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Adherence to the Mediterranean diet and lymphoma risk in the European Prospective Investigation into Cancer and Nutrition

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Running title: Mediterranean diet and lymphoma in EPIC

Key words: lymphoma, Mediterranean diet, Europe, prospective studies, risk.

Abbreviations: arMED, adapted relative Mediterranean diet; BMI, body mass index; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic leukemia; CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; EPIC, European Prospective Investigation into Cancer and Nutrition; FL, follicular lymphoma; HL, Hodgkin lymphoma; HR, hazard ratio; MD, Mediterranean diet; MM/PCN, multiple myeloma/plasma cell neoplasm; NHL, Non-Hodgkin lymphoma; WCRF/AICR World Cancer Research Fund/American Institute for Cancer Research.

Novelty and impact: Known risk factors explain only a small proportion of lymphoma cases. Several studies have pointed out the potential role of dietary factors on lymphoma risk, but evidence is still inconclusive. Here, using data from the European Prospective Investigation into Cancer and Nutrition study, the authors found for the first time that adherence to a Mediterranean diet was modestly associated with a reduced risk of overall lymphoma. Further studies are needed to confirm these findings.

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Abstract

There is growing evidence of the protective role of the Mediterranean diet (MD) on cancer. However, no prospective study has yet investigated its influence on lymphoma. We evaluated the association between adherence to the MD and risk of lymphoma and its subtypes in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. The analysis included 476,160 participants, recruited from ten European countries between 1991 and 2001. Adherence to the MD was estimated through an adapted relative Mediterranean diet (arMED) score excluding alcohol. Cox proportional hazards regression models were used while adjusting for potential confounders. During an average follow-up of 13.9 years, 3,136 lymphomas (135 Hodgkin lymphoma (HL), 2,606 non-Hodgkin lymphoma and 395 lymphoma NOS) were identified. Overall, a 1-unit increase in the arMED score was associated with a 2% lower risk of lymphoma (95% CI: 0.97; 1.00, p-trend=0.03) while a statistically non-significant inverse association between a high versus low arMED score and risk of lymphoma was observed (HR: 0.91 (95% CI 0.80; 1.03), p-trend=0.12). Analyses by lymphoma subtype did not reveal any statistically significant associations. Albeit with small numbers of cases (N= 135), a suggestive inverse association was found for HL (HR 1-unit increase= 0.93 (95% CI: 0.86; 1.01), p-trend=0.07). However, the study may have lacked statistical power to detect small effect sizes for lymphoma subtype. Our findings suggest that an increasing arMED score was inversely related to the risk of overall lymphoma in EPIC, but not by subtypes. Further large prospective studies are warranted to confirm these findings.

1. Introduction

Lymphomas are a heterogeneous group of malignancies particularly prevalent in Western countries. Although some lymphoid neoplasms have been consistently linked to certain infections and severe immunosuppression, their etiology remains elusive, and evidence from epidemiologic studies increasingly points to etiologic heterogeneity among subtypes[1].

An increase in the incidence of lymphoma has been observed in many regions during the last decades[2], and a change in lifestyle might be one possible explanation for this pattern. However, there is limited evidence regarding extrinsic-risk factors, particularly diet, and lymphoma risk[3,4]. In the recently released Third Expert Report on 'Diet, Nutrition, Physical Activity, and Cancer' by the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR)[5], no conclusive associations for specific dietary factors and hematological malignancies were reported. Studies from the European Prospective Investigation into Nutrition and Cancer (EPIC) study have neither shown consistent associations between consumption of meat and dairy[6] nor vegetables[7] and overall lymphoma risk, although some statistically significant associations were seen for several lymphoma subtypes.

There is evidence that the Mediterranean diet (MD) has a protective role on risk of overall[8] and specific types of cancer[9], such as breast[10], colorectal[11] or gastric cancers[12]. However, epidemiological research into the effect of a MD pattern on lymphoma remains limited. To our knowledge, no study has yet evaluated the influence of validated *a priori* MD score on lymphoma risk, while studies on *a posteriori* healthy-like dietary patterns have yielded inconsistent results for overall lymphoma as well as its subtypes[13–15].

The aim of this study is to investigate the association between adherence to the Mediterranean dietary pattern and lymphoma risk within the EPIC population. The EPIC study provides the opportunity to examine this relation in a prospective design and within a European population with a wide spectrum of dietary habits.

2. Material and Methods

Study population

EPIC is a large prospective cohort study designed to investigate the relationship between diet, lifestyle, environmental factors and cancer. The rational, 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 1992-2000 in 23 centers from ten European countries (Denmark, France, Germany, Greece, the Nederland's, Italy, Norway, United Kingdom, Spain and Sweden). The ethical review boards from the International Agency for Research on Cancer (IARC) and all local participating centers approved the study, and all participants gave their informed consent.

Of the 521,324 EPIC cohort participants, we excluded prevalent cancer cases (n= 25,184), subjects 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). Therefore, the current analysis was based on 476,160 subjects among whom 3,136 incident lymphoma cases occurred.

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 – arMED

The level of adherence to the MD was assessed using the adapted relative MD (arMED) score[10], which excludes alcoholic beverages as they have been inversely associated with several lymphoma subtypes[19]. The scoring system, adapted from the original index designed by Trichopoulou *et al*.[20], has been detailed previously[12]. In brief, the arMED is a 16-point linear score that incorporates eight key dietary components: six components presumed to reflect the MD [fruit (including nuts and seeds), vegetables, legumes, fish (including seafood), olive oil and cereals] and two components consumed in low quantity in the MD (dairy products and meat). Intake of each component was calculated as a function of energy density (g/day/1000kcal) and divided into tertiles (estimated using the overall study population). A score of 0 to 2 was assigned for the first, second and third tertile of intakes for the components presumed to fit the MD, while the scoring

was inverted for the components presumed to not fit the MD (giving a lower score for higher intakes). The scoring for olive oil was adapted owing the low consumption of non-Mediterranean countries, by assigning 0 to non-consumers, 1 for subjects below the median and 2 for subjects equal or above this median (the median was calculated using the overall study population and considering only consumers). The points were summed to define the arMED score, that ranged from 0 to 16 (from the lowest to the highest adherence), and was in turn divided into three categories: low (0-5), medium(6-9) and high(10-16) as described previously[12].

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, including cancer and pathology registries, health insurance records, and active follow-up contacting participants or their next-of-kin. 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 current 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 2008 WHO classification, was used to categorize lymphoma histologic subtypes[1].

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), follicular lymphoma (FL), chronic lymphocytic leukemia (CLL) (including small lymphocytic leukemia), 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).

Statistical analysis

Cox proportional hazard models were used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) of the association between the arMED score and lymphoma risk. The arMED score was analyzed both as a continuous variable (per 1-unit increase) and as a categorical variable (low, medium and high level of adherence). In addition, Cox models were fitted with the arMED ordinal variable as continuous to test for linear trend for comparison with published literature on solid cancers. 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), educational 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). We tested for interaction by age, sex, alcohol intake and smoking 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) including alcohol in the score computation, ii) censoring participants and excluding cases with less than two years of follow-up (n=259 cases), (iii) excluding participants without complete data (n=226 cases), and (iv) restricting HL analysis to classical HL cases. Schoenfeld residuals were used to ensure that the proportional hazard assumption was met in all models. Two-sided p-values were reported with statistical significance set at $p<0.05$. All analyses were performed by using STATA statistical software, version 14 (Stata Corporation, College Station, Texas).

3. Results

During an average follow-up of 13.9 years, 3,136 lymphoma cases (2,606 NHL, 135 HL and 395 lymphoma NOS) were diagnosed. A detailed distribution of cases by lymphoma subtype and country is displayed in Table 1. As expected, the highest levels of the arMED score were found in Mediterranean regions (i.e. Greece, Spain and Italy), while the lowest scores were found in

Sweden, the Netherland's and Denmark. Baseline characteristics of the study participants according to category of the arMED score are shown in Table 2. In general, participants with a higher arMED score were more likely to be women, slightly younger, never smokers, physically inactive, and to have a higher educational level and lower alcohol intake compared to those with a low arMED score.

Table 3 shows basic and multivariable HR estimates for category of arMED score associated with lymphoma risk, overall and by subgroups. Overall, a 1-unit increase in the arMED score was associated with a 2% lower risk of lymphoma (95% CI: 0.97; 1.00, p-trend=0.03) while a statistically non-significant inverse association between a high versus low arMED score and risk of lymphoma was observed (HR: 0.91 (95% CI 0.80; 1.03), p-trend=0.12). No statistically significant associations were observed between the arMED score and HL, NHL or any NHL subtypes. However, albeit with smaller numbers of cases, the lowest HR were observed for HL ($HR_{high\ vs.\ low}$=0.64 (95% CI: 0.34; 1.19), p-trend=0.16; $HR_{1\text{-unit increase}}$=0.93 (95% CI: 0.86; 1.01), p-trend=0.07). Following restriction to classical HL (n=127), although the results were still not statistically significant, the inverse association seemed to be strengthened ($HR_{high\ vs.\ low}$= 0.57 (95% CI: 0.30; 1.09), p-trend=0.09; $HR_{1\text{-unit increase}}$=0.76 (95% CI: 0.55; 1.05), p-trend= 0.09) (*data not shown*). The results for the unclassified lymphoma (N= 395) as well as following restriction to lymphoma with known subtype classification did not modify materially the association (HR for a 1-unit increase in the arMED score: 0.98 (95% CI: 0.94; 1.03), p-value= 0.43, and 0.98 (95% CI: 0.96 to 1.00), p-value= 0.04, respectively) (*data not shown*).

No significant modifications in the association between lymphoma or its subtypes and the arMED score were observed for age, sex, and alcohol intake and smoking (Supplementary material, Table S1). Similarly, no significant differences were observed among countries (Supplementary material, Figure S1).

In sensitivity analyses, including alcohol in the scoring did not affect the estimates for most of the lymphoma subtypes, although statistically significant associations were found for HL ($HR_{1\text{-unit increase}}$=0.93 (95% CI: 0.86; 0.99), p-trend= 0.04)) and DLBCL ($HR_{1\text{-unit increase}}$=0.96 (95% CI: 0.92; 0.99), p-trend= 0.02)) (Supplementary material, Table S2). Moreover, excluding the first 2 years of follow-up and those individuals with no information on adjustment variables from the analyses did not materially alter the results (*data not shown*).

4. Discussion

This is the first prospective study to investigate the association between a Mediterranean dietary score and risk of lymphoma and its subtypes. Our findings suggest that a higher adherence to the MD is modestly associated with a lower risk of lymphoma.

Current evidence on the adherence to MD and the etiology of lymphoma is scarce. To our knowledge, only one case-control study has evaluated the association of an *a priori* MD score and lymphoma, yielding no significant association for overall cases and only reporting an inverse association for DLBCL[21]. However, those results require cautious interpretation due to the retrospective study design, small sample size (322 cases for the particular subgroup analysis), and the use of a non-validated adaptation of the arMED score which did not include olive oil, white meat or dairy products. Other studies have extracted healthy-like dietary patterns from their population using data-driven analyses[13–15], but also failed in finding patterns with all the MD features (e.g. none of them included olive oil). With the exception of the prospective study of Erber *et al.*[14] who reported an inverse association between a pattern rich in vegetables and fruits and NHL among Caucasian women, none of the other case-control studies found any associations with overall HL[15] or NHL[13]. However, given the heterogeneity in types of foods eaten within these patterns, the range and absolute amounts of food intakes and cut-offs used to define adherence, direct comparison of study results should be made with caution.

Similarly, there is a lack of consistency for associations between questionnaire-derived dietary components and lymphoma risk. In the 2007 report by the WCRF/AICR[22], the panel did not make any judgements regarding the causality of associations between specific dietary factors and lymphoid neoplasms. However, several suggestive associations were pointed out: i) vegetables, fruits, and alcoholic beverages were associated with decreased risk of lymphoma, ii) meat, total fat, and body fatness with increased risk of lymphoma, and iii) dairy products with increased risk of NHL. Although numerous studies have subsequently emerged, most of them targeted NHL patients, were mainly case-control studies and did not show consistent associations. Indeed, in the recently released third report of the WCRF/AICR, no additional information has been provided for hematological neoplasms[5]. Recent meta-analyses have shed light on this relationship: i) two meta-analyses found inverse relationships of vegetables and vegetables and fruit (combined) intake with NHL[23,24], ii) another on foods of animal origin (including red, processed and white meat, fish and seafood, dairy products and eggs) reported positive associations with red meat and dairy intake and NHL[25], iii) while cohort studies on specific micronutrients point to null

associations between supplemented vitamins A, C and E, total vitamin D intake, as well as dietary lycopene intake, and risk of NHL[26]. Overall, our results suggest that, more than specific dietary components, is the combined effect of a range of nutrients along with the putative biological interactions that take place between them that may be mediating the modest influence of adherence to the MD on lymphoma risk

In an exploratory analysis, we observed strong inverse associations with HL albeit statistically non-significant. Given the small number of HL (N= 135), we may have lacked statistical power to detect significant associations within this subgroup. Previous studies of diet and HL risk are scarcer and limited in power[6,7,15,21,27–34]. Although no consistent associations have been reported for single-food items, the first study on dietary patterns and HL provided some insight[15]. The authors found a suggestive inverse association between a diet characterized by high intake of fruit and low-fat dairy products and mixed cellularity HL. In addition, positive associations were reported between Western-like patterns (rich in meat or desserts and sweets) and specific HL entities and age-groups. Together, these and our results suggest that HL might be a lymphoma prone to be influenced by dietary patterns. Thus, further studies with prospective design and with histological subtype-specific analyses, feasible though pooling data from consortium studies, are warranted.

The original MD score included alcohol scored dichotomous variable[12]: two points were assigned for moderate consumers (5–25 g/day for women and 10–50 g/day for men) and 0 points for those above and below the sex-specific range, owing its beneficial effects if consumed in moderation. Convincing evidence suggests that alcohol increases the risk of several carcinomas (e.g. mouth, pharynx and larynx, esophagus, liver, colorectal, breast and stomach)[5] and indeed, the WCRF/AICR recommendations currently promote lowering alcohol consumption[5]. However, accumulating evidence showed a moderate inverse association between increasing alcohol intake and NHL, especially on DLCBL and FL[19]. Thus, for the current analyses, alcohol was not included in the score, and models were adjusted and further stratified by alcohol intake. In sensitivity analyses, including alcohol in the score, statistically significant associations were found for HL and DLBCL. The influence of alcohol in lymphomagenesis remains largely unknown, and further studies are needed to clarify its role and possible interaction with dietary factors.

Certain dietary features of the MD and their potentially anti-carcinogenic mechanisms make the association with lymphoma plausible from a mechanistic point of view. The abundance of plant-based foods in the MD provides a diet rich in flavonoids, carotenoids, vitamin C or E, whose

important antioxidant properties can neutralize free radicals or prevent DNA damage[22,35]. Indeed, total antioxidant intake has been inversely associated with lymphoma[36,37]. Moreover, it presents a high monounsaturated to saturated fatty acid ratio, and its believed that circulating fatty acids may influence lymphoma risk by modulating inflammation or lymphocyte membrane stability[38]. In addition, several studies have consistently linked chronic inflammation or autoimmune conditions with lymphomagenesis[3,39] and reported associations between plasma levels of cytokines, or other inflammatory markers, and lymphoma[40–42]. Recent studies are supporting the inflammatory potential of diet[43]; in particular for lymphoid neoplasms, positive associations have been recently reported between a pro-inflammatory dietary score and NHL[44]. Thus, the MD's favorable fatty acid profile, as well as a high intake of fiber, vitamins and flavonoids, may be relevant owing its properties[43].

Interestingly, for the years 2000-2002, the incidence of total lymphoid malignances, in particular HL, was higher in Southern Europe (Italy, Malta, and Spain) in comparison with other European regions[45]. We are not aware of studies that have attempted to correlate known risk factors for lymphoid neoplasms with regional variations in incidence. Further research on other dietary patterns (e.g. adherence to a Western-like or a pro-inflammatory diet) or the nutrition transition towards non-Mediterranean dietary patterns in many Mediterranean countries[46] is warranted to elucidate these incidence patterns.

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 adherence to the MD. Although our adjustment for total energy intake would partly remove some of these errors[47,48] we cannot rule out that they have affected risk estimates. 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 prediagnostic 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, we lacked data on other potential confounders (e.g. occupational exposures or pesticide use) and, despite adjusting for all known lymphoma's risk factors, residual confounding by other unmeasured or unknown exposure cannot be dismissed. In addition, given the number of comparisons performed, we cannot exclude chance findings. Moreover, despite the large number of enrolled subjects at baseline, the number of observed incident cases of some lymphoma subtype was low (e.g. 135 HL). Therefore, the study might not have sufficient power to detect significant associations within those subgroups. Finally, the arMED score has also limitations, as similar

weight is given to each component and the foods within them, assuming that they have the same effects on health. However, according to current evidence, these groupings did not include dietary components which have distinct effects on lymphoma risk. In addition, the EPIC study included participants from both Mediterranean and non-Mediterranean regions, which may have distinct dietary intakes, food sources and socio-demographic, anthropometric and lifestyle characteristics that cannot be considered when using cohort-wide tertiles to construct the score. However, several studies have found similar associations' when using study-wide or country-specific cut-offs[8,49] and no interactions were found by country in our study.

The strengths of this study include its prospective design, long follow-up and large sample size which allowed us to carry out analyses by lymphoma subentities. In addition, its multi-centric European design allowed the inclusion of a geographically diverse population, covering a wide range of dietary patterns and lifestyle habits. Finally, we assessed adherence to the MD with a widely-used score in cancer epidemiology, which directly includes olive oil intake, a key feature of this dietary pattern. Moreover, it uses tertiles of intake as cut-offs instead of the frequently used medians to give a better distribution of the subjects with different intakes.

In summary, this is the first prospective study to examine the association between the MD and lymphoma risk. Our findings suggest that an increasing arMED score, reflecting adherence to the MD was modestly inversely associated with the risk of overall lymphoma. Further studies are needed to confirm these findings.

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Supplementary material

Table S1: Association between adherence to the arMED score and risk of lymphoma, HL, NHL and mature B-cell NHL by sex, age, alcohol consumption and smoking in the EPIC study.

Table S2: Association between adherence to the arMED score including alcohol and risk of lymphoma and its subtypes in the EPIC study.

Figure S1: Association between adherence to the arMED score and risk of lymphoma, Hodgkin lymphoma and non-Hodgkin lymphoma by country in the EPIC study.

Table S1

	Lymphoma (n=3,136)		HL (n=135)		NHL[1] (n=2,606)		Mature B-cell (n=2,402)	
	HR[2] (95% CI)	P-value[3]	HR[2] (95% CI)	P-value[3]	HR[2] (95% CI)	P-value[3]	HR[2] (95% CI)	P-value[3]
Age								
<50	1.00 (0.96; 1.04)	0.93	0.93 (0.83; 1.06)	0.28	**1.01 (0.96; 1.05)**	**0.80**	1.00 (0.96; 1.05)	0.85
50-75	**0.98 (0.96; 0.99)**	**0.01**	0.94 (0.84; 1.04)	0.21	**0.98 (0.96; 1.00)**	**0.03**	**0.98 (0.96; 1.00)**	**0.05**
>75	1.19 (0.98; 1.46)	0.09	Not estimated[5]	-	1.23 (0.97; 1.57)	0.09	1.16 (0.91; 1.48)	0.23
P-value$_{int}$[4]	0.79		0.21		0.53		0.59	
Sex								
Men	0.98 (0.96; 1.01)	0.21	0.98 (0.86; 1.11)	0.72	0.98 (0.95; 1.01)	0.20	0.98 (0.95; 1.01)	0.15
Women	0.98 (0.96; 1.00)	0.08	**0.90 (0.81; 1.00)**	**0.04**	0.99 (0.96; 1.01)	0.27	0.99 (0.97; 1.01)	0.37
P-value$_{int}$[4]	0.75		0.61		0.99		0.80	
Smoking status								
Never	0.98 (0.96; 1.00)	0.11	0.95 (0.84; 1.08)	0.42	0.98 (0.95; 1.01)	0.14	0.98 (0.95; 1.01)	0.12
Former	0.99 (0.96; 1.02)	0.54	1.01 (0.87; 1.17)	0.89	0.98 (0.95; 1.02)	0.36	0.98 (0.95; 1.02)	0.34
Current	0.98 (0.94; 1.01)	0.24	**0.85 (0.74; 0.99)**	**0.03**	1.00 (0.96; 1.05)	0.86	1.01 (0.97; 1.05)	0.74
P-value$_{int}$[4]	0.15		0.41		0.86		0.90	
Alcohol intake (g/day)[5]								
Low	0.98 (0.96; 1.01)	0.20	0.94 (0.84; 1.04)	0.23	0.99 (0.96; 1.01)	0.37	0.99 (0.97; 1.02)	0.51
Moderate	**0.92 (0.86; 0.97)**	**0.004**	0.94 (0.68; 1.28)	0.68	**0.93 (0.87; 0.99)**	**0.02**	**0.92 (0.87; 0.99)**	**0.02**
High	0.99 (0.97; 1.02)	0.51	0.93 (0.81; 1.06)	0.28	0.99 (0.96; 1.02)	0.52	0.99 (0.96; 1.02)	0.46
P-value$_{int}$[4]	0.08		0.58		0.24		0.10	

HR, hazard ratio; CI, confidence interval; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; 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] NHL subtypes, excluding 37 precursor NHL and 37 individuals with NHL without B- or T-cell information.

[2]HR per 1-unit increase in the arMED; 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 fitted with the arMED continuous variable.

[4]P-value for interaction based upon the likelihood ratio (LR) test

[5]Not estimated due to small sample size (1 failure).

[6]Alcohol intake at recruitment categorized according to rMED categories for alcohol consumption: moderate (5–25 g/day for women and 10–50 g/day for men), low (below the sex-specific range) and high (above the sex-specific range).

In bold: p<0.05

Table S2

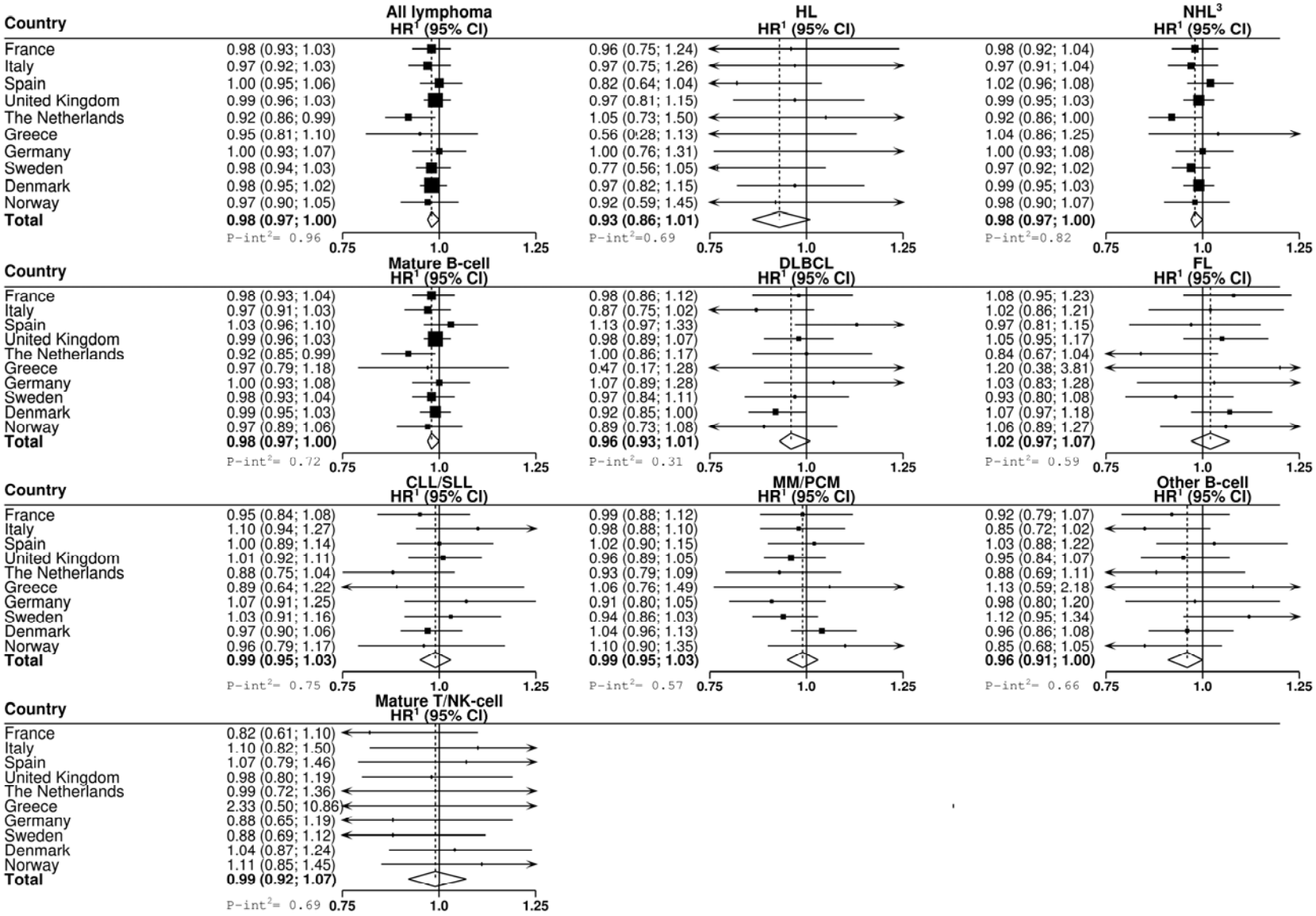
	arMED score					
	Low (0-7)	Medium (6-10)	High (11-18)	P-value trend[4]	1-unit increase	P-value[5]
Lymphoma, n	1,016	1,371	749			
HR[1] (95% CI)	Ref	0.95 (0.86; 1.03)	0.89 (0.78; 1.02)	0.09	0.98 (0.97; 1.00)	0.04
HR[2] (95% CI)	Ref	0.95 (0.87; 1.04)	0.90 (0.79; 1.03)	0.13	0.99 (0.97; 1.00)	0.06
HL, n	39	65	31			
HR[1] (95% CI)	Ref	0.84 (0.54; 1.30)	0.64 (0.34; 1.21)	0.17	0.93 (0.86; 0.99)	0.03
HR[2] (95% CI)	Ref	0.84 (0.54; 1.32)	0.64 (0.33; 1.22)	0.18	0.93 (0.86; 0.99)	0.04
NHL, n	835	1,128	643			
HR[1] (95% CI)	Ref	0.95 (0.86; 1.04)	0.92 (0.79; 1.06)	0.20	0.99 (0.97; 1.00)	0.07
HR[2] (95% CI)	Ref	0.95 (0.86; 1.05)	0.93 (0.80; 1.07)	0.27	0.99 (0.97; 1.00)	0.10
NHL subtypes[3]						
Mature T/NK-cell, n	47	54	29			
HR[1] (95% CI)	Ref	0.88 (0.57; 1.35)	1.10 (0.58; 2.09)	0.97	1.03 (0.96; 1.10)	0.48
HR[2] (95% CI)	Ref	0.88 (0.57; 1.36)	1.14 (0.60; 2.19)	0.89	1.03 (0.96; 1.11)	0.43
Mature B-cell, n	766	1,043	593			
HR[1] (95% CI)	Ref	0.95 (0.85; 1.05)	0.92 (0.79; 1.07)	0.23	0.98 (0.97; 1.00)	0.04
HR[2] (95% CI)	Ref	0.95 (0.86; 1.05)	0.93 (0.80; 1.09)	0.31	0.98 (0.97; 1.00)	0.06
DLBCL, n	147	245	96			
HR[1] (95% CI)	Ref	1.02 (0.82; 1.27)	0.80 (0.56; 1.13)	0.35	0.96 (0.92; 0.99)	0.02
HR[2] (95% CI)	Ref	1.04 (0.83; 1.29)	0.81 (0.57; 1.16)	0.43	0.96 (0.92; 0.99)	0.02
FL, n	111	154	116			
HR[1] (95% CI)	Ref	1.00 (0.78; 1.29)	1.25 (0.88; 1.78)	0.30	1.01 (0.97; 1.05)	0.62
HR[2] (95% CI)	Ref	1.00 (0.77; 1.30)	1.26 (0.88; 1.81)	0.28	1.01 (0.97; 1.05)	0.62
CLL/SLL, n	182	213	142			
HR[1] (95% CI)	Ref	1.04 (0.84; 1.30)	1.00 (0.73; 1.38)	0.89	0.99 (0.96; 1.03)	0.78
HR[2] (95% CI)	Ref	1.03 (0.83; 1.28)	0.99 (0.71; 1.37)	0.98	0.99 (0.96; 1.03)	0.66
MM/PCN, n	226	283	167			
HR[1] (95% CI)	Ref	0.81 (0.66; 0.98)	0.85 (0.64; 1.14)	0.14	0.99 (0.96; 1.02)	0.57
HR[2] (95% CI)	Ref	0.87 (0.65; 1.17)	0.87 (0.65; 1.17)	0.20	1.00 (0.96; 1.03)	0.82
Other B-cell ,n	100	148	72			
HR[1] (95% CI)	Ref	0.90 (0.68; 1.18)	0.76 (0.50; 1.14)	0.19	0.96 (0.92; 1.00)	0.06
HR[2] (95% CI)	Ref	0.90 (0.68; 1.20)	0.76 (0.50; 1.16)	0.22	0.96 (0.91; 1.00)	0.06

HR, hazard ratio; CI, confidence interval; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; 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 NHL subtype is unknown or does not fall within the more common subtypes).

[1]HR per 1-unit increase in the arMED; 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]NHL subtypes, excluding 37 precursor NHL and 37 individuals with NHL without B- or T-cell information.
[4]P-value of Cox proportional model fitted with the arMED continuous variable.
[5]P-value for interaction based upon the likelihood ratio (LR) test
In bold: P-value<0.05

Figure S1



HR, hazard ratio; CI, confidence interval; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; 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 NHL subtype is unknown or does not fall within the more common subtypes).

[1]HR per 1-unit increase in the arMED; 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.
[2]P-int: P-value for interaction based upon the likelihood ratio test. [3]NHL subtypes, excluding 37 precursor NHL and 37 individuals with NHL without B- or T-cell information

Table and figure legend

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

Table 2. Baseline characteristics of participants in the EPIC study according to adherence to the arMED score.

Table 3. Association between adherence to the arMED score and risk of lymphoma and its subtypes in the EPIC study.

Table 1

				Lymphoma subtypes			NHL subtypes[1]		Mature B-cell subtypes					
	Total cohort	Person-years	Overall	NHL	HL	NOS	Mature B-cell	Mature T /NK-cell	DLBCL	FL	CLL/SLL	MM/PCN	Other B-cell	arMED mean (SD)
Denmark	55,014	815,096.8	631	538	29	64	506	23	121	78	118	123	66	5.9 (2.4)
France	67,403	869,362.5	228	216	11	1	205	8	40	44	44	45	32	8.5 (2.4)
Germany	48,557	504,479.0	231	190	13	28	170	12	30	20	39	55	26	6.4 (2.1)
Greece	26,048	281,283.6	62	44	3	15	38	2	3	3	13	15	4	11.8 (1.7)
Italy	44,545	630,951.3	298	241	15	42	218	11	38	33	44	73	30	10.1 (2.1)
Norway	33,975	452,171.1	163	147	5	11	129	14	26	31	26	24	22	7.7 (2.0)
Spain	39,989	637,947.4	241	211	14	16	194	10	35	27	51	51	30	10.4 (2.2)
Sweden	48,674	801,130.2	517	381	13	123	344	20	57	48	74	132	33	4.6 (2.1)
The Netherlands	36,539	524,670.7	201	186	7	8	172	10	43	26	41	43	19	5.6 (2.1)
United Kingdom	75,416	1,122,765	564	452	25	87	426	20	95	71	87	115	58	8.6 (2.5)
Total	476,160	6,639,857.5	3,136	2,606	135	395	2,402	130	488	381	537	676	320	7.8 (3.0)

NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; NOS, not otherwise specified; DLBCL, diffuse large B-cell lymphoma; 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); arMED, adapted relative Mediterranean diet; SD, standard deviation.

[1]There were 37 precursor NHL and 37 individuals with NHL without B- or T-cell information.

Table 2

	Total cohort	arMED score		
		Low (0-5) (mean 3.9)	Medium (6-9) (mean 7.5)	High (10-16) (mean 11.4)
Total cohort, n	476,160	116,128	214,649	145,383
Sex (%)				
Men	29.9	45.1	25.0	24.9
Women	70.1	54.9	75.0	75.1
Age at recruitment (mean [SD], years)	51.2 (9.9)	52.0 (10.0)	51.4 (9.5)	50.3 (10.4)
Energy intake (mean [SD], kcal/day)	2,075.1 (619.2)	2,178.5 (648.0)	2,039.8 (604.1)	2,044.6 (608.6)
Alcohol intake (median [25th-75th percentile], g/day)	5.3 (0.9; 14.9)	6.2 (1.4; 17.0)	5.6 (1.1; 15.2)	4.2 (0.4; 13.0)
BMI (mean [SD], kg/m^2)	25.4 (4.3)	25.6 (4.1)	25.1 (4.1)	25.8 (4.5)
Height (mean [SD], cm)	166.0 (8.9)	169.6 (9.2)	165.9 (8.5)	163.2 (8.4)
Smoking status (%)				
Never	49.0	41.5	49.2	54.5
Former	26.6	27.7	27.7	24.3
Current	22.4	29.6	20.8	19.0
Unknown	2.0	1.24	2.3	2.3
Physical activity (%)				
Inactive	21.0	17.6	18.1	27.8
Moderately inactive	32.9	31.7	33.6	32.9
Moderately active	26.4	25.2	28.4	24.3
Active	17.9	22.3	17.8	14.5
Unknown	1.85	3.2	2.0	0.5
Educational level (%)				
None	4.4	0.5	2.4	10.5
Primary school	25.6	30.2	22.4	26.6
Technical/professional school	22.2	30.5	23.8	13.3
Secondary school	20.4	17.1	21.9	20.9
University	23.8	20.0	25.2	24.8
Unknown	3.6	1.7	4.3	3.9

BMI: body mass index; SD: standard deviation; arMED: adapted relative Mediterranean dietary score.

Table 3

	arMED score					
	Low	Medium	High	P-value trend[4]	1-unit increase	P-value[5]
Lymphoma, n	1,016	1,371	749			
HR[1] (95% CI)	Ref	0.92 (0.84; 1.01)	0.90 (0.79; 1.02)	0.08	0.98 (0.97; 1.00)	0.02
HR[2] (95% CI)	Ref	0.93 (0.85; 1.02)	0.91 (0.80; 1.03)	0.12	0.98 (0.97; 1.00)	0.03
HL, n	39	65	31			
HR[1] (95% CI)	Ref	0.96 (0.61; 1.51)	0.64 (0.34; 1.18)	0.15	0.93 (0.86; 1.00)	0.07
HR[2] (95% CI)	Ref	0.97 (0.61; 1.53)	0.64 (0.34; 1.19)	0.16	0.93 (0.86; 1.01)	0.07
NHL, n	835	1,128	643			
HR[1] (95% CI)	Ref	0.90 (0.81; 0.99)	0.93 (0.81; 1.06)	0.23	0.98 (0.97; 1.00)	0.06
HR[2] (95% CI)	Ref	0.90 (0.82; 1.00)	0.94 (0.82; 1.08)	0.31	0.98 (0.97; 1.00)	0.10
NHL subtypes[3]						
Mature T/ NK-cell, n	47	54	29			
HR[1] (95% CI)	Ref	0.73 (0.47; 1.13)	0.76 (0.42; 1.40)	0.31	0.99 (0.91; 1.07)	0.72
HR[2] (95% CI)	Ref	0.72 (0.47; 1.14)	0.78 (0.42; 1.44)	0.35	0.99 (0.91; 1.07)	0.80
Mature B-cell, n	766	1,043	593			
HR[1] (95% CI)	Ref	0.91 (0.82; 1.01)	0.94 (0.82; 1.08)	0.31	0.98 (0.97; 1.00)	0.08
HR[2] (95% CI)	Ref	0.91 (0.82; 1.01)	0.95 (0.82; 1.10)	0.40	0.98 (0.97; 1.00)	0.11
DLBCL, n	147	245	96			
HR[1] (95% CI)	Ref	1.09 (0.87; 1.37)	0.83 (0.60; 1.14)	0.35	0.96 (0.92; 1.00)	0.07
HR[2] (95% CI)	Ref	1.10 (0.88; 1.39)	0.84 (0.61; 1.17)	0.43	0.96 (0.93;1.01)	0.09
FL, n	111	154	116			
HR[1] (95% CI)	Ref	0.84 (0.64; 1.11)	1.25 (0.90; 1.76)	0.19	1.02 (0.97; 1.07)	0.45
HR[2] (95% CI)	Ref	0.84 (0.64; 1.11)	1.27 (0.90; 1.79)	0.17	1.02 (0.97; 1.07)	0.43
CLL/SLL, n	182	213	142			
HR[1] (95% CI)	Ref	0.80 (0.64; 0.99)	0.95 (0.70; 1.27)	0.54	0.99 (0.96; 1.03)	0.75
HR[2] (95% CI)	Ref	0.78 (0.63; 0.98)	0.92 (0.68; 1.25)	0.45	0.99 (0.95; 1.03)	0.64
MM/PCN, n	226	283	167			
HR[1] (95% CI)	Ref	0.93 (0.77; 1.14)	0.98 (0.75; 1.28)	0.82	0.98 (0.95; 1.02)	0.40
HR[2] (95% CI)	Ref	0.95 (0.78; 1.16)	1.01 (0.77; 1.34)	0.98	0.99 (0.95; 1.03)	0.55
Other B-cell ,n	100	148	72			
HR[1] (95% CI)	Ref	0.85 (0.64; 1.13)	0.67 (0.45; 1.00)	0.05	0.96 (0.91; 1.00)	0.08
HR[2] (95% CI)	Ref	0.85 (0.64; 1.14)	0.68 (0.46; 1.01)	0.06	0.96 (0.91; 1.00)	0.09

arMED: adapted relative Mediterranean dietary score; n, number of cases; HR, hazard ratio; CI, confidence interval; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; 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 NHL subtype is unknown or does not fall within the more common subtypes); arMED, adapted relative Mediterranean diet; SD, standard deviation.

[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, educational level, height, physical activity, smoking status, and alcohol intake.

[3] NHL subtypes, excluding 37 precursor NHL and 37 individuals with NHL without B- or T-cell information.
[4] P-value of Cox proportional model fitted with the arMED ordinal variable as continuous to test for lineal trend.
[5] P-value of Cox proportional model fitted with the arMED continuous variable.
In bold: P-value<0.05