Inflammatory potential of diet and risk of lymphoma in the European Prospective Investigation into Cancer and Nutrition

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Names for PubMed indexing

Solans, Benavente, Saez, Agudo, Jakszyn, Ferrari, Hosnijeh, Gunter, Huybrechts, Naudin, Besson, Mahamat-Saleh, Boutron-Ruault, Kühn, Kaaks, Boeing, Lasheras, Sánchez, Amiano, Chirlaque, Ardanaz, Schmidt, Vineis, Riboli, Trichopoulou, Karakatsani, Valanou, Masala, Agnoli, Tumino, Sacerdote, Mattiello, Skeie, Weiderpass, Jerkeman, Alves Dias, Späth, Nilsson, Dahm, Overvad, Petersen, Tjønneland, de Sanjose, Vermeulen, Nieters, Casabonne

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Short running head: Inflammatory potential of diet and lymphoma risk

Sources of support

European Commission (DG-SANCO), International Agency for Research on Cancer, Danish Cancer Society (Denmark), Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Generale de l'Education Nationale, Institut National de la Sante et de la Recherche Medicale (INSERM) (France), German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF), Deutsche Krebshilfe, Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research (Germany), the Hellenic Health Foundation (Greece), Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy), Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); Grant number: ERC2009-AdG 232997; Grant sponsors: Nordforsk, Nordic Centre of Excellence programme on Food, Nutrition and Health (Norway); Grant sponsor: Spanish Ministry of Economy and Competitiveness - Carlos III Institute of Health cofunded by FEDER funds/European Regional Develpment Fund (ERDF) - a way to build Europe, Grant numbers: [PI13/00061 (to Granada), PI13/01162 (to EPIC-Murcia, Regional Governments of Andalucıa, Asturias, Basque Country, Murcia and Navarra), PI17/01280 and PI14/01219 (to Barcelona), Centro de Investigación Biomédica en Red: Epidemiología y Salud Pública (CIBERESP, Spain)]; Grant sponsor: AGAUR; Grant number (2017SGR1085); Grant sponsor: ISCIII RETIC; Grant number: RD06/0020 (Spain); Grant sponsors: Swedish Cancer Society, Swedish Research Council and County Councils of Skåne and Vasterbotten (Sweden) and Cancer Research UK; Grant numbers: 14136 (to EPIC-Norfolk), C570/A11692, C570/A16491 and C8221/A19170 (to EPIC-Oxford); Grant sponsor: Medical Research Council; Grant numbers: 1000143 (to EPIC-Norfolk), MR/M012190/1 (to EPIC-Oxford, UK).

This study is listed on the ISRCTN registry with the study ID ISRCTN12136108.

Availability of data and materials: For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at http://epic.iarc.fr/access/index.php.

Conflict of Interest Statement: None of the authors declared a conflict of interest.

Abbreviations list

BMI: body mass index

CLL/SLL: chronic lymphocytic leukemia, small lymphocytic lymphoma

DII: dietary inflammatory index

DLBCL: diffuse large B-cell lymphoma

EPIC: European Prospective Investigation into Cancer and Nutrition

FL: follicular lymphoma

HL: Hodgkin lymphoma

ISD: inflammatory score of diet

MM/PCN: multiple myeloma/plasma cell neoplasm

NHL: Non-Hodgkin lymphoma

WCRF/AICR: World Cancer Research Fund/American Institute for Cancer Research.

Word count:

- Abstract: 244 words
- Text: 3,246 words
- Tables and figures: 3 tables
- Online Supplemental material: 2 tables and 1 figure

Abstract

Background: Chronic inflammation plays a critical role in lymphomagenesis and several dietary factors seem to be involved in the regulation of this process.

Objective: The aim of the current study was to assess the association between the inflammatory potential of the diet and the risk of lymphoma and its subtypes in the European Investigation into Cancer and Nutrition (EPIC) study.

Design: The analysis included 476,160 subjects with an average follow-up of 13.9 years, during which 3,136 lymphomas (135 Hodgkin lymphoma (HL), 2,606 non-Hodgkin lymphoma (NHL) and 395 NOS) were identified. The dietary inflammatory potential was assessed by means of an inflammatory score of the diet (ISD), calculated using 28 dietary components and their corresponding inflammatory weights. The association between the ISD and lymphoma risk was estimated by hazard ratios (HR) and 95% confidence intervals (CI) calculated by multivariable Cox regression models adjusted for potential confounders.

Results: We did not find a statistically significant association between the ISD and overall lymphoma. Among lymphoma subtypes, positive associations between the ISD and mature B-cell NHL (HR for a 1-SD increase: 1.07 (95%CI: 1.01; 1.14), p-trend=0.03) were observed. No statistically significant associations where found among other subtypes; however, albeit with smaller number of cases, high HR were observed for HL (HR for a 1 SD increase= 1.22 (95% CI 0.94; 1.57), p-trend 0.06).

Conclusions: Our findings suggest that low-grade chronic inflammation induced by the diet may be modestly associated with risk of B-cell lymphoma subtypes. Further studies are warranted to confirm these findings.

Key words: Chronic inflammation; inflammatory score of the diet; lymphoma; nutrition; prospective studies

Introduction

Lymphomas are a heterogeneous group of malignancies that arise from the lymphatic system. Their etiology remains largely unknown, with few well-established risk factors including immunosuppression, certain infections and other chronic inflammatory conditions(1–3). In addition, several individual dietary factors have been linked to lymphoma risk, although to the date, no conclusive associations have been reported(4).

Chronic inflammation is known to play an important role in carcinogenesis(5) and several lines of evidence suggest that this process may be influenced by specific dietary factors(6). Indeed, several food components have an impact on blood concentrations of inflammatory markers, including cytokines, chemokines, acute-phase proteins, soluble adhesion molecules and cytokine receptors(6,7). Recently, promising tools have emerged to assess the inflammatory potential of diet – the dietary inflammatory index (DII)(8) and the inflammatory score of diet (ISD)(9), scores combining the intake of dietary constituents and their association with well-known inflammatory markers. Epidemiological studies have assessed the association between the DII/ISD and several solid neoplasms, such as breast(10), gastric(9), oral and pharyngeal(11), renal(12) or colorectal(13) cancers. To date, however, evidence on haematological malignancies is scarce, with no prospective data and only two case-control studies reporting a positive association between a pro-inflammatory diet and NHL(14) and no associations for HL(15).

The aim of this study is to investigate the association between the inflammatory potential of diet, measured by means of the ISD, and lymphoma risk within the European Prospective Investigation into Cancer and Nutrition (EPIC) population.

Methods

Study population

EPIC is an ongoing prospective cohort study involving 23 centers from ten European countries (Denmark, France, Germany, Greece, the Nederland's, Italy, Norway, United Kingdom, Spain and Sweden). The rationale, full methods and study design have been described previously(16,17). In brief, 521,324 subjects, mostly aged 30 to 70 years, were recruited between 1992 and 2000. Written informed consent was provided by all participants. The ethical review boards from the International Agency for Research on Cancer (IARC) and from all local centers approved the study. Prior to analysis, the following exclusions were made: participants with a prevalent cancer (n= 25,184), with missing follow-up information (n= 4,148), with incomplete/ no dietary information (n= 6,259), or those in the highest and lowest 1% of the distribution for the ratio of energy intake to estimate energy requirement (n= 9,573). Thus, our final study population included 476,160 EPIC participants among whom 3,136 incident lymphoma cases occurred during an average follow-up of 13.9 years.

Data collection

Validated country-specific questionnaires were used to record the usual diet during the previous year(17,18); namely through quantitative or semi-quantitative food frequency questionnaires (FFQs) (administered through a personal interview or self-administered), although few countries used semi-quantitative FFQs combined with a food record. Lifestyle questionnaires were used to obtain information on sociodemographic characteristics, physical activity, reproductive history, use of oral contraceptives and hormone replacement therapy, medical history and alcohol and tobacco consumption. Anthropometric measures were also ascertained at recruitment.

Exposure assessment: ISD

The inflammatory potential of diet was assessed using the ISD. Its scoring system has been described elsewhere(9). In brief, 28 food parameters (e.g. carbohydrates, fats, vitamins or flavonoids) available in the EPIC databases for all centers were selected. The intake of each food parameter was standardized using the mean and standard deviation of our study population (Supplementary material, **Table S1**). These z-scores were then converted to percentile scores to avoid the right skewness of data, and then centred on 0 by doubling each percentile score and subtracting 1. The centred percentile values were then multiplied by its respective inflammatory weight, also used to construct the DII, obtained after a literature review according to the pro- or anti-inflammatory effect of the food parameter, the level of evidence of the studies and the number of articles reviewed (8). The food parameter-specific inflammatory score was then summed to obtain the overall ISD for each individual. Overall, the ISD is a relative index that allows categorizing individuals' diets on a continuum from maximally anti-inflammatory (corresponding to lower scores) to maximally pro-inflammatory (higher scores).

The procedure of construct the ISD is similar to the DII(8) with a few modifications. First, we used 28 food parameters instead of the 45 included in the DII (Supplementary material, **Table S1**). Information on total fats was dismissed because its inflammatory effect is likely to be represented by the weights of all separate components of fats (i.e. saturated, mono-unsaturated, and polyunsaturated fats), and thus, including them in the scoring calculation could imply an overestimation of its inflammatory effect. For the remaining food parameters, information was not available or not specific enough to be used (e.g. type of tea, green/black). Second, we used a different weight for alcohol owing its dose-dependent effect. In the DII, alcohol is considered to be anti-inflammatory (it has a negative weight, -0.278 for all levels of consumption), but this property has only been

reported in literature for moderate consumers (less than 30-40 g/day). Therefore, we restricted this weight to moderate consumers (Supplementary material, **Table S1**). Finally, each individual item intake was standardized using the mean and standard deviation (SD) of our study population (Supplementary material, **Table S1**), whereas the DII used data from a regional worldwide database taken as "referent" population. Given that comparing the inflammatory potential of diet was not the aim of this study, but assessing whether the inflammatory potential of diet was associated with cancer risk, we gave priority to internal validity and used our own population to standardize the intakes of the ISD components.

Follow-up and outcome assessment

Incident lymphoma cancer cases were identified by population cancer registries for Denmark, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. A combination of methods was used in France, Germany and Greece, as detailed previously(17). Mortality data were also obtained from regional or national mortality registries. The follow-up period was defined from the age at recruitment to the age at first cancer diagnosis, death or last complete follow-up, depending on which occurred first. Censoring dates for the last complete follow-up ranged from June 2008 to December 2013, depending on the EPIC center.

Initially, the diagnosis of lymphoma cases was based on the second revision of the International Classification of Diseases for Oncology (ICD-O-2). Later, all cases were reclassified into the ICD-O-3 using a conversion program available on the web site of the Surveillance Epidemiology and End Results (SEER) program (http://seer.cancer.gov/tools/conversion/ICD02- 3manual.pdf) and involving a pathology expert and experts from the EPIC centers. Because not all ICD-O-2 diagnostics can be

translated unequivocally into the ICD-O-3 classification, we left the respective lymphomas unclassified (not otherwise specified ‘‘NOS’’) when further detailed specification failed. Finally, the InterLymph Pathology Working Group classification, which is based in the current 2008 WHO classification, was used to categorize lymphoma histologic subtypes(19).

In the current analysis, the following groups were considered: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL); within NHL, mature B-cell lymphoma and mature T/NK-cell lymphoma; and among mature B-cell lymphoma, the following entities: diffuse large B-cell lymphoma (DLBCL) (including Burkitt lymphoma), follicular lymphoma (FL) (all grades), chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL), multiple myeloma/plasma cell neoplasm (MM/PCN), and other B-cell lymphoma (i.e. those cases in which the B-cell lymphoma subtype is unknown or does not fall within the above mentioned subtypes). Other entities were not considered due to small numbers (**Table 1**). Overall, during an average follow-up of 13.9 years, 3,136 lymphoma cases were diagnosed.

Statistical analysis

Cox proportional hazard models were used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) to examine the association between the ISD and lymphoma risk. Entry time was defined as age at recruitment and exit time was age at diagnosis (cases), death, or end of follow-up, whichever came first. Two models with two levels of adjustment were used: a basic model, stratified by center, sex and age at recruitment (in 1-year categories), and a multivariable model, further adjusted for body mass index (BMI) (<25, 25-30, ≥ 30 kg/m^2), total energy intake (continuous, kcal/day), education level (no formal education, primary school, secondary school, technical or professional training,

university, unknown [3.6%]), height (continuous, cm), physical activity level based on the Cambridge Physical Activity Index (inactive, moderately inactive, moderately active, active, unknown [1.9%]), smoking status (never, former, current and, unknown [2.0%]), and alcohol intake at recruitment (continuous, g/day).

The ISD was analysed both as a continuous variable (1-standard deviation [SD] increase) and as a categorical variable (in quartiles). The ISD categorical variable was scored from 1 to 4, and trend tests were calculated on these scores. In addition, we tested for interaction by age, sex, smoking status and alcohol intake by including a cross-product term along with the armed score (continuous) in the multivariable Cox model. The statistical significance of the cross-product term was evaluated using likelihood ratio test.

Sensitivity analyses were performed by repeating main Cox analyses (i) censoring participants and excluding cases with less than two years of follow-up (n=259), (ii) excluding participants without complete data (n=226), and (iii) restricting HL analysis to classical HL cases. Moreover, given that alcohol has been shown to be inversely associated with several lymphoma subtypes(20), we excluded it from the ISD construction to confirm it was not the only element driving the associations found. Schoenfeld residuals were assessed to ensure that the assumptions of proportional hazards were met in all models. Two-sided p-values were reported with statistically significance set at $p<0.05$. All analyses were performed by using STATA statistical software, version 14 (Stata Corporation, College Station, Texas).

Results

Distributions of all the EPIC participants and of the lymphoma cases by country are displayed in **Table 1**. The inflammatory potential of diet in the whole cohort, measured by the ISD, had a mean of 0.26 with SD of 1.00 and a ranged from -6.38 (the maximum anti-inflammatory value) to 5.01 (the maximum pro-inflammatory value). Lower ISD means were observed in the UK and Greece whereas higher ISD means were seen in Norway and Sweden.

Baseline characteristics of the study participants according to the ISD are detailed in **Table 2**. In general, participants with higher values of the ISD (more pro-inflammatory diet) were more likely to be women, ever smokers, and physically inactive, with a lower education level, alcohol and energy intake compared with those with a lower ISD score (more anti-inflammatory diet).

The association of the inflammatory potential of the diet with lymphoma and its subtypes is presented in **Table 3**. Overall, the ISD was not associated with risk of lymphoma (HR_{Q4vsQ1}= 1.07 (95% CI 0.93; 1.22, p-trend =0.34); HR for a 1-SD increase = 1.05 (95% CI 1.00; 1.11), p-trend= 0.06). Among lymphoma subtypes, each SD increase in the ISD was associated with a 6% higher risk of having NHL (95% CI 1.00; 1.13, p-trend= 0.04), and within them, there were modest positive associations for mature B-cell NHL (HR for a 1-SD increase= 1.07 (95% CI 1.01; 1.14), p-trend= 0.03) and other B-cell neoplasms (HR_{Q4vsQ1}= 1.54 (1.01; 2.34), p-trend= 0.07). No statistically significant associations where found among other lymphoma subtypes; however, albeit with smaller number of cases, high HR were observed for HL (HR_{Q4vsQ1}= 1.90 (95% CI 0.97; 3.71; p trend= 0.08); HR for a 1SD increase= 1.22 (95% CI 0.94; 1.57), p-trend 0.06). Following the exclusion of non-classical HL (n=8) risk showed similar results (HR_{Q4vsQ1}= 1.98 (95% CI: 0.99; 3.97), p-trend= 0.09; HR for a 1-SD increase= 1.23 (95% CI: 0.94; 1.59), p-trend= 0.13). Neither age, sex, smoking status nor alcohol consumption modified the

associations of the ISD and risk of lymphoma, HL, NHL or mature B-cell NHL (Supplementary material, **Table S2).** Likewise, no statistically significant interactions were detected for the rest of mature B-cell NHL subtypes (*data not shown*). Similarly, no significant differences in the association of lymphoma and its subtypes were observed by country, with the exception of DLBCL (Supplementary material, **Figure S1**).

In sensitivity analyses, excluding alcohol from the ISD construction, excluding first 2 years of follow-up or those individuals with no information on adjustment variables from the analyses did not substantially alter the observed associations (*data not shown*).

Discussion

In this large European prospective study, the inflammatory potential of diet, measured by means of the ISD was not associated with overall lymphoma risk and showed a modest association with B-cell lymphoma subtypes.

In the recently released Third Expert Report by the WCRF/AICR(21), the Panel did not make any judgements regarding the causality of associations between specific dietary factors and lymphoid neoplasms. During the last decades, most nutritional epidemiological studies have shifted to dietary pattern analyses, which represent a broader picture of subject's diet, and may thus be more predictive of disease risk than individual foods or nutrients(22). Among them, the ISD and DII represents a promising tool to evaluate a set of dietary exposures with cumulative and interactive effects on both low-grade inflammation and health outcomes(8). While it has been largely studied in solid neoplasms(9–13,23,24), studies on hematological malignancies are utterly scarce, mostly arising from case-control studies restricted to NHL patients without detailed information for specific subtypes.

To the best of our knowledge, this is the first prospective study to investigate the link between the inflammatory potential of diet and risk of lymphoma and its subtypes. Our results are in line with those reported in a multicenter case-control Italian study with 536 NHL cases and 934 matched controls(14). The adjusted odds ratio (OR) comparing the highest to the lowest quartile of the DII for NHL was 1.61 (95% CI: 1.07; 2.43); p trend= 0.01)) and when analyses were carried out using continuous DII, the OR for 1-unit increment in the score was 1.14 (95% CI 1.02; 1.27). Stratified analyses revealed stronger associations between DII and NHL among males and an association between a pro-inflammatory diet and DLBCL was also reported. By contrast, no associations between the DII and HL (n=179) were reported in the same case-control study(15). However, although the DII and ISD have been shown to highly correlate in the EPIC population (Pearson's correlation coefficient: 0.91; p-value<0.001)(9), data from both studies cannot be directly compared with ours, since they are based upon different indexes and study designs. In addition, the Italian case-control study lacked information on potential confounders (e.g. BMI or physical activity) as well as on NHL entities other than DLBCL or FL. In the EPIC study, a positive association between the ISD and other B-cell neoplasms (which included Burkitt lymphoma, hairy cell leukemia, lymphoplasmatic lymphoma, mantle cell lymphoma, marginal zone lymphoma, primary effusion lymphoma, and B-cell prolymphocytic lymphoma) was observed, but unfortunately a limited sample size did not allow further specific subtype analyses. Thus, more prospective studies with larger sample size and with detailed lymphoma classification schemes are needed to shed light into this observed relationship.

The role of inflammation, mediated by dietary factors, in the pathogenesis of lymphoma has a strong biological plausibility. Certain autoimmune and chronic inflammatory conditions characterized by severe immune dysregulation such as immunosuppression,

Sjögren's syndrome, systemic lupus erythematosus, and rheumatoid arthritis have been established as strong risk factors for lymphoma(1,2,25). In addition, several infectious agents have been specifically linked to certain subtypes of lymphoma, including the Human immunodeficiency virus, Epstein-Bar virus (EBV), human T-cell lymphotrophic virus-1, human herpes virus-8, and hepatitis C virus, and the bacteria *Helicobacter pylori*, *Borrelia burgdorferi* ,*Chlamydia psittaci* and *Campylobacter jejunei*(1–3,25). Most of these agents are believed to exert their lymphomagenic mechanisms primarily or partially through chronic immune stimulation(2,3,25). In particular for HL, it is widely believed that its clinical and histological features are primarily due to the effects of a plethora of cytokines and chemokines produced by Reed-Sternberg cells and their surrounding cellular infiltrate in response to inflammatory signals triggered by etiological factors such as EBV(26). Moreover, it is unclear whether subclinical immunologic perturbations influence lymphoma risk. However, recent studies within general population cohorts incorporating serologic measurements of cytokines, chemokines, and other immune markers have provided important evidence supporting a role for subtle immunologic effects in lymphomagenesis(27–36). The modest associations between the ISD and B-cell lymphoma subtypes suggest that inflammation induced by diet may be also implied in this process and merit further research.

Incidence of lymphoid neoplasms exhibits a marked geographical variability, with the highest incidence rates in western countries, and the lowest found in Asia and Eastern Europe(37,38). In addition, incidence patterns of both HL and NHL vary with migration and nativity, suggesting an influence of acculturation on lymphoma risk (39,40). Indeed, markedly lowered rates of lymphoid malignancies among Asians relative to other racial/ethnic groups in the United States and among foreign-born Asians compared to United states-born Asians(39) have suggested some kind of protection from

lymphomagenic processes, but it is still unclear whether this protection relies genetic, environmental differences or a combination. In addition, a Western dietary pattern, characterized by higher intakes of red and processed meats, sweets, desserts, French fries, and refined grains, has been positively associated with inflammatory biomarkers(41). Thus, a westernization of diet, characterized by the inclusion of foods and nutrients with a pro-inflammatory profile, could partly explain these incidence trends.

Limitations of our study should be considered when interpreting the results, including potential measurement errors derived from dietary questionnaires, which could lead to systematic and random errors when estimating the ISD. Although our adjustment for total energy intake and exclusion of subjects with implausible diets (those in the highest and lowest 1% of the distribution of the ratio between energy intake and estimated energy requirement) would partly remove some of these errors(42,43) we cannot rule out that they have modified risk estimates. However, since dietary information was collected on healthy individuals at the beginning of the study, measurement errors would be expected to be non-differential and thus, their effect would most likely dilute the true association. In addition, we were unable to take into account any possible changes in dietary and lifestyle habits over time. In particular, cases might have modified their diet during the early pre-diagnostic period of the disease, although sensitivity analyses excluding incident cases diagnosed in the first 2 years of follow-up did not alter the association. Moreover, despite adjusting for multiple lymphoma risk factors, residual confounding cannot be dismissed. In addition, because of the high number of comparisons performed, we cannot exclude chance findings. Finally, we lacked of information on the usual consumption of anti-inflammatory drugs or supplements, nor was information collected on foods preserved by salting or sodium intake; all these factors could have influenced the inflammatory potential of diet. Similarly, information on several parameters

considered in the DII was not available or not specific enough to be used (i.e type of tea, green/black). However, a study reported that seven components explained 91% of the inter-individual variance in DII(44); all of them included in the ISD, and therefore we can assume that the exclusions made have not had a major impact in the estimation of the inflammatory potential of diet.

Among the strengths of our study are its prospective design and high statistical power, owing to a large number of cases, an accurate case-ascertainment, and the ability to carry out specific analyses according to lymphoma subtypes. The latter is particularly relevant since there is growing evidence that lymphoma subtypes have different pathological and epidemiological features(1). In addition, its multi-centric European design allowed the inclusion of a geographically diverse population, covering a wide range of dietary intakes and lifestyle habits.

In summary, our results suggest that a pro-inflammatory diet may be modestly associated with B-cell lymphomas. Further research including biomarkers of inflammation together with the inflammatory potential of the diet would help to better understand the mechanisms underlying the role of diet-related inflammation and lymphomagenesis for these lymphoma subtypes.

Acknowledgments: We thank all participants of the EPIC study. We thank Catalina Bonet for data management support and Bertrand Hémon at IARC for his valuable work and technical support with the EPIC database.

Conflict of Interest Statement: None of the authors declared a conflict of interest.

Authors' Contribution: DC designed and conducted the research, contributed to the data analysis and manuscript writing, and had primary responsibility for the final content of the manuscript. MSo designed and conducted the research, performed the statistical analysis, wrote the manuscript, and had primary responsibility for the final content of the manuscript. YB, AA,

PJ contributed to the data analysis and YB contributed to manuscript writing. MSa contributed to the statistical analysis. ER is the overall coordinator of the EPIC study. All authors contributed to recruitment, data collection and acquisition, biological sample collection, and follow-up and/or management of the EPIC cohort and to the interpretation of the present findings and approval of the final version of the manuscript for publication.

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Table 1. Distribution of lymphoma cases in the EPIC study.

				Lymphoma subgroups			NHL subgroups[1]		mature B-cell subgroups					
	Total cohort	Person-years	Overall	NHL	HL	NOS	Mature B-cell	Mature T/ NK-cell	DLBCL	FL	CLL/SLL	MM/PCN	Other B-cell	ISD mean[2] (SD)
Denmark	55,014	815,096.8	631	538	29	64	506	23	121	78	118	123	66	0.20 (0.92)
France	67,403	869,362.5	228	216	11	1	205	8	40	44	44	45	32	0.11 (0.91)
Germany	48,557	504,479.0	231	190	13	28	170	12	30	20	39	55	26	0.54 (0.84)
Greece	26,048	281,283.6	62	44	3	15	38	2	3	3	13	15	4	-0.19 (0.95)
Italy	44,545	630,951.3	298	241	15	42	218	11	38	33	44	73	30	0.56 (0.86)
Norway	33,975	452,171.1	163	147	5	11	129	14	26	31	26	24	22	0.97 (0.75)
Spain	39,989	637,947.4	241	211	14	16	194	10	35	27	51	51	30	0.26 (1.00)
Sweden	48,674	801,130.2	517	381	13	123	344	20	57	48	74	132	33	0.77 (0.83)
The Netherlands	36,539	524,670.7	201	186	7	8	172	10	43	26	41	43	19	0.47 (0.76)
United Kingdom	75,416	1,122,765	564	452	25	87	426	20	95	71	87	115	58	-0.53 (1.00)
Total	476,160	6,639,857.5	3,136	2,606	135	395	2,402	130	488	381	537	676	320	0.26 (1.00)

NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; NOS, not otherwise specified; DLBCL, diffuse large B-cell lymphoma (including Burkitt); FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic leukemia; MM/PCN, multiple myeloma/ plasma cell neoplasm; Other B-cell (those cases for which the mature B-cell NHL subtype is unknown or does not fall within the more common subtypes ; ISD, inflammatory score of diet; SD, standard deviation.

[1]Three individuals with NHL without B- or T-cell information.

[2]ISD: positive values indicate a more pro-inflammatory diet and negative values correspond to a more anti-inflammatory diet

Table 2. Baseline characteristics of participants in the EPIC study according to the ISD.

		ISD			
	Total cohort	Q1 (mean = -1.09, range -3.52; -0.43)	Q2 (mean =-0.02, range: -0.43; 0.34)	Q3 (mean =0.68 range: 0.34; 1.02)	Q4 (mean =1.47 range: 1.02 ;2.76)
Total cohort, n	476,160	119,040	119,040	119,040	119,040
Females (%)	70.1	64.8	67.5	71.4	76.8
Age at recruitment (mean [SD], years)	51.2 (9.9)	50.7 (11.1)	51.5 (9.9)	51.5 (9.5)	51.2 (9.2)
Energy intake (mean [SD], kcal/day)	2,075.1 (619.2)	2,523.2 (640.3)	2,198.1 (540.9)	1,954.7 (468.9)	1,624.3 (421.4)
Alcohol intake (median [25th-75th percentiles], g/day)	5.3 (0.9; 14.9)	7.4 (1.6; 17.9)	6.4 (1.3; 16.7)	5.3 (0.9; 14.9)	2.8 (0.4; 10.6)
BMI (mean [SD], kg/m^2)	25.4 (4.3)	25.4 (4.3)	25.4 (4.3)	25.4 (4.2)	25.5 (4.3)
Height (mean [SD], cm)	166.0 (8.9)	166.9 (9.0)	166.4 (9.1)	165.8 (8.9)	164.9 (8.7)
Smoking status (% ever)	49.0	45.8	48.2	49.9	52.3
Physical activity (% inactive)	21.0	19.2	20.5	21.0	23.2
Educational level (% ≤ primary school)	30.0	23.8	28.3	31.0	36.9

ISD, inflammatory score of diet; Q, quartile; n, total number ; SD: standard deviation; BMI: body mass index.

Table 3. Association between the ISD and risk of lymphoma and its subtypes in the EPIC study.

	ISD						
	Q1	Q2	Q3	Q4	P-trend[3]	1-SD increase	P-trend[4]
Lymphoma, n	784	783	786	783			
HR[1] (95% CI)	Ref	0.99 (0.89; 1.09)	0.99 (0.89; 1.10)	1.00 (0.89; 1.11)	1.00	1.01 (0.97; 1.05)	0.56
HR[2] (95% CI)	Ref	1.01 (0.91; 1.13)	1.04 (0.92; 1.16)	1.07 (0.93; 1.22)	0.34	1.05 (1.00; 1.11)	0.06
HL, n	25	35	35	40			
HR[1] (95% CI)	Ref	1.51 (0.89; 2.55)	1.64 (0.96; 2.80)	**1.99 (1.15; 3.43)**	**0.02**	**1.25 (1.03; 1.52)**	**0.02**
HR[2] (95% CI)	Ref	1.48 (0.86; 2.57)	1.60 (0.88; 2.90)	1.90 (0.97; 3.71)	0.08	1.22 (0.94; 1.57)	0.13
NHL, n	658	659	647	642			
HR[1] (95% CI)	Ref	0.98 (0.88; 1.10)	0.97 (0.86; 1.09)	0.98 (0.87; 1.11)	0.72	1.00 (0.96; 1.05)	0.88
HR[2] (95% CI)	Ref	1.03 (0.91; 1.15)	1.04 (0.92; 1.19)	1.10 (0.94; 1.27)	0.24	**1.06 (1.00; 1.13)**	**0.04**
Mature T/ NK-cell, n	34	35	31	30			
HR[1] (95% CI)	Ref	0.93 (0.57; 1.51)	0.79 (0.47; 1.33)	0.72 (0.42; 1.25)	0.20	0.99 (0.81; 1.20)	0.91
HR[2] (95% CI)	Ref	0.86 (0.51; 1.43)	0.70 (0.39; 1.25)	0.61 (0.31; 1.19)	0.12	0.99 (0.76; 1.29)	0.95
Mature B-cell, n	603	608	596	595			
HR[1] (95% CI)	Ref	1.00 (0.89; 1.12)	0.99 (0.88; 1.12)	1.02 (0.90; 1.16)	0.79	1.01 (0.96; 1.06)	0.67
HR[2] (95% CI)	Ref	1.05 (0.93; 1.19)	1.08 (0.94; 1.23)	1.15 (0.99; 1.35)	0.08	**1.07 (1.01; 1.14)**	**0.03**
DLBCL, n	126	121	118	123			
HR[1] (95% CI)	Ref	1.00 (0.77; 1.29)	1.00 (0.77; 1.31)	1.12 (0.85; 1.47)	0.46	1.05 (0.95; 1.16)	0.38
HR[2] (95% CI)	Ref	1.03 (0.78; 1.34)	1.06 (0.78; 1.42)	1.21 (0.86; 1.70)	0.29	1.09 (0.96; 1.25)	0.20
FL, n	98	95	98	90			
HR[1] (95% CI)	Ref	0.98 (0.73; 1.31)	1.00 (0.74; 1.35)	0.91 (0.66; 1.25)	0.62	0.99 (0.89; 1.11)	0.89
HR[2] (95% CI)	Ref	1.05 (0.78; 1.43)	1.13 (0.81; 1.58)	1.10 (0.74; 1.62)	0.58	1.09 (0.94; 1.27)	0.25
CLL/SLL, n	129	149	135	124			
HR[1] (95% CI)	Ref	1.13 (0.89; 1.44)	1.05 (0.81; 1.35)	1.02 (0.78; 1.34)	0.97	1.00 (0.91; 1.10)	0.99
HR[2] (95% CI)	Ref	1.13 (0.88; 1.46)	1.07 (0.80; 1.42)	1.04 (0.75; 1.45)	0.95	1.01 (0.89; 1.15)	0.88
MM/PCN, n	170	160	171	175			
HR[1] (95% CI)	Ref	0.90 (0.72; 1.12)	0.94 (0.75; 1.18)	0.96 (0.76; 1.21)	0.85	0.99 (0.91; 1.08)	0.84
HR[2] (95% CI)	Ref	0.94 (0.75; 1.19)	1.02 (0.79; 1.31)	1.08 (0.81; 1.45)	0.48	1.05 (0.93; 1.17)	0.43
Other B-cell ,n	80	83	74	83			
HR[1] (95% CI)	Ref	1.05 (0.77; 1.44)	0.96 (0.69; 1.34)	1.16 (0.83; 1.62)	0.51	1.03 (0.91; 1.17)	0.64
HR[2] (95% CI)	Ref	1.18 (0.85; 1.65)	1.17 (0.80; 1.69)	**1.54 (1.01; 2.34)**	0.07	1.16 (0.98; 1.37)	0.08

ISD: inflammatory score of diet; HR, hazard ratio; CI, confidence interval; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma (including Burkitt); FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic leukemia; MM/PCN, multiple myeloma/ plasma cell neoplasm; Other B-cell (those cases for which the mature B-cell NHL subtype is unknown or does not fall within the more common subtypes.

[1]Basic model: Cox proportional hazard model stratified by age (in 1-year categories), center and sex

[2]Multivariate model: Cox proportional hazard model stratified by age (in 1-year categories), center and sex and further adjusted for body mass index, total energy intake, education, height, physical activity, smoking status, and alcohol intake.

[3]P value of Cox proportional model fitter with the ISD ordinal variable as continuous to test for lineal trend.

[4]P value of Cox proportional model fitted with the ISD continuous variable.

In bold: $p<0.05$