

## **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 Development Fund (ERDF) - a way to build Europe, Grant numbers: [PI13/00061 (to Granada), PI13/01162 (to EPIC-Murcia, Regional Governments of Andalucia, 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

## 1 **Abstract**

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

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

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

14 **Results:** We did not find a statistically significant association between the ISD and overall  
15 lymphoma. Among lymphoma subtypes, positive associations between the ISD and mature B-cell  
16 NHL (HR for a 1-SD increase: 1.07 (95%CI: 1.01; 1.14), p-trend=0.03) were observed. No  
17 statistically significant associations were found among other subtypes; however, albeit with  
18 smaller number of cases, high HR were observed for HL (HR for a 1 SD increase= 1.22 (95% CI  
19 0.94; 1.57), p-trend 0.06).

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

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

## 25 **Introduction**

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

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

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

48

## 49 **Methods**

### 50 *Study population*

51 EPIC is an ongoing prospective cohort study involving 23 centers from ten European  
52 countries (Denmark, France, Germany, Greece, the Netherlands, Italy, Norway, United  
53 Kingdom, Spain and Sweden). The rationale, full methods and study design have been  
54 described previously(16,17). In brief, 521,324 subjects, mostly aged 30 to 70 years, were  
55 recruited between 1992 and 2000. Written informed consent was provided by all  
56 participants. The ethical review boards from the International Agency for Research on  
57 Cancer (IARC) and from all local centers approved the study. Prior to analysis, the  
58 following exclusions were made: participants with a prevalent cancer (n= 25,184), with  
59 missing follow-up information (n= 4,148), with incomplete/ no dietary information (n=  
60 6,259), or those in the highest and lowest 1% of the distribution for the ratio of energy  
61 intake to estimate energy requirement (n= 9,573). Thus, our final study population  
62 included 476,160 EPIC participants among whom 3,136 incident lymphoma cases  
63 occurred during an average follow-up of 13.9 years.

### 64 *Data collection*

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



73 *Exposure assessment: ISD*

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

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

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

#### 107 *Follow-up and outcome assessment*

108 Incident lymphoma cancer cases were identified by population cancer registries for  
109 Denmark, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. A  
110 combination of methods was used in France, Germany and Greece, as detailed  
111 previously(17). Mortality data were also obtained from regional or national mortality  
112 registries. The follow-up period was defined from the age at recruitment to the age at first  
113 cancer diagnosis, death or last complete follow-up, depending on which occurred first.  
114 Censoring dates for the last complete follow-up ranged from June 2008 to December  
115 2013, depending on the EPIC center.

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

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

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

### 137 *Statistical analysis*

138 Cox proportional hazard models were used to estimate the hazard ratio (HR) and 95%  
139 confidence intervals (CI) to examine the association between the ISD and lymphoma risk.  
140 Entry time was defined as age at recruitment and exit time was age at diagnosis (cases),  
141 death, or end of follow-up, whichever came first. Two models with two levels of  
142 adjustment were used: a basic model, stratified by center, sex and age at recruitment (in  
143 1-year categories), and a multivariable model, further adjusted for body mass index (BMI)  
144 (<25, 25-30,  $\geq 30$  kg/m<sup>2</sup>), total energy intake (continuous, kcal/day), education level (no  
145 formal education, primary school, secondary school, technical or professional training,

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

150 The ISD was analysed both as a continuous variable (1-standard deviation [SD] increase)  
151 and as a categorical variable (in quartiles). The ISD categorical variable was scored from  
152 1 to 4, and trend tests were calculated on these scores. In addition, we tested for interaction  
153 by age, sex, smoking status and alcohol intake by including a cross-product term along  
154 with the armed score (continuous) in the multivariable Cox model. The statistical  
155 significance of the cross-product term was evaluated using likelihood ratio test.

156 Sensitivity analyses were performed by repeating main Cox analyses (i) censoring  
157 participants and excluding cases with less than two years of follow-up (n=259), (ii)  
158 excluding participants without complete data (n=226), and (iii) restricting HL analysis to  
159 classical HL cases. Moreover, given that alcohol has been shown to be inversely  
160 associated with several lymphoma subtypes(20), we excluded it from the ISD  
161 construction to confirm it was not the only element driving the associations found.  
162 Schoenfeld residuals were assessed to ensure that the assumptions of proportional hazards  
163 were met in all models. Two-sided p-values were reported with statistical significance  
164 set at  $p < 0.05$ . All analyses were performed by using STATA statistical software, version  
165 14 (Stata Corporation, College Station, Texas).

166

167

168 **Results**

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

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

180 The association of the inflammatory potential of the diet with lymphoma and its subtypes  
181 is presented in **Table 3**. Overall, the ISD was not associated with risk of lymphoma  
182 ( $HR_{Q4vsQ1} = 1.07$  (95% CI 0.93; 1.22, p-trend = 0.34); HR for a 1-SD increase = 1.05 (95%  
183 CI 1.00; 1.11), p-trend = 0.06). Among lymphoma subtypes, each SD increase in the ISD  
184 was associated with a 6% higher risk of having NHL (95% CI 1.00; 1.13, p-trend = 0.04),  
185 and within them, there were modest positive associations for mature B-cell NHL (HR for  
186 a 1-SD increase = 1.07 (95% CI 1.01; 1.14), p-trend = 0.03) and other B-cell neoplasms  
187 ( $HR_{Q4vsQ1} = 1.54$  (1.01; 2.34), p-trend = 0.07). No statistically significant associations  
188 were found among other lymphoma subtypes; however, albeit with smaller number of  
189 cases, high HR were observed for HL ( $HR_{Q4vsQ1} = 1.90$  (95% CI 0.97; 3.71; p trend =  
190 0.08); HR for a 1SD increase = 1.22 (95% CI 0.94; 1.57), p-trend 0.06). Following the  
191 exclusion of non-classical HL (n=8) risk showed similar results ( $HR_{Q4vsQ1} = 1.98$  (95%  
192 CI: 0.99; 3.97), p-trend = 0.09; HR for a 1-SD increase = 1.23 (95% CI: 0.94; 1.59), p-  
193 trend = 0.13). Neither age, sex, smoking status nor alcohol consumption modified the

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

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

202

## 203 **Discussion**

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

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

218 To the best of our knowledge, this is the first prospective study to investigate the link  
219 between the inflammatory potential of diet and risk of lymphoma and its subtypes. Our  
220 results are in line with those reported in a multicenter case-control Italian study with 536  
221 NHL cases and 934 matched controls(14). The adjusted odds ratio (OR) comparing the  
222 highest to the lowest quartile of the DII for NHL was 1.61 (95% CI: 1.07; 2.43); p trend=  
223 0.01)) and when analyses were carried out using continuous DII, the OR for 1-unit  
224 increment in the score was 1.14 (95% CI 1.02; 1.27). Stratified analyses revealed stronger  
225 associations between DII and NHL among males and an association between a pro-  
226 inflammatory diet and DLBCL was also reported. By contrast, no associations between  
227 the DII and HL (n=179) were reported in the same case-control study(15). However,  
228 although the DII and ISD have been shown to highly correlate in the EPIC population  
229 (Pearson's correlation coefficient: 0.91; p-value<0.001)(9), data from both studies cannot  
230 be directly compared with ours, since they are based upon different indexes and study  
231 designs. In addition, the Italian case-control study lacked information on potential  
232 confounders (e.g. BMI or physical activity) as well as on NHL entities other than DLBCL  
233 or FL. In the EPIC study, a positive association between the ISD and other B-cell  
234 neoplasms (which included Burkitt lymphoma, hairy cell leukemia, lymphoplasmatic  
235 lymphoma, mantle cell lymphoma, marginal zone lymphoma, primary effusion  
236 lymphoma, and B-cell prolymphocytic lymphoma) was observed, but unfortunately a  
237 limited sample size did not allow further specific subtype analyses. Thus, more  
238 prospective studies with larger sample size and with detailed lymphoma classification  
239 schemes are needed to shed light into this observed relationship.

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

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

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



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

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

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

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

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

310

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

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

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

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

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

	Total cohort	Person-years	Lymphoma subgroups			NHL subgroups <sup>1</sup>		mature B-cell subgroups					ISD mean <sup>2</sup> (SD)	
			Overall	NHL	HL	NOS	Mature B-cell	Mature T/ NK-cell	DLBCL	FL	CLL/SLL	MM/PCN		Other B-cell
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)
<b>Total</b>	<b>476,160</b>	<b>6,639,857.5</b>	<b>3,136</b>	<b>2,606</b>	<b>135</b>	<b>395</b>	<b>2,402</b>	<b>130</b>	<b>488</b>	<b>381</b>	<b>537</b>	<b>676</b>	<b>320</b>	<b>0.26 (1.00)</b>

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.

<sup>1</sup>Three individuals with NHL without B- or T-cell information.

<sup>2</sup>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.

	Total cohort	ISD			
		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	<b>476,160</b>	119,040	119,040	119,040	119,040
Females (%)	<b>70.1</b>	64.8	67.5	71.4	76.8
Age at recruitment (mean [SD], years)	<b>51.2 (9.9)</b>	50.7 (11.1)	51.5 (9.9)	51.5 (9.5)	51.2 (9.2)
Energy intake (mean [SD], kcal/day)	<b>2,075.1 (619.2)</b>	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)	<b>5.3 (0.9; 14.9)</b>	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 <sup>2</sup> )	<b>25.4 (4.3)</b>	25.4 (4.3)	25.4 (4.3)	25.4 (4.2)	25.5 (4.3)
Height (mean [SD], cm)	<b>166.0 (8.9)</b>	166.9 (9.0)	166.4 (9.1)	165.8 (8.9)	164.9 (8.7)
Smoking status (% ever)	<b>49.0</b>	45.8	48.2	49.9	52.3
Physical activity (% inactive)	<b>21.0</b>	19.2	20.5	21.0	23.2
Educational level (% ≤ primary school)	<b>30.0</b>	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				P-trend <sup>3</sup>	1-SD increase	P-trend <sup>4</sup>
	Q1	Q2	Q3	Q4			
<b>Lymphoma, n</b>	784	783	786	783			
HR <sup>1</sup> (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 <sup>2</sup> (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
<b>HL, n</b>	25	35	35	40			
HR <sup>1</sup> (95% CI)	Ref	1.51 (0.89; 2.55)	1.64 (0.96; 2.80)	<b>1.99 (1.15; 3.43)</b>	<b>0.02</b>	<b>1.25 (1.03; 1.52)</b>	<b>0.02</b>
HR <sup>2</sup> (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
<b>NHL, n</b>	658	659	647	642			
HR <sup>1</sup> (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 <sup>2</sup> (95% CI)	Ref	1.03 (0.91; 1.15)	1.04 (0.92; 1.19)	1.10 (0.94; 1.27)	0.24	<b>1.06 (1.00; 1.13)</b>	<b>0.04</b>
<b>Mature T/ NK-cell, n</b>	34	35	31	30			
HR <sup>1</sup> (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 <sup>2</sup> (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
<b>Mature B-cell, n</b>	603	608	596	595			
HR <sup>1</sup> (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 <sup>2</sup> (95% CI)	Ref	1.05 (0.93; 1.19)	1.08 (0.94; 1.23)	1.15 (0.99; 1.35)	0.08	<b>1.07 (1.01; 1.14)</b>	<b>0.03</b>
<b>DLBCL, n</b>	126	121	118	123			
HR <sup>1</sup> (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 <sup>2</sup> (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
<b>FL, n</b>	98	95	98	90			
HR <sup>1</sup> (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 <sup>2</sup> (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
<b>CLL/SLL, n</b>	129	149	135	124			
HR <sup>1</sup> (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 <sup>2</sup> (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
<b>MM/PCN, n</b>	170	160	171	175			
HR <sup>1</sup> (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 <sup>2</sup> (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
<b>Other B-cell, n</b>	80	83	74	83			
HR <sup>1</sup> (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 <sup>2</sup> (95% CI)	Ref	1.18 (0.85; 1.65)	1.17 (0.80; 1.69)	<b>1.54 (1.01; 2.34)</b>	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).

<sup>1</sup>Basic model: Cox proportional hazard model stratified by age (in 1-year categories), center and sex

<sup>2</sup>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.

<sup>3</sup>P value of Cox proportional model fitter with the ISD ordinal variable as continuous to test for lineal trend.

<sup>4</sup>P value of Cox proportional model fitted with the ISD continuous variable.

In bold: p<0.05