, so human subjects' approval was waived.

Statistical analysis

Person-years were calculated from the date of interview to the date of death or the end of the follow-up (31 December 2015), whichever came first. We used the multivariable Cox proportional hazards regression model to estimate the hazard ratios (HR) and 95 % CI of deaths associated with EDIP score. The model was stratified simultaneously by age and year of survey, enabling the finest possible control of confounding for age and secular trends. Model 1 was adjusted for age (years), year of survey, sex and total energy intake. Model 2 was further adjusted for race/ethnicity, education, marital status, ratio of family income to poverty, physical activity and smoking. Selection of these variables for adjustment was based on observed baseline incomparability (see table for distribution of the baseline characteristics) and the previously established risk factors for the outcomes (overall, cancer and CVD mortality). We additionally adjusted for BMI and diabetes in model 3, considering that diabetes and BMI might be possible intermediates in the association between inflammatory potential of diet and death risk. A missing value indicator was created for each covariate in the models. We presented HR by quintile categories and per 1-SD increase of EDIP, and linear trend test was conducted by assigning medians to each quintile as continuous variable in the models. The dose–response relationship of EDIP with mortality risk was assessed using restricted cubic spline regression.

Subgroup analysis and the potential for effect modification were tested for the associations between EDIP score and death risk by age, sex, race/ethnicity, education level, ratio of family income to poverty, smoking status, physical activity, BMI, diabetes and marital status. We used Wald test to examine whether the cross-product terms between these variables and exposures were statistically significant.

In the secondary analysis, accounting for the influence of potential bias from reverse causality, we conducted a sensitivity analysis by excluding participants with follow-up time less than 3 years. We also repeated analyses within participants who are free of CVD and cancer at baseline. Besides, we performed a sensitivity analysis within participants who had two 24-h dietary interviews, considering that a single 24-h recall may not reflect usual diet. To reduce measurement errors, we also repeated analysis utilising EDIP score adjusted for total energy intake using residual model[35]. Because of many tests being conducted, we used the Bonferroni correction to define the statistical significance as $P < 0{\cdot}0025$ (0·05/20 subgroups) for subgroup analysis to account for multiple comparisons. All statistical tests were two-sided and performed using SAS version 9.4 (SAS Institute Inc).

Results

Development of empirical dietary inflammatory pattern score

The flow chart of how we developed and validated the EDIP score was shown in online Supplementary Fig. S1. A total of twenty-five food intake components were included in EDIP, including eight pro-inflammatory (i.e. regular carbonated drinks, low energy carbonated drinks, high fat dairy, low fat dairy, tea, coffee, margarine and eggs) and seventeen anti-inflammatory foods (i.e. poultry, dark meat fish, dark-yellow vegetables, leafy-green vegetables, wine, snacks, fruits, pizza, nuts, sweets desserts, whole grains, refined grains, oil and vinegar salad dressing, condiments, other vegetables, regular fruit drinks and beer). In sensitivity analysis, three alternative versions of EDIP were developed, their component food groups were similar to those in the current version (online Supplementary Table S2). In the validation set, the EDIP score and its three alternative

British Journal of Nutrition

versions showed a significant weak correlation with the concentrations of hs-CRP and leucocyte count, with the same spearman correlation coefficients of 0·13 for hs-CRP and 0·14 for leucocyte count (online Supplementary Table S3). In both age- and multivariable-adjusted models, the EDIP was significantly associated with concentrations of the two biomarkers (hs-CRP and leucocyte count), with a statistically significant linear trend for each biomarker across quintiles of the EDIP (all $P_{trend} < 0·001$), indicating that the current EDIP has a high ability to predict dietary inflammatory potential (Table 1).

Baseline characteristics of participants

After a median follow-up of 7·8 years among 40 074 participants who aged 18–85 years (mean age, 47·3 years; (SD 19·4) years), a total of 4904 deaths including 1029 CVD-specific deaths and 1068 cancer-specific deaths were identified. EDIP scores ranged from a median of −0·23 (interquartile range: −0·32 to −0·18) in lowest quintile to 0·19 (interquartile range: 0·15–0·26) in the highest quintile. Compared to participants with lower EDIP scores, those in the highest quintile were less educated, tended to be widowed or divorced or separated, had lower ratio of family income to poverty, were less active, had higher BMI and were more likely to be current smokers and have a history of diabetes (Table 2).

Association between empirical dietary inflammatory pattern and risk of mortality

After adjusting for potential confounders, participants with higher EDIP scores had an increased risk of total mortality (the highest *v.* lowest quintile of EDIP scores: HR = 1·19, 95 % CI 1·08–1·32, $P_{trend} = 0·002$) and cancer-specific mortality (HR = 1·41, 95 % CI 1·14, 1·74, $P_{trend} = 0·017$, Table 3). We found a positive association between adherence to EDIP and CVD-specific mortality with borderline significance (HR per 1-SD increase = 1·06, 95 % CI 0·99, 1·14, P_{trend} across quintiles of EDIP score = 0·211).

In the secondary analysis, these positive associations were not essentially changed after exclusion of participants with follow-up years less than 3 (*n* 6176, 15·4 %), or after exclusion of individuals who were suffering from CVD or cancer at baseline (*n* 6716, 16·8 %), or after exclusion of participants with a single 24-h dietary recall (*n* 12 494, 31·2 %). Likewise, the results were similar to those in the main analysis when we used energy-adjusted EDIP score in the Cox regression models (online Supplementary Table S4). Restricted multivariable cubic spline analyses showed significantly linear associations between EDIP score and overall, cancer and CVD mortality (all *P* for linearity < 0·01, Fig. 1).

In subgroup analysis, the association between EDIP score and risk of all-cause mortality appeared stronger in individuals under 65 years of age (HR per 1-SD increase = 1·11, 95 % CI 1·04, 1·18), compared with those who aged 65 years or older (HR per 1-SD increase = 1·02, 95 % CI 0·98, 1·07, $P_{interaction} = 0·001$, Fig. 2). In contrast, we found no differential associations of the overall mortality with a 1-SD increment of EDIP score across population subsets by sex, race/ethnicity, education level, ratio of family income to poverty, smoking

Table 1. Adjusted relative concentrations of plasma inflammatory markers across quintiles of the EDIP score in the validation set in the NHANES*
(95 % confidence intervals)

	Quintile 1	Quintile 2		Quintile 3		Quintile 4		Quintile 5		
	Relative concentrations	Relative concentrations	95 % CI	Relative concentrations	95 % CI	Relative concentrations	95 % CI	Relative concentrations	95 % CI	P_{trend}†
Hs-CRP										
Age-adjusted	1 (Reference)	1·16	1·07, 1·25	1·35	1·25, 1·47	1·44	1·33, 1·56	1·49	1·37, 1·61	< 0·001
Multivariable-adjusted‡	1 (Reference)	1·10	1·02, 1·19	1·27	1·17, 1·37	1·33	1·23, 1·44	1·41	1·30, 1·53	< 0·001
Leucocyte count										
Age-adjusted	1 (Reference)	1·05	1·03, 1·07	1·05	1·03, 1·07	1·09	1·07, 1·11	1·13	1·11, 1·15	< 0·001
Multivariable-adjusted‡	1 (Reference)	1·04	1·02, 1·06	1·04	1·02, 1·06	1·08	1·06, 1·10	1·11	1·08, 1·13	< 0·001

EDIP, empirical dietary inflammatory pattern; hs-CRP, high-sensitivity C-reactive protein; NHANES, National Health and Nutrition Examination Survey.
* Values were relative concentrations (95 % CI) of biomarkers (i.e. the relative differences in plasma concentration of hs-CRP and leucocyte count between higher index quintiles and the lowest quintile as reference). Values were back-transformed (e^x) because all inflammation biomarker levels were natural logarithm (loge) transformed before analyses.
† Linear trend test was conducted by assigning medians to each quintile as continuous variable in the models.
‡ Model was adjusted for age (18–45, 46–65 and ≥ 66 years), sex (male, female), race/ethnicity (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black or other race), physical activity (< 8·3, 8·3–16·7 or > 16·7 METS-h/week), smoking (never smokers, former smokers or current smokers), diabetes (no, yes), cancer (no, yes) and CHD (no, yes).

Table 2. Age-adjusted characteristics of participants according to EDIP scores in NHANES (1999–2014)* (Mean values and standard deviations)

	EDIP score				
	Quintile 1 (*n* 8014)	Quintile 2 (*n* 8015)	Quintile 3 (*n* 8015)	Quintile 4 (*n* 8015)	Quintile 5 (*n* 8015)
EDIP score					
Median	–0·23	–0·08	0·01	0·08	0·19
IQR	–0·32– –0·18	–0·10– –0·05	–0·01–0·03	0·06–0·10	0·15–0·26
Age, years					
Mean	45·7	46·7	47·9	48·9	47·5
SD	18·6	19·6	20·0	20·0	18·7
BMI, kg/m^2					
Mean	27·6	28·4	28·6	29·2	29·1
SD	6·1	6·7	6·7	6·9	6·9
Total energy, kcal/d					
Mean	2413	2034	1862	1785	1944
SD	724	681	666	683	729
Female, %	44·3	53·3	57·2	57·2	49·9
Diabetes, %	9·3	10·9	13·0	14·1	13·9
Race/ethnicity, %					
Mexican American	13·6	17·2	20·6	23·3	20·6
Other Hispanic	6·6	8·0	8·5	8·0	5·2
Non-Hispanic white	44·4	41·8	41·1	44·7	58·8
Non-Hispanic black	25·4	24·8	22·9	19·3	11·7
Other race	10·1	8·3	6·8	4·7	3·7
Education, %					
≤ 12th grade	19·8	25·6	30·2	33·3	35·5
High school graduate/GED or equivalent	19·5	22·8	24·2	25·8	27·5
More than high school	60·7	51·5	45·4	40·8	36·9
Marital status, %					
Married	57·3	55·4	55·8	55·7	56·4
Widowed/divorced/separated	17·9	19·5	20·6	21·5	22·6
Never married	21·0	20·9	19·6	19·1	17·5
Ratio of family income to poverty					
< 1·30	22·8	25·9	29·6	32·8	34·7
1·30–3·49	31·4	34·8	35·6	35·0	35·4
≥ 3·50	38·6	30·9	26·2	24·0	22·6
Physical activity, METS-h/week					
< 8·3	32·9	38·3	41·9	44·1	45·5
8·3–16·7	12·3	12·9	11·9	12·2	12·1
> 16·7	54·5	48·4	45·8	43·2	41·9
Smoking, %					
Never smokers	54·5	55·4	53·3	50·1	38·1
Former smokers	25·6	23·3	22·4	22·8	23·7
Current smokers	13·6	14·5	17·2	20·1	31·6

EDIP, empirical dietary inflammatory pattern; GED, general educational development; IQR, interquartile range; METS, metabolic equivalent tasks; NHANES, National Health and Nutrition Examination Survey.
* Values were means (SD) or percentages and were standardised to the age distribution of the study population except for age and EDIP score. Of note, the summing proportions for some categories is not 100 % due to missing values or rounding.

status, physical activity, BMI, marital status and diabetes (all *P* values for interaction were greater than Bonferroni-adjusted *P* value of 0·0025).

Discussion

This is the first study to investigate the association between EDIP and mortality risk in a large, nationally representative prospective cohort. We found that persons who consumed a more pro-inflammatory diet, as reflected in higher EDIP score, had increased risk of overall and cancer mortality. These positive associations remained in sensitivity analysis and in the analysis with further adjustments for diabetes and BMI. In addition, the association between EDIP and mortality appeared stronger among individuals under 65 years of age.

Diets are complex combinations of nutrients and other compounds that act synergistically within individual foods and across food combinations[36]; thus, assessing the association of dietary pattern with health outcomes may capture dietary effects on health more completely. DII is a dietary pattern to measure the inflammatory potential of overall diet based on forty-five dietary factors that have been shown to influence levels of six inflammation markers: IL-1, IL-4, IL-6, IL-10, TNF and CRP. These forty-five dietary factors focused mainly on nutrients (e.g. *β*-carotene, caffeine, dietary fibre, iron, *trans* fat, cholesterol) and were determined from a literature review of 1943 peer-reviewed articles published up to 2010[27]. DII score has

https://doi.org/10.1017/S0007114521002907 Published online by Cambridge University Press
British Journal of Nutrition

Table 3. All-cause and cause-specific mortality by quintiles of EDIP score in NHANES (1999–2014) (Hazard ratios and 95 % confidence intervals)

	Quintile 1	Quintile 2		Quintile 3		Quintile 4		Quintile 5		Per 1-SD		
		HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI	P_{trend}*
All-cause mortality												
No. of deaths/person-years	650/62 415	845/62 027		1022/63 184		1148/66 029		1239/72 249				
Model 1†	1 (Reference)	1·17	1·06, 1·30	1·34	1·21, 1·48	1·32	1·19, 1·46	1·49	1·35, 1·64	1·15	1·11, 1·19	< 0·001
Model 2‡	1 (Reference)	1·13	1·02, 1·25	1·22	1·10, 1·35	1·17	1·06, 1·29	1·20	1·09, 1·33	1·06	1·02, 1·09	< 0·001
Model 3§	1 (Reference)	1·14	1·03, 1·27	1·21	1·09, 1·34	1·15	1·04, 1·27	1·19	1·08, 1·32	1·05	1·02, 1·08	0·002
Cancer-specific mortality												
No. of deaths/person-years	146/62 415	209/62 027		201/63 184		218/66 029		294/72 249				
Model 1†	1 (Reference)	1·37	1·11, 1·70	1·25	1·01, 1·56	1·22	0·98, 1·51	1·64	1·34, 2·01	1·15	1·07, 1·22	< 0·001
Model 2‡	1 (Reference)	1·35	1·09, 1·67	1·18	0·95, 1·47	1·12	0·90, 1·40	1·40	1·13, 1·73	1·07	1·01, 1·15	0·019
Model 3§	1 (Reference)	1·35	1·09, 1·68	1·22	0·95, 1·48	1·13	0·90, 1·40	1·41	1·14, 1·74	1·08	1·01, 1·15	0·017
CVD-specific mortality												
No. of deaths/person-years	125/62 415	184/62 027		212/63 184		244/66 029		264/72 249				
Model 1†	1 (Reference)	1·27	1·01, 1·60	1·37	1·09, 1·71	1·36	1·09, 1·70	1·54	1·24, 1·92	1·17	1·09, 1·26	< 0·001
Model 2‡	1 (Reference)	1·22	0·97, 1·54	1·26	1·00, 1·58	1·21	0·96, 1·51	1·25	1·00, 1·56	1·08	1·00, 1·15	0·111
Model 3§	1 (Reference)	1·24	0·99, 1·57	1·23	0·98, 1·55	1·17	0·93, 1·47	1·22	0·98, 1·53	1·06	0·99, 1·14	0·211

EDIP, empirical dietary inflammatory pattern; HR, hazard ratio; METS, metabolic equivalent tasks; NHANES, National Health and Nutrition Examination Survey.

* Linear trend test was conducted by assigning medians to each quintile as continuous variable in the models.

† Model 1 was stratified for age (18–45, 46–65 and ≥ 66 years) and year of survey (assigned values from 1 to 8) with further adjustment for sex (male, female) and total energy intake (kcal/d, tertile).

‡ Model 2 was stratified for age (18–45, 46–65 and ≥ 66 years) and year of survey (assigned values from 1 to 8) and had the same adjustments as model 1 plus race/ethnicity (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black or other race), education (≤ 12th grade, high school graduate/GED or equivalent, or more than high school), marital status (married, widowed/divorced/separated or never married), ratio of family income to poverty (< 1·30, 1·30–3·49 or ≥ 3·50), physical activity (< 8·3, 8·3–16·7 or > 16·7 METS-h/week) and smoking (never smokers, former smokers or current smokers).

§ Model 3 was stratified for age (18–45, 46–65 and ≥ 66 years) and year of survey (assigned values from 1 to 8) and had the same adjustments as model 2 plus BMI (calculated as weight in kg divided by height in m^2) (< 18·5, 18·5–24·9, 25·0–29·, and ≥ 30·0) and diabetes (no, yes).

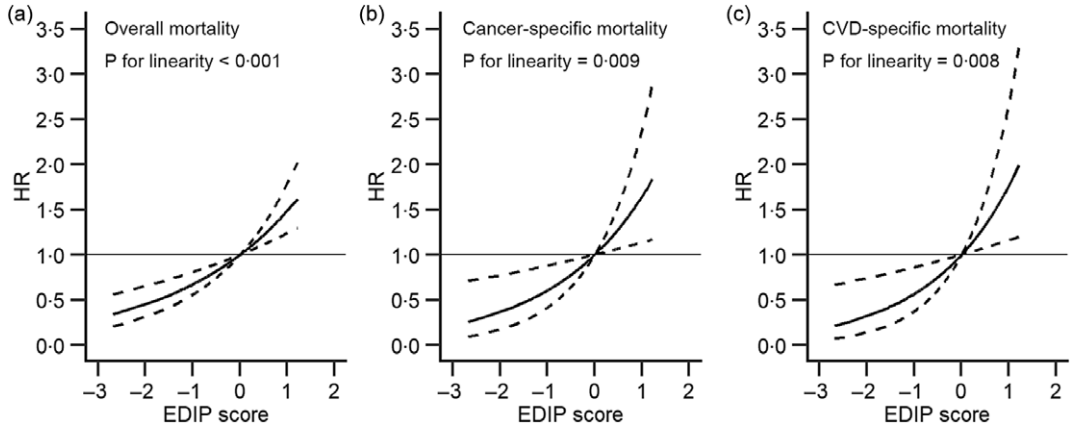

Fig. 1. Association between empirical dietary inflammatory pattern score and overall mortality (a), cancer-specific (b) and major CVD-specific (c) mortality in NHANES (1999–2014)*. EDIP, empirical dietary inflammatory pattern; HR, hazard ratio. *Models were adjusted for age, sex, race/ethnicity, education, marital status, ratio of family income to poverty, physical activity, smoking status, BMI, diabetes and total energy. Reference levels were set to the median EDIP value (0·008). Reference levels were set to the median EDIP value. Solid lines indicate HR, and dashed lines depict 95 % CI.

Subgroup	No. of Deaths	Person-years	HR (95%CI)	P for Interaction
Age, y				0·001
≤ 65	1,266	208,946	1·11(1·04-1·18)	
>65	2,615	50,005	1·02(0·98-1·07)	
Sex				0·939
Male	2,205	120,560	1·05(1·00-1·11)	
Female	1,676	138,391	1·04(0·98-1·10)	
Race/ethnicity				0·962
Non-Hispanic white	2,344	127,941	1·06(1·01-1·11)	
Other	1,537	131,011	1·04(0·99-1·11)	
Educational level				0·025
High school or below	2,577	131,523	1·02(0·98-1·07)	
More than high school	1,304	127,429	1·10(1·03-1·17)	
Family income to poverty ratio				0·252
<2·5	2,540	136,308	1·05(1·01-1·10)	
≥ 2·5	1,341	122,644	1·05(0·98-1·11)	
Smoking status				0·964
Never smokers	1,573	139,383	1·02(0·96-1·08)	
Ever smokers	2,308	119,568	1·07(1·03-1·13)	
Physical activity				0·138
Light physical activity	2,301	104,253	1·03(0·98-1·08)	
Moderate to vigorous physical activity	1,580	154,699	1·07(1·01-1·13)	
BMI				0·049
<30	2,690	169,066	1·04(0·99-1·09)	
≥ 30	1,191	89,886	1·08(1·01-1·15)	
Marital status				0·532
Married	2,054	163,655	1·06(1·01-1·12)	
Other	1,827	95,297	1·04(0·98-1·09)	
Diabetes				0·577
No	2,855	229,556	1·05(1·01-1·09)	
Yes	1,026	29,396	1·05(0·98-1·13)	

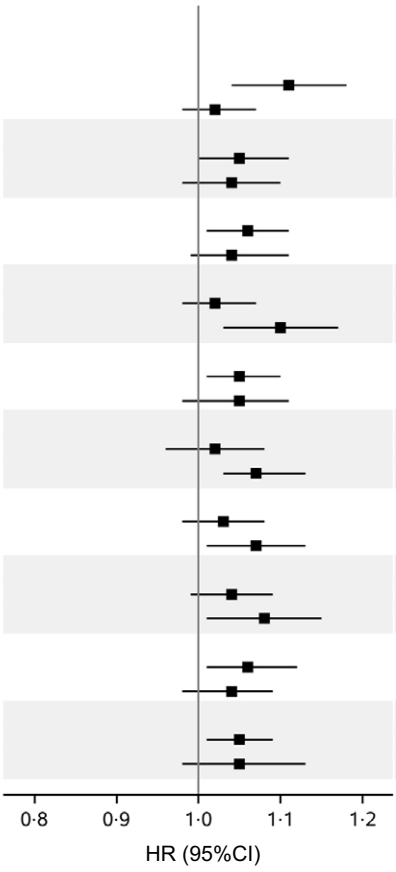

Fig. 2. Association between EDIP score (per 1 SD increase) and overall mortality according to subgroups in NHANES (1999–2014)*. EDIP, empirical dietary inflammatory pattern; HR, hazard ratio; METS, metabolic equivalent tasks; NHANES, National Health and Nutrition Examination Survey. *Covariates adjusted in the models were the same as those in model 3 in Table 3 (see Table 3 footnote). Of note, variables examined in this figure were not adjusted. Light physical activity was defined as participants with physical activity less than 8·3 METS-h per week, and moderate to vigorous activity was defined as participants who had physical activity of 8·3 METS-h per week or more. We excluded participants with any missing values in covariates.

been validated to significantly predict inflammation markers in several populations[37–39]. In line with the current observations, previous DII studies[16–26] consistently showed that higher inflammatory potential of diets was associated with elevated risk of overall and some cause-specific mortality. Nonetheless, findings from DII studies on health outcomes are difficult to be

translated readily into public health interventions, given that DII comprises mainly of nutrients.

In contrast, EDIP is empirically derived based exclusively on food groups. In the current study, we re-derived the EDIP score using data from NHANES. Although the current version and the version of EDIP by Tabung *et al.*[10] shared nine food intake components such as leafy green vegetables, snacks and pizza, most components differed. Of note, coffee and tea intakes were positively related to concentrations of the inflammation markers in our analysis, which was partly consistent with the findings from other studies[40–42], but showed an inverse association in Tabung's version. When entering caffeinated and decaffeinated coffee separately into the RRR model or excluding participants who had only a 24-h dietary recall, tea and coffee remained in the alternative versions of EDIP and showed a significantly positive correlation with both hs-CRP and leucocyte count.

Similarly, intakes of both whole and refined grains were inversely associated with levels of inflammation markers in our study, whereas an opposite association for refined grains was observed in Tabung's version. Allowing for a moderate correlation between whole and refined grains, we also entered the residuals of both grains that mutually adjusted for each other into the RRR model, while these two components remained in the alternative version of EDIP and both showed an inverse association with inflammatory biomarkers. The aforementioned discrepancies could be partly due to different methods of diet measurement (i.e. FFQ in three Harvard cohorts *v.* 24-h recall in NHANES), study populations (i.e. participants from matched case–-control studies within three Harvard cohorts of US health professionals, which consist largely of well-educated non-Hispanic whites *v.* participants from a nationally representative sample of US adults in NHANES) and inflammatory markers used (i.e. CRP, IL-6 and TNFαR2 in three Harvard cohorts *v.* CRP and leucocyte count in NHANES) in the studies. However, both versions can assess the dietary inflammatory potential and showed high ability to predict inflammatory markers in their study populations (Table 1).

We observed a significant interaction between age and EDIP on the risk of all-cause mortality, with a stronger association between EDIP and mortality among younger participants (i.e. under 65 years). This finding was in line with previous epidemiological studies showing a stronger positive association of EDIP with the risk of developing type 2 diabetes[15] and prostate cancer[43] among younger US adults. However, the reasons for these significant interactions remain unclear. A possible explanation is that younger persons generally have higher levels of insulin-like growth factor-1[44,45], a surrogate measure of growth hormone/insulin-like growth factor-1 system activity. Experimental studies[46,47] showed that diminishing growth hormone and/or insulin-like growth factor-1 secretion or signalling extends lifespan and healthspan, which was confirmed in some but not all epidemiological studies[48–50]. Inflammation is closely related to hyperinsulinaemia, and the possible role of inflammation on the insulin-like growth factor axis through hyperinsulinaemia and insulin resistance[51] may therefore contribute to the association between EDIP and mortality among younger adults in our study. Alternatively, the results might be due to chance. Future studies are warranted to confirm these findings and clarify the underlying mechanisms.

The strengths of the current study include use of a nationally representative sample of US adults, prospective cohort design and data collection utilising validated measures. However, our study has several limitations. First, self-reported diet and other lifestyle factors from questionnaires have measurement errors, although we used several methods[29,30,35] to reduce measurement error and improve estimates of usual intake. Second, 24-h recalls may lead to misreporting of dietary data and could not reflect long-term dietary habits. For example, participants with higher BMI tended to underreport their energy intake[52], while high BMI was associated with higher EDIP score, which may lead to misclassification of EDIP score and some covariates such as energy intake. This misclassification bias in cohort study could be non-differential in most situations and is likely to lead to the underestimation of the observed association if exposure data are binary[53]. While in the present study, the misclassification can lead to bias in either direction even the misclassification is non-differential, given the continuous or polytomous exposure data in the current analysis. Third, dietary information was collected based on a single measurement at baseline, and participants may change their dietary habits during the follow-up. Fourth, we had only a single measure of inflammation biomarkers, which may underestimate validity of EDIP score assessed by correlation coefficients with the inflammation biomarkers in the validation set[54].

In conclusion, our findings add to previous studies suggesting that diets with a higher inflammatory potential were associated with increased risk of mortality, particularly among the individuals with age less than 65 years old. Inflammation may partly mediate the association of diet with death risk, and dietary interventions to reduce the adverse role of an inflammatory dietary pattern may therefore promote health and longevity.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (82073651), Anhui Provincial Natural Science Foundation (2008085MH262) and grant of the Scientific Research of BSKY from Anhui Medical University (XJ201935).

Drs X. L. and Z. Z. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: W. Y., X. L. Acquisition, analysis or interpretation of data: all authors. Drafting of the manuscript: X. L., W. Y. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: X. L., W. Y. Obtained funding: W. Y. Administrative, technical or material support: B. C., Z. Z., W. Y. Study supervision: W. Y.

There are no conflicts of interest.

Supplementary material

For supplementary materials referred to in this article, please visit https://doi.org/10.1017/S0007114521002907

References

1. Hotamisligil GS (2006) Inflammation and metabolic disorders. *Nature* **444**, 860–867.
2. Krintus M, Kozinski M, Kubica J, *et al.* (2014) Critical appraisal of inflammatory markers in cardiovascular risk stratification. *Crit Rev Clin Lab Sci* **51**, 263–279.
3. Guina T, Biasi F, Calfapietra S, *et al.* (2015) Inflammatory and redox reactions in colorectal carcinogenesis. *Ann NY Acad Sci* **1340**, 95–103.
4. Donath MY & Shoelson SE (2011) Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol* **11**, 98–107.
5. Dibaba DT, Judd SE, Gilchrist SC, *et al.* (2019) Association between obesity and biomarkers of inflammation and metabolism with cancer mortality in a prospective cohort study. *Metabolism* **94**, 69–76.
6. Kabagambe EK, Judd SE, Howard VJ, *et al.* (2011) Inflammation biomarkers and risk of all-cause mortality in the reasons for geographic and racial differences in stroke cohort. *Am J Epidemiol* **174**, 284–292.
7. Adriaensen W, Mathei C, Vaes B, *et al.* (2015) Interleukin-6 as a first-rated serum inflammatory marker to predict mortality and hospitalization in the oldest old: a regression and CART approach in the BELFRAIL study. *Exp Gerontol* **69**, 53–61.
8. Due A, Toubro S, Stender S, *et al.* (2005) The effect of diets high in protein or carbohydrate on inflammatory markers in overweight subjects. *Diabetes Obes Metab* **7**, 223–229.
9. Asgharpour A, Cazanave SC, Pacana T, *et al.* (2016) A diet-induced animal model of non-alcoholic fatty liver disease and hepatocellular cancer. *J Hepatol* **65**, 579–588.
10. Tabung FK, Smith-Warner SA, Chavarro JE, *et al.* (2016) Development and validation of an empirical dietary inflammatory index. *J Nutr* **146**, 1560–1570.
11. Li J, Lee DH, Hu J, *et al.* (2020) Dietary inflammatory potential and risk of cardiovascular disease among men and women in the U.S. *J Am Coll Cardiol* **76**, 2181–2193.
12. Tabung FK, Huang T, Giovannucci EL, *et al.* (2017) The inflammatory potential of diet and ovarian cancer risk: results from two prospective cohort studies. *Br J Cancer* **117**, 907–911.
13. Tabung FK, Liu L, Wang W, *et al.* (2018) Association of dietary inflammatory potential with colorectal cancer risk in men and women. *JAMA Oncol* **4**, 366–373.
14. Yang W, Sui J, Zhao L, *et al.* (2021) Association of inflammatory and insulinemic potential of diet and lifestyle with risk of hepatocellular carcinoma. *Cancer Epidemiol Biomarkers Prev* **30**, 789–796.
15. Lee DH, Li J, Li Y, *et al.* (2020) Dietary inflammatory and insulinemic potential and risk of type 2 diabetes: Results from three prospective US cohort studies. *Diabetes Care* **43**, 2675–2683.
16. Wesselink E, Staritsky LE, van Zutphen M, *et al.* (2021) The association between the adapted dietary inflammatory index and colorectal cancer recurrence and all-cause mortality. *Clin Nutr* **40**, 4436–4443.
17. Okada E, Shirakawa T, Shivappa N, *et al.* (2019) Dietary inflammatory index is associated with risk of all-cause and cardiovascular disease mortality but not with cancer mortality in middle-aged and older Japanese adults. *J Nutr* **149**, 1451–1459.
18. Kaluza J, Hakansson N, Harris HR, *et al.* (2019) Influence of anti-inflammatory diet and smoking on mortality and survival in men and women: two prospective cohort studies. *J Intern Med* **285**, 75–91.
19. Garcia-Arellano A, Martinez-Gonzalez MA, Ramallal R, *et al.* (2019) Dietary inflammatory index and all-cause mortality in large cohorts: the SUN and PREDIMED studies. *Clin Nutr* **38**, 1221–1231.
20. Park SY, Kang M, Wilkens LR, *et al.* (2018) The dietary inflammatory index and all-cause, cardiovascular disease, and cancer mortality in the Multiethnic Cohort Study. *Nutrients* **10**, 1844.
21. Hodge AM, Bassett JK, Dugue PA, *et al.* (2018) Dietary inflammatory index or Mediterranean diet score as risk factors for total and cardiovascular mortality. *Nutr Metab Cardiovasc Dis* **28**, 461–469.
22. Shivappa N, Steck SE, Hussey JR, *et al.* (2017) Inflammatory potential of diet and all-cause, cardiovascular, and cancer mortality in National Health and Nutrition Examination Survey III Study. *Eur J Nutr* **56**, 683–692.
23. Shivappa N, Hebert JR, Kivimaki M, *et al.* (2017) Alternative Healthy Eating Index 2010, Dietary Inflammatory Index and risk of mortality: results from the Whitehall II cohort study and meta-analysis of previous Dietary Inflammatory Index and mortality studies. *Br J Nutr* **118**, 210–221.
24. Shivappa N, Harris H, Wolk A, *et al.* (2016) Association between inflammatory potential of diet and mortality among women in the Swedish Mammography Cohort. *Eur J Nutr* **55**, 1891–1900.
25. Shivappa N, Blair CK, Prizment AE, *et al.* (2016) Association between inflammatory potential of diet and mortality in the Iowa Women's Health study. *Eur J Nutr* **55**, 1491–1502.
26. Graffouillere L, Deschasaux M, Mariotti F, *et al.* (2016) Prospective association between the Dietary Inflammatory Index and mortality: modulation by antioxidant supplementation in the SU.VI.MAX randomized controlled trial. *Am J Clin Nutr* **103**, 878–885.
27. Shivappa N, Steck SE, Hurley TG, *et al.* (2014) Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr* **17**, 1689–1696.
28. Centers for Disease Control and Prevention (2020) National Health and Nutrition Examination Survey (NHANES) NHANES Procedure Manuals. https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/manuals.aspx?BeginYear=2019 (accessed March 2021).
29. Ahluwalia N, Dwyer J, Terry A, *et al.* (2016) Update on NHANES dietary data: focus on collection, release, analytical considerations, and uses to inform public policy. *Adv Nutr* **7**, 121–134.
30. Tooze JA, Midthune D, Dodd KW, *et al.* (2006) A new statistical method for estimating the usual intake of episodically consumed foods with application to their distribution. *J Am Diet Assoc* **106**, 1575–1587.
31. Stikbakke E, Richardsen E, Knutsen T, *et al.* (2020) Inflammatory serum markers and risk and severity of prostate cancer: the PROCA-life study. *Int J Cancer* **147**, 84–92.
32. Fest J, Ruiter R, Ikram MA, *et al.* (2018) Reference values for white blood-cell-based inflammatory markers in the Rotterdam Study: a population-based prospective cohort study. *Sci Rep* **8**, 10566.
33. Wirth MD, Sevoyan M, Hofseth L, *et al.* (2018) The Dietary Inflammatory Index is associated with elevated white blood cell counts in the National Health and Nutrition Examination Survey. *Brain Behav Immun* **69**, 296–303.
34. Centers for Disease Control and Prevention (2020) National Health and Nutrition Examination Survey (NHANES) Laboratory Procedure Manual of High Sensitivity C-Reactive Protein (hs-CRP). – https://bfdogplmndidlpjfhoijckpakkdjkkil/pdf/viewer.html?file=https%3A%2F%2Fwwwn.cdc.gov%2Fnchs%2Fdata%2Fnhanes%2F2017–2018%2Flabmethods%2FHSCRP-J-MET-508.pdf (accessed March 2021).
35. Willett WC, Howe GR & Kushi LH (1997) Adjustment for total energy intake in epidemiologic studies. *Am J Clin Nutr* **65**, 1220S–1228S.

36. Tapsell LC, Neale EP, Satija A, *et al.* (2016) Foods, nutrients, and dietary patterns: interconnections and implications for dietary guidelines. *Adv Nutr* **7**, 445–454.
37. Tabung FK, Steck SE, Zhang J, *et al.* (2015) Construct validation of the dietary inflammatory index among postmenopausal women. *Ann Epidemiol* **25**, 398–405.
38. Shivappa N, Steck SE, Hurley TG, *et al.* (2014) A population-based dietary inflammatory index predicts levels of C-reactive protein in the Seasonal Variation of Blood Cholesterol Study (SEASONS). *Public Health Nutr* **17**, 1825–1833.
39. Shivappa N, Hebert JR, Rietzschel ER, *et al.* (2015) Associations between dietary inflammatory index and inflammatory markers in the Asklepios Study. *Br J Nutr* **113**, 665–671.
40. Zampelas A, Panagiotakos DB, Pitsavos C, *et al.* (2004) Associations between coffee consumption and inflammatory markers in healthy persons: the ATTICA study. *Am J Clin Nutr* **80**, 862–867.
41. Moua ED, Hu C, Day N, *et al.* (2020) Coffee consumption and C-reactive protein levels: a systematic review and meta-analysis. *Nutrients* **12**, 1349.
42. Fukino Y, Shimbo M, Aoki N, *et al.* (2005) Randomized controlled trial for an effect of green tea consumption on insulin resistance and inflammation markers. *J Nutr Sci Vitaminol* **51**, 335–342.
43. Fu BC, Tabung FK, Pernar CH, *et al.* (2021) Insulinemic and inflammatory dietary patterns and risk of prostate cancer. *Eur Urol* **79**, 405–412.
44. Goodman-Gruen D & Barrett-Connor E (1997) Epidemiology of insulin-like growth factor-I in elderly men and women: the Rancho Bernardo Study. *Am J Epidemiol* **145**, 970–976.
45. O'Connor KG, Tobin JD, Harman SM, *et al.* (1998) Serum levels of insulin-like growth factor-I are related to age and not to body composition in healthy women and men. *J Gerontol A Biol Sci Med Sci* **53**, M176–M182.
46. Holzenberger M, Dupont J, Ducos B, *et al.* (2003) IGF-1 receptor regulates lifespan and resistance to oxidative stress in mice. *Nature* **421**, 182–187.
47. Broughton SJ, Piper MD, Ikeya T, *et al.* (2005) Longer lifespan, altered metabolism, and stress resistance in Drosophila from ablation of cells making insulin-like ligands. *Proc Natl Acad Sci USA* **102**, 3105–3110.
48. Schutte AE, Conti E, Mels CM, *et al.* (2016) Attenuated IGF-1 predicts all-cause and cardiovascular mortality in a Black population: a five-year prospective study. *Eur J Prev Cardiol* **23**, 1690–1699.
49. Bourron O, Le Bouc Y, Berard L, *et al.* (2015) Impact of age-adjusted insulin-like growth factor 1 on major cardiovascular events after acute myocardial infarction: results from the fast-MI registry. *J Clin Endocrinol Metab* **100**, 1879–1886.
50. Zhang WB, Aleksic S, Gao T, *et al.* (2020) Insulin-like growth factor-1 and IGF binding proteins predict all-cause mortality and morbidity in older adults. *Cells* **9**, 1368.
51. Giovannucci E (2018) A framework to understand diet, physical activity, body weight, and cancer risk. *Cancer Causes Contr* **29**, 1–6.
52. Murakami K & Livingstone MB (2015) Prevalence and characteristics of misreporting of energy intake in US adults: NHANES 2003–2012. *Br J Nutr* **114**, 1294–1303.
53. Jurek AM, Greenland S, Maldonado G, *et al.* (2005) Proper interpretation of non-differential misclassification effects: expectations vs observations. *Int J Epidemiol* **34**, 680–687.
54. Perrier F, Giorgis-Allemand L, Slama R, *et al.* (2016) Within-subject pooling of biological samples to reduce exposure misclassification in biomarker-based studies. *Epidemiology* **27**, 378–388.

British Journal of Nutrition