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A Higher Dietary Inflammatory Index Score Is Associated With a Higher Risk of Breast Cancer Among Chinese Women: A Case–Control Study

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Dietary inflammatory index and risk of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma: a population-based case–control study

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Abstract

The dietary inflammatory index (DII™) is a novel composite score based on a range of nutrients and foods known to be associated with inflammation. DII scores have been linked to the risk of a number of cancers, including oesophageal squamous cell cancer and oesophageal adenocarcinoma (OAC). Given that OAC stems from acid reflux and that the oesophageal epithelium undergoes a metaplasia-dysplasia transition from the resulting inflammation, it is plausible that a high DII score (indicating a pro-inflammatory diet) may exacerbate risk of OAC and its precursor conditions. The aim of this analytical study was to explore the association between energy-adjusted dietary inflammatory index (E-DII™) in relation to risk of reflux oesophagitis, Barrett's oesophagus and OAC. Between 2002 and 2005, reflux oesophagitis (*n* 219), Barrett's oesophagus (*n* 220) and OAC (*n* 224) patients, and population-based controls (*n* 256), were recruited to the Factors influencing the Barrett's Adenocarcinoma Relationship study in Northern Ireland and the Republic of Ireland. E-DII scores were derived from a 101-item FFQ. Unconditional logistic regression analysis was applied to determine odds of oesophageal lesions according to E-DII intakes, adjusting for potential confounders. High E-DII scores were associated with borderline increase in odds of reflux oesophagitis (OR 1·87; 95 % CI 0·93, 3·73), and significantly increased odds of Barrett's oesophagus (OR 2·05; 95 % CI 1·22, 3·47), and OAC (OR 2·29; 95 % CI 1·32, 3·96), when comparing the highest with the lowest tertiles of E-DII scores. In conclusion, a pro-inflammatory diet may exacerbate the risk of the inflammation-metaplasia-adenocarcinoma pathway in oesophageal carcinogenesis.

Key words: Diets: Inflammation: Reflux oesophagitis: Barrett's oesophagus: Oesophageal adenocarcinoma

Oesophageal cancer is the eighth most common cancer and sixth most common cause of cancer-related death worldwide, with 456 000 new oesophageal cancer cases and 400 000 deaths in 2012[1]. Oesophageal adenocarcinoma (OAC) arises from glandular cells of the lower third of the oesophagus, whereas squamous cell carcinoma of the oesophagus originates from the epithelial cells. The incidence of OAC has risen at an alarming rate in Western populations since the early 1970s; however, rates of oesophageal squamous cell carcinoma, which were much higher relative to adenocarcinomas decades ago, have remained steady for many decades[2,3]. Barrett's oesophagus (BE), a condition of the distal oesophagus wherein the stratified squamous epithelium is replaced by columnar intestinal epithelium, is a recognised precursor of adenocarcinoma[3]. There is also growing evidence linking chronic inflammation to OAC[4,5]. Major risk factors for this cancer and its precursor conditions include cigarette smoking and obesity[6]; whereas, there is consistent evidence showing that frequent use of non-steroidal anti-inflammatory drugs lowers risk of OAC[7,8]. Several studies have been conducted exploring the association between dietary factors and OAC and BE, with strong epidemiological evidence for an inverse relationship between intake of vitamin C, β-carotene, dietary fibre, fruits and vegetables and the risk of OAC and BE[9,10].

The dietary inflammatory index (DII™) was developed to assess the inflammatory potential of an individual's diet[11]. A pro-inflammatory diet is characterised by a high consumption of foods rich in SFA and carbohydrates, and a low consumption

Abbreviations: BE, Barrett's oesophagus; DII, dietary inflammatory index; E-DII, energy-adjusted dietary inflammatory index; OAC, oesophageal adenocarcinoma; RE, reflux esophagitis.

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of foods rich in fibre, PUFA, flavonoids and other antioxidant dietary components. The DII has been validated in a variety of longitudinal and cross-sectional studies with various inflammatory markers, including C-reactive protein (CRP)[12], IL-6[13] and TNF-α[14]. The DII has been associated with risk of colorectal cancer in case–control studies in Spain and Italy[15,16]; in three cohort studies from the USA[17–19], and risk of pancreatic, prostate, hepatocellular and oesophageal squamous cell cancers in case–control studies in Italy[20–23]. Only one previous study, conducted in Sweden, has investigated the association between DII and OAC; it demonstrated 4-fold increased odds of OAC amongst those consuming the most inflammatory diets[24]. To our knowledge, no previous study has investigated the relationship between DII scores and pre-malignant conditions of the oesophagus. The aim of this investigation was to evaluate the association between DII and risk of reflux esophagitis (RE), BE and OAC in an all-Ireland population-based case–control study.

Methods

Study design

Participants of the all-Ireland Factors influencing the Barrett's Adenocarcinoma Relationship (FINBAR) study[25–27] were utilised for this analysis. The FINBAR study recruited four participant groups: (i) patients with incident, histologically confirmed, OAC (n 227), (ii) patients with long-segment BE, defined as >3 cm of non-dysplastic specialised intestinal metaplasia (n 224), (iii) patients with RE (n 230), defined as having oesophageal erosions scored as grades 2–4 on the Savary-Miller/Hetzel-Dent scale or grades B, C or D on the Los Angeles scale[28] and (iv) population-based controls (n 260) with no previous history of BE, oesophageal or other gastrointestinal cancer. Population controls, RE and BE patients were frequency matched by sex and 5-year age strata to OAC patients following recruitment of OAC patients[25–27].

Recruitment has been described in detail in previous publications[25–27]. In brief, patients with oesophageal lesions were identified from electronic pathology records in Northern Ireland and hospital clinical records in Dublin and Cork in the Republic of Ireland. Eligible control subjects were adults without a history of oesophageal or other gastrointestinal cancer or a known diagnosis of BE. Northern Ireland controls were selected at random from the General Practice Master Index (a province-wide database of all persons registered with a general practitioner). Republic of Ireland controls were selected at random from four general practices (two urban and two rural) in the Dublin and Cork areas chosen by the researchers. Study participants were recruited between March 2002 and July 2004, with the exception of RE patients, who were recruited in Northern Ireland only between 2004 and 2005. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Research Ethics Committees of Queen's University Belfast, Northern Ireland, Clinical Research Ethics Committee of Cork Teaching Hospitals and Research Ethics Committee Board of St. James's Hospital, Dublin. Written informed consent was provided by all FINBAR study participants.

Data collection

Trained interviewers collected information on demographics, lifestyle, medication and co-morbidities from study participants using a standardised electronic questionnaire. Participants were asked to self-report their weight 5 years before interview in order to calculate BMI at that time, by dividing self-reported weight (kg) by current height (m^2), as measured by the interviewer. Serum samples were taken and *Helicobacter pylori* infection status assessed using a Western blot assay, as previously described[29].

Dietary assessment and dietary inflammatory index calculation

Dietary intake was assessed using a 101-item FFQ. Participants were asked to recall their dietary habits 5 years before interview when completing the FFQ, to minimise the impact of disease on changes in dietary intakes. The FFQ was adapted for the Irish population from the European Prospective Investigation into Cancer and Nutrition study FFQ[30], by incorporating additional foods reported as commonly eaten in the Northern/Southern Ireland Food Consumption Survey[31]. Mean daily nutrient and food intakes were calculated from the FFQ using Q-Builder (Tinuviel Software).

In order to compute the DII score, dietary information for each study participant is first linked to the regionally representative database that provided a global estimate of mean intake for each of the forty-five parameters (i.e. foods, nutrients and other food components) along with its standard deviation considered in the DII definition[11]. These parameters then are used to derive the participant's exposure relative to the standard global mean as a z-score, derived by subtracting the mean of the regionally representative database from the amount reported, and dividing this value by the parameter's standard deviation. These z-scores are converted to percentiles (expressed as a proportion; i.e. with values ranging from 0 to 1) and then centring by doubling and subtracting 1. Clinical interpretation remains clear with these additional steps and inappropriate weighting is avoided and higher (i.e. more positive) DII scores invariably represent more pro-inflammatory diets. The resulting value is then multiplied by the corresponding food parameter effect score (derived from a literature review on the basis of 1943 articles[11]).

All of these food parameter-specific DII scores are then summed to create the overall DII score for every subject in the study. To control for the potential confounding effect of total energy intake, the energy-adjusted dietary inflammatory index (E-DII) was calculated per 1000 kcal (equivalent to 4180 kJ) energy content of food consumed wherein all the food parameters were divided by energy intake and multiplied by 1000 kcal (equivalent to 4180 kJ). A total of twenty-five of the forty-five possible food parameters were used for DII calculation based on the FFQ in this study and these were as follows: energy, carbohydrate, protein, fat, alcohol, fibre, cholesterol, SFA, MUFA, PUFA, niacin, thiamin, riboflavin, vitamin B_{12}, vitamin B_6, Fe, Mg, Zn, Se, vitamin A, vitamin C, vitamin D, vitamin E, folic acid and β-carotene. The missing food parameters were anthocyanidins, flavonols, flavan-3-ol, flavonones, isoflavanoids, flavones,

eugenol, caffeine, tea, garlic, ginger, onion, saffron, turmeric, pepper, thyme/oregano, rosemary, *n*-3, *n*-6 and *trans*-fat. Energy was not included as the DII is already adjusted for it. Fig. 1 describes the steps involved in DII calculation.

Statistical analysis

Participants were excluded from the analysis if they failed to complete the FFQ (*n* 22). A total of 256 controls, 219 RE, 220 BE and 224 OAC cases were available in the analytical data set. All statistical analysis was performed using Intercooled Stata® version 11.0 (StataCorp LP).

Characteristics were compared between patient groups and controls using independent *t* tests for continuous variables and χ^2 tests for categorical variables. RE analyses were restricted to Northern Ireland controls only, because these patients were recruited in Northern Ireland only. Tertiles of E-DII intakes were defined by distribution in the appropriate controls. Unconditional logistic regression analysis was applied to generate OR and corresponding 95 % CI for oesophageal lesions according to tertiles of E-DII. In order to test for trend, each individual was assigned the median intake value for the tertile into which they were classified, and this was included in the regression model as a continuous variable.

Known confounders for oesophageal lesions within this study population[25,26,29,32–35] were included in the regression models. These included log energy intake (log kJ/d (kcal/d)), age (years) and sex for model 1, and added smoking status (current/previous/never), education (years), BMI 5 years before interview (kg/m^2), occupation (manual/non-manual), alcohol intake (g/d), regular non-steroidal inflammatory drug use (weekly use for at least 6 months duration), *H. pylori* infection (seronegative/seropositive) and geographical location (Northern Ireland/Republic of Ireland) in model 2. In a third model, we further tested for regular gastro-oesophageal reflux symptoms (ever/never), because it is debatable whether reflux symptoms may confound or be on the causal pathway between oesophageal lesion risk and DII intake. To investigate this further, we also conducted stratified analysis by reported experience of gastro-oesophageal reflux symptoms. Stratified analysis by *H. pylori* infection status, BMI and smoking status also were conducted, as these confounders most significantly influenced the association between E-DII and oesophageal lesion risk in regression models.

Results

As shown in Table 1, OAC patients were more likely to be smokers, consume less alcohol and have higher energy intake, have a higher BMI, have worked in manual occupations and completed fewer years of education and were less likely to have a history of *H. pylori* infection compared with controls. Similar trends were observed for BE and RE patients compared with controls, although these differences were not always statistically significant. All three patient groups were more likely to have experienced gastro-oesophageal reflux symptoms and consume higher E-DII diets compared with controls. The range of E-DII scores was −3·08 to +4·74.

The association between E-DII scores and disease risk is shown in Table 2. Strong dose–response associations were observed for E-DII and odds of all three diseases in models adjusted for age, sex and energy intakes. When known confounders were added into the model, E-DII was no longer significantly associated with RE (OR 1·87; 95 % CI 0·93, 3·73). When comparing high *v.* low tertiles of E-DII, significantly increased odds of BE and OAC remained following further adjustment for additional confounders (OR 2·05; 95 % CI 1·22, 3·47 and OR 2·29; 95 % CI 1·32, 3·96, respectively).

In exploratory analysis with further adjustment for gastro-oesophageal reflux symptoms, the general direction of associations remained but statistical significance became attenuated, suggesting there may be an interaction between reflux symptoms, E-DII and risk of oesophageal lesions (Table 2). Stratified analysis by reflux symptoms indicated relatively consistent increased odds of RE and BE for individuals consuming a high E-DII diet regardless of symptom experience, although statistical power was limited and again statistical significance was lost (Table 3). However, a stronger positive association between high E-DII score and odds of OAC was observed for individuals who reported experiencing regular gastro-oesophageal reflux symptoms (T3 *v.* T1: OR 2·76; 95 % CI 0·99, 7·71) compared with those not reporting regular symptoms (T3 *v.* T1: OR 1·73; 95 % CI 0·87, 3·45), although the interaction test was not significant ($P = 0·34$)

In analysis stratified by *H. pylori* infection status (Table 4), we observed stronger positive associations between high E-DII intakes and odds of RE, BE, but not OAC, in *H. pylori* positive individuals compared with *H. pylori* negative individuals. However, formal tests for statistical interaction were not significant.

No clear patterns emerged in stratified analysis of E-DII and oesophageal lesion risk by smoking status or BMI (online Supplementary Tables S1 and S2). Again, statistical tests for interaction between E-DII and smoking or BMI in relation to disease risk were not significant.

Discussion

In this all-Ireland population-based study, a pro-inflammatory diet, as evidenced by high E-DII scores, was associated with increased odds of RE, BE and OAC, with statistically significant associations being observed for the latter two conditions. These results are in line with the only previous study to explore DII and OAC, where increasing inflammatory potential of diet was also associated with increased odds of OAC (OR Quartile 4 *v.* 1: 3·59; 95 % CI 1·87, 6·89)[24]. To our knowledge, this is the first study to have examined the association between DII and BE and RE.

Previously, results from this case–control study have demonstrated that folate intake was associated with reduced risk of OAC whereas vitamin B_6 intake was associated with reduced risk of OAC, BE and RE and vitamin B_{12} was associated with increased risk of OAC[36] and dietary Mg intakes were inversely associated with RE and BE[37]. In the context of the DII; folate, vitamins B_6, and Mg have anti-inflammatory effect scores whereas vitamin B_{12} has a pro-inflammatory effect score[11], therefore our results are biologically plausible and consistent with previous findings.

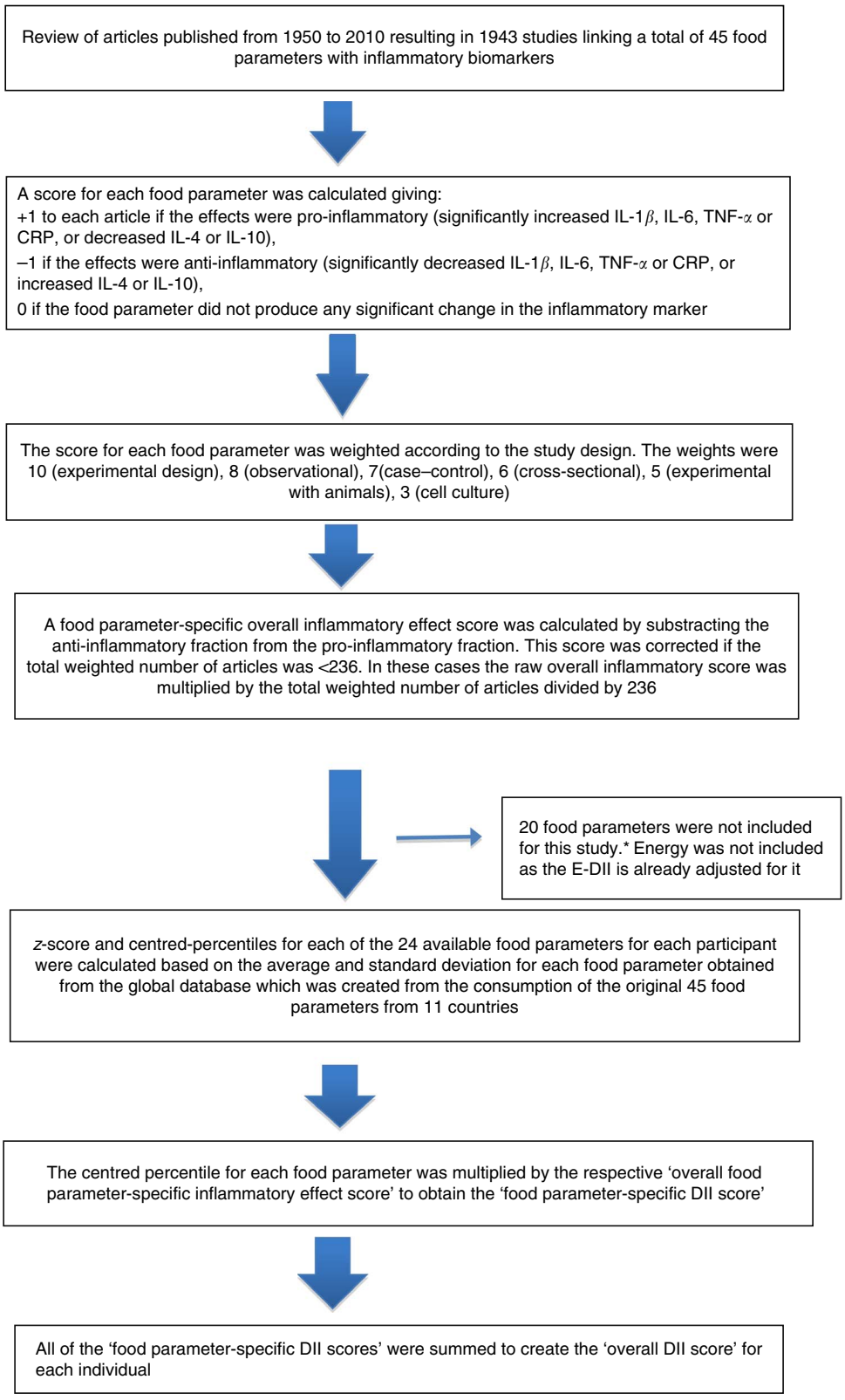

Fig. 1. Sequence of steps in creating the dietary inflammatory index in the Factors influencing the Barrett's Adenocarcinoma Relationship study. CRP, C-reactive protein; E-DII, energy-adjusted dietary inflammatory index; DII, dietary inflammatory index. *Missing food items were anthocyanidins, flavonols, flavan3ol, flavonones, isoflavanoids, flavones, eugenol, caffeine, tea, garlic, ginger, onion, saffron, turmeric, pepper, thyme/oregano, rosemary, *n*-3, *n*-6 and *trans*-fat.

Table 1. Characteristics of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma cases and controls, Factors influencing the Barrett's Adenocarcinoma Relationship study (Numbers and percentages; mean values and standard deviations)

	Northern Ireland controls (*n* 119)		Reflux oesophagitis (*n* 219)			All controls (*n* 256)		Barrett's oesophagus (*n* 220)			Oesophageal adenocarcinoma (*n* 224)		
Characteristics	*n*	%	*n*	%	*P**	*n*	%	*n*	%	*P*†	*n*	%	*P*†
Age (years)	68·1	10·3	61·9	11·5	<0·001	63·0	12·9	62·3	12·0	0·50	64·3	11·2	0·25
Males	83	69·8	183	83·6	0·003	216	84·4	181	82·3	0·54	189	84·4	1·00
Location													
Northern Ireland	119	100	219	100	–	119	46·5	150	68·2	<0·001	114	50·9	0·34
Republic of Ireland	0	0	0	0		137	53·5	70	31·8		110	49·1	
Smoking status													
Never	51	43·6	106	49·5	0·27	100	40·2	87	39·7	0·33	45	20·6	<0·001
Previous	44	37·6	62	29·0		105	42·2	82	37·4		98	44·8	
Current	22	18·8	46	21·5		44	17·7	50	22·8		76	34·7	
Occupation type													
Manual	54	47·0	106	49·5	0·66	123	49·4	127	58·5	0·05	131	60·1	0·02
Non-manual	61	53·0	108	50·5		126	50·6	90	41·5		87	39·9	
Regular GOR symptoms‡	28	23·5	87	39·7	0·003	49	19·2	159	72·3	<0·001	108	48·2	<0·001
Regular NSAID use§	15	12·8	38	17·4	0·27	31	12·2	29	13·2	0·75	23	10·3	0·52
Helicobacter·pylori positive	76	65·0	92	42·4	<0·001	145	58·5	106	50·5	0·09	102	49·0	0·04
	Mean	SD	Mean	SD		Mean	SD	Mean	SD		Mean	SD	
Education (years)	11·1	2·6	10·7	2·1	0·15	12·0	3·2	11·3	2·9	0·02	10·7	2·6	<0·001
BMI 5 years before interview (kg/m^2)	27·2	4·1	27·7	4·5	0·25	27·1	3·9	26·9	4·0	0·74	28·6	4·9	0·001
Alcohol intake (g/d)	13·2	0·7	16·3	20·8	0·20	19·2	23·1	16·5	23·9	0·21	14·1	20·6	0·01
Energy (kJ/d)	10 828	3736	11 263	3125		10 777	3393	11 385	3222		11 531	3402	0·02
Energy (kcal/d)	2588	893	2692	747	0·26	2576	811	2721	770	0·05	2756	813	
E-DII (DII/4184 kJ/d (1000 kcal/d))	0·8	1·7	1·6	1·5	<0·001	1·1	1·6	1·6	1·6	<0·001	1·7	1·7	<0·001

GOR, gastro-oesophageal reflux; NSAID, non-steroidal anti-inflammatory drug; E-DII, energy-adjusted dietary inflammatory index; DII, dietary inflammatory index.
* Cases compared with Northern Ireland controls only, calculated using the *t* test (continuous variables) or χ^2 test (categorical variables).
† Cases compared with all controls, calculated using the *t* test (continuous variables) or χ^2 test (categorical variables).
‡ Heartburn/acid reflux symptoms experienced at least once weekly or >50 times/year >5years before interview date.
§ Ever use defined as use at least once weekly for ≥6 months duration.

Table 2. Dietary inflammatory index density and risk of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma, Factors influencing the Barrett's Adenocarcinoma Relationship study
(Odds ratios and 95 % confidence intervals)

			Model 1*		Model 2†		Model 3‡	
	Controls (*n*)	Cases (*n*)	OR	95 % CI	OR	95 % CI	OR	95 % CI
Reflux oesophagitis§	119	219						
E-DII								
<−0·12	39	34	1·00		1·00		1·00	
−0·12–<1·91	40	82	1·74	0·93, 3·27	1·43	0·72, 2·84	1·41	0·71, 2·82
≥1·91	40	103	2·14	1·15, 3·98	1·87	0·93, 3·73	1·82	0·90, 3·67
$P_{for\ trend}$				0·02		0·08		0·09
Barrett's oesophagus	256	220						
E-DII								
<0·34	85	45	1·00		1·00		1·00	
0·34–<1·98	86	76	1·71	1·06, 2·77	1·75	1·04, 2·95	1·60	0·87, 2·93
≥1·98	85	99	2·30	1·43, 3·71	2·05	1·22, 3·47	1·75	0·95, 3·20
$P_{for\ trend}$				0·001		0·008		0·08
Oesophageal adenocarcinoma	256	224						
E-DII								
<0·34	85	45	1·00		1·00		1·00	
0·34–<1·98	86	71	1·67	1·03, 2·73	1·61	0·92, 2·82	1·44	0·81, 2·57
≥1·98	85	108	2·59	1·61, 4·14	2·29	1·32, 3·96	1·96	1·11, 3·47
$P_{for\ trend}$				<0·001		0·003		0·02

DII, dietary inflammatory index.
* Model 1: adjusted for age (years), sex and energy intake.
† Model 2: adjusted for model 1 + smoking status (current/previous/never), BMI 5 years before interview, education (years), occupation (manual/non-manual), alcohol (g/d), regular non-steroidal inflammatory drug use (ever/never), *Helicobacter pylori* infection (seropositive/seronegative) and location (Northern Ireland/Republic of Ireland).
‡ Model 3: adjusted for model 2 + regular gastro-oesophageal reflux symptoms (ever/never).
§ Analysis limited to Northern Ireland controls only.

Table 3. Dietary inflammatory index density and risk of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma, stratified by gastro-oesophageal reflux symptom experience, Factors influencing the Barrett's Adenocarcinoma Relationship study
(Odds ratios and 95 % confidence intervals)

	No regular reflux symptoms			Regular reflux symptoms			
		Adjusted*			Adjusted*		
	Controls/cases	OR	95 % CI	Controls/cases	OR	95 % CI	$P_{for\ interaction}$
Reflux oesophagitis†							
E-DII							
<−0·12	33/20	1·00		6/14	1·00		
−0·12–<1·91	31/49	1·55	0·68, 3·55	9/33	1·67	0·36, 7·66	
≥1·91	27/63	2·33	1·00, 5·46	13/40	0·83	0·20, 3·48	
$P_{for\ trend}$			0·05			0·70	0·32
Barrett's oesophagus							
E-DII							
<0·34	72/14	1·00		13/31	1·00		
0·34–<1·98	72/21	1·56	0·68, 3·57	14/55	1·85	0·71, 4·80	
≥1·98	62/26	2·05	0·89, 4·76	22/73	1·69	0·68, 4·21	
$P_{for\ trend}$			0·09			0·31	0·97
Oesophageal adenocarcinoma							
E-DII							
<0·34	72/28	1·00		13/17	1·00		
0·34–<1·98	72/34	1·08	0·53, 2·17	14/37	2·81	0·94, 8·42	
≥1·98	62/54	1·73	0·87, 3·45	22/54	2·76	0·99, 7·71	
$P_{for\ trend}$			0·10			0·08	0·34

DII, dietary inflammatory index.
* Adjusted for age (years), sex, energy intake, smoking status (current/previous/never), BMI 5 years before interview, education (years), occupation (manual/non-manual), alcohol (g/d), regular non-steroidal inflammatory drug use (ever/never), *Helicobacter pylori* infection (seropositive/seronegative) and location (Northern Ireland/Republic of Ireland).
† Analysis limited to Northern Ireland controls only.

Results from other studies exploring dietary components that contribute to the DII score and OAC have been largely in line with the diet-associated inflammation hypothesis. For example, reports from a meta-analyses on eight studies showed an inverse association between dietary fibre intake and OAC[10]. In another meta-analysis, increased fish intake was associated with reduced risk[38]. Dietary fibre and *n*-3 in fish have anti-inflammatory DII scores[11].

Table 4. Dietary inflammatory index density and risk of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma, stratified by *Helicobacter pylori* status, Factors influencing the Barrett's Adenocarcinoma Relationship study
(Odds ratios and 95 % confidence intervals)

	H. pylori negative			*H. pylori* positive			
		Adjusted*			Adjusted*		
	Controls/cases	OR	95 % CI	Controls/cases	OR	95 % CI	$P_{for\ interaction}$
Reflux oesophagitis†							
E-DII							
<−0·12	9/15	1·00		30/19	1·00		
−0·12 – <1·91	16/51	1·35	0·42, 4·30	22/30	1·72	0·67, 4·39	
≥1·91	16/59	1·58	0·49, 5·08	24/43	2·35	0·92, 6·01	
$P_{for\ trend}$			0·45			0·07	0·85
Barrett's oesophagus							
E-DII							
<0·34	26/23	1·00		57/21	1·00		
0·34– <1·98	43/41	1·01	0·47, 2·21	41/33	2·48	1·18, 5·23	
≥1·98	34/40	1·25	0·55, 2·81	47/52	2·74	1·32, 5·65	
$P_{for\ trend}$			0·57			0·008	0·21
Oesophageal adenocarcinoma							
E-DII							
<0·34	26/19	1·00		57/21	1·00		
0·34– <1·98	43/32	0·97	0·40, 2·31	41/35	2·45	1·15, 5·22	
≥1·98	34/55	2·26	0·94, 5·41	47/46	2·38	1·15, 4·91	
$P_{for\ trend}$			0·04			0·03	0·13

DII, dietary inflammatory index.
* Adjusted for age (years), sex, energy intake, smoking status (current/previous/never), BMI 5 years before interview, education (years), occupation (manual/non-manual), alcohol (g/d), regular non-steroidal inflammatory drug use (ever/never), and location (Northern Ireland/Republic of Ireland).
† Analysis limited to Northern Ireland controls only.

The results from this study showing a positive association between a pro-inflammatory diet and OAC, BE and RE can be considered promising for diet-based prevention or chemoprevention of these conditions. Phytochemicals in the diet have been shown to increase necrosis and apoptosis in Barrett's cells through inhibiting the inflammatory reaction, and to exhibit a similar effect on OAC cells[39]. Resveratrol, which is present in relatively large quantities in grapes, was found to be a natural COX-2 inhibitor that is involved in the anti-inflammatory pathway[40]. Another phytochemical, curcumin, which can down-regulate inflammation, was demonstrated to be capable of abolishing the ability of deoxycholic acid to activate NF-κB[41]. *n*-3 Fatty acids, which are abundant in fish and have been associated with a protective effect concerning oesophageal cancer, can stimulate anti-inflammatory signalling molecules[42]. This, again, demonstrates the biological plausibility of the results shown.

We also observed a stronger association between the E-DII and odds of oesophageal lesions among subjects with *H. pylori* infection. As the statistical test for interaction was not significant, these results should be viewed with caution; however, the possible reason for this observation could be that *H. pylori* activates the NF-κB pathway, which is an important promoter of carcinogenesis through the process of inflammation[5,43], and this could be accelerated with a pro-inflammatory diet, as indicated by increasing DII scores.

It is clear that analyses should be controlled for total energy intake. However, such control requires careful consideration. This is because there are two countervailing effects between energy and nutrient intake. The first is the tendency to eat more of all nutrients as one increases energy intake; this results in a positive correlation between energy intake and nutrient intake. The other is what may be termed the 'healthy eater' effect (i.e. due to the intention of careful, health-conscious people to choose nutrient-dense, energy-sparse foods – in preference to energy-dense, nutrient-sparse foods). Of course, its opposite is the 'unhealthy eater' effect (i.e. showing a preference for energy-dense, nutrient-sparse foods). Both of these types of eaters produce results that show negative correlations between DII scores and total energy intake. In previous research we have observed that there is considerable variability in how these eating behaviours are distributed across different populations. The consequence is that there is variability in results based on whether or not we control for energy, as well as the method of control.

Regarding the specific method of control, the multivariate nutrient density model is similar to, but not mathematically equivalent to, the residual method of energy adjustment. Consequently, results from the two methods are usually highly correlated. In the multivariate nutrient density model, the coefficient has a substitution interpretation but is in units of the percentage of energy from the nutrient. It can therefore be directly translated into public health recommendations that are expressed in these units. Because of the long-standing use of nutrient densities by nutritionists and the application of nutrient densities in public health recommendations, the multivariate nutrient density model appears to deserve more widespread use[44]. We have additionally adjusted for energy intake as recommended by Willett *et al.*[44] under the multivariate nutrient density model.

There are several strengths of our population-based case–control study, including the ability to study the DII in

relation to early inflammatory disease through to pre-malignant and malignant lesions of the oesophagus. We also were able to account for several potential confounders, most notably *H. pylori* infection. Despite its strengths, we acknowledge that the study has several limitations. First, it was necessary to enquire about habitual dietary intakes 5 years before interview in order to overcome reverse causation bias from the presence of disease. This will have incurred the potential for recall bias in our dietary assessment. In addition response rates of population-based controls were considerably lower than that of patient groups. However, previous comparisons with national dietary surveys in Ireland suggest that dietary habits of our controls are representative of the general population[45]. A further limitation of our study is that we were able to derive DII from only twenty-five of the potential forty-five food and nutrient items that can be used to compute this index. However, other published studies also derive DII scores from a sub-optimal number of items, and the ability to still detect significant associations suggests that this has only led to a potential underestimate of the association between E-DII scores and oesophageal lesion risk. However, some of the missing food parameters such as saffron, ginger and turmeric are consumed infrequently in this population; so, non-availability of these parameters may not have exerted a major impact. Further to this issue of calculating DII from fewer food parameters, we have previously demonstrated in the Seasonal Variation of Blood Cholesterol Study that DII scores calculated from forty-four food parameters using the 24-h recalls and DII scores calculated from twenty-seven food parameters using 7-d dietary recall resulted in the same OR, where CRP (>3 mg/l) was the study outcome[11]. Reviewing all previous publications on the DII, on average twenty-seven food parameters can be derived from a structured dietary assessment tool such as an FFQ to calculate the DII, and the range is between nineteen and thirty-four depending on the detail provided by the FFQ, the nature of the nutrient database and whether flavonoids were calculated.

In conclusion, our study suggests that subjects with OAC and BE (and to a lesser extent RE) were more likely to have a pro-inflammatory diet, as shown by higher DII scores. However, this finding requires replication in other studies, including prospective cohorts. This may require large consortia efforts to achieve the sample sizes needed to study this rarer cancer site.

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Dr J. R. H. owns the controlling interest in Connecting Health Innovations LLC (CHI), a company planning to license the right to his invention of the DII from the University of South Carolina in order to develop computer and smart phone applications for patient counselling and dietary intervention in clinical settings. Dr N. S. is an employee of CHI.

None of the authors has any conflicts of interest to declare.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114517001131

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