Healthy lifestyle and the risk of lymphoma in the EPIC study

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Abbreviations
HLI: healthy lifestyle index
CI: confidence interval
EPIC: European Prospective Investigation into Cancer and Nutrition
NHL: non-Hodgkin lymphoma
HL: Hodgkin lymphoma
BCL: mature B-cell lymphoma
MT/NK: mature T and natural killer-cell lymphoma
DLBCL: diffuse large B-cell lymphoma
FL: follicular lymphoma
CLL/SLL: chronic lymphocytic leukemia and small lymphocytic leukemia
PCN/MM: plasma cell neoplasm and multiple myeloma
HR: hazard ratio

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Novelty and impact statements (Words=75)

The role of lifestyle factors in the etiology of lymphoma remains unclear and most epidemiological studies faced limited statistical power to evaluate lymphoma subtypes in prospective investigations. In this study, the relationship between a score combining lifestyle exposures and the occurrence of lymphoma subtypes was examined within a large European prospective cohort. Although an inverse association was observed with the risk of Hodgkin lymphoma, findings indicated a limited role of lifestyle factors in lymphoma etiology.

Abstract (Words = 248)

Limited evidence exists on the role of modifiable lifestyle factors on the risk of lymphoma. In this work, the associations between adherence to healthy lifestyles and risks of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) were evaluated in a large-scale European prospective cohort. Within the European Prospective Investigation into Cancer and Nutrition (EPIC), 2,999 incident lymphoma cases (132 HL and 2,746 NHL) were diagnosed among 453,808 participants after 15 years (median) of follow-up. The healthy lifestyle index (HLI) score combined information on smoking, alcohol intake, diet, physical activity and BMI, with large values of HLI expressing adherence to healthy behavior. Cox proportional hazards models were used to estimate lymphoma hazard ratios (HR) and 95% confidence interval (CI). Sensitivity analyses were conducted by excluding, in turn, each lifestyle factor from the HLI score. The HLI was inversely associated with HL, with HR for a 1-standard deviation (SD) increment in the score equal to 0.78 (95%CI: 0.66, 0.94). Sensitivity analyses showed that the association was mainly driven by smoking and marginally by diet. NHL risk was not associated with the HLI, with HRs for a 1-SD increment equal to 0.99 (0.95, 1.03), with no evidence for heterogeneity in the association across NHL subtypes. In the EPIC study, adherence to healthy lifestyles was not associated with overall lymphoma or NHL risk, while an inverse association was observed for HL, although this was largely attributable to smoking. These findings suggest a limited role of lifestyle factors in the etiology of lymphoma subtypes.

Introduction (Words = 2,481)

Lymphoma comprises a heterogeneous group of malignancies occurring in the lymphatic system, traditionally grouped as Hodgkin (HL) and non-Hodgkin lymphoma (NHL),[1] which accounts for about 3.2% of cancers worldwide.[2] During recent decades, lymphomas incidence rates increased with relatively higher rates in high-income countries[2] and significant disparities among ethnic groups,[3] suggesting an influence of lifestyle factors in lymphomagenesis that are more prevalent in the Western world.

Although the roles of lifestyle factors have been extensively investigated in association with solid neoplasms, evidence on lymphoma risk remains unclear.[4] Obesity and alcohol consumption have been most consistently associated with lymphoma, with positive[5] and inverse[6] relationships, respectively. However, most studies, predominantly case-control, faced differential recall bias for the assessment of lifestyle habits and sample size limitations for the investigation of lymphoma subtypes. Additionally, lifestyle factors were often evaluated independently in etiological models.

In this study, a set of modifiable exposures, including smoking, alcohol intake, dietary habits, body mass index (BMI), and physical activity were combined into the Healthy Lifestyle Index (HLI) to reflect adherence to healthy habits. The HLI was previously related to the risks of site-specific and overall cancers in prospective studies.[7] In this analysis, associations between the HLI and lymphoma risks were examined within the EPIC study. The contributing role of each component of the HLI to lymphoma risk was also investigated.

Methods

Study population. EPIC is a multicenter prospective study designed to investigate the etiology of cancer in relation to diet and lifestyle factors. From 1992 to 2000, a total of 521,324 participants (70% women, 35–70 years of age at baseline) were recruited in 10 European countries, mostly from the general population, as explained previously.[8] In France, Norway, Utrecht and Naples, only women were recruited. Approval was obtained from IARC and participating institutions' ethical review boards and participants provided informed consent before completing questionnaires at baseline.

Ascertainment of outcome. Cancer cases were identified during follow-up based on population cancer registries in Denmark, Italy, Netherlands, Spain, Sweden, Norway and the United Kingdom, and on a combination of methods, including health insurance records, cancer and pathology registries, and active follow-up of EPIC participants and their next of kin in France,

Naples, Germany, and Greece. Clinical and morphological data were standardized using a common protocol across centers.[8] Mortality data were collected from cancer or mortality registries at the regional or national level.

The most recent vital status and cancer diagnosis update was used. Vital status was known for 98.4% of all EPIC subjects while 1.6% of participants had emigrated, withdrawn or were lost to follow-up. The follow-up period ended between June 2008 and December 2012 depending on the recruitment centers.[7]

Diagnoses of primary incident lymphoma cases were classified based on the International Classification of Diseases Oncology, 3rd edition (ICD-O-3), and grouped according to recommendations of the InterLymph Pathology Working Group,[1] as: Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL) and lymphoma not otherwise specified (NOS); within NHL as: mature B-cell lymphoma (BCL), mature T and natural killer-cell lymphoma (MT/NK) and other NHL; among BCL as: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), chronic lymphocytic leukemia and small lymphocytic leukemia (CLL/SLL), multiple myeloma and plasma cell neoplasm (MM/PCN) and other BCL, as detailed in **Table 1**.

Exposure assessment. Habitual diet, including alcohol intake, during the year preceding recruitment was assessed at recruitment using validated center-specific self-reported dietary questionnaires.[8] Data on anthropometry (self-reported in France and the UK Oxford center), physical activity, smoking habits, and prevalent chronic conditions were collected using lifestyle questionnaires.[8]

A diet score was built from the combination of six dietary factors reflecting diet quality,[7] i.e. cereal fibers, red and processed meat, the ratio of polyunsaturated to saturated fatty acids, margarine (to express industrially produced trans-fats), glycemic load, and fruits and vegetables. For each dietary factor, country-specific residuals were computed in models with total energy intake, grouped into country-specific deciles and scored from 0 to 9 with 0 being the least healthy (i.e. high intake of red meat/processed meat, margarine, and glycaemic load, and low intake of fruits and vegetables, cereal fibres, and ratio of polyunsaturated to saturated fatty acids). Individual scores were summed up and categorized into quintiles.

Definition of HLI. Scores of 0 to 4 were assigned to each individual variable category attributing larger values to the healthier behaviours for smoking (current smoking >15 cigarettes/day=0, current smoking ≤15 cigarettes/day=1, ex-smokers quit≤10-years=2, ex-smokers quit>10 years=3, never smokers=4), alcohol consumption (in g/day) at recruitment (>48=0, 24–47.9=1, 12–23.9=2, 6–11.9=3, and <6 =4), diet score (1st quintile=0

to the 5th quintile=4), physical activity index (inactive=1, moderately inactive=2, moderately active=3, active=4), and body mass index at recruitment (BMI, kg/m^2: >30=0, 26–29.9=1, <22=2, 24–25.9=3, 22–23.9=4). The final score was the arithmetic sum of the scores for each lifestyle factor and ranged from 1 to 20.

Statistical analysis.

The association between the HLI and the risk of lymphoma was evaluated using multivariable Cox proportional hazards models, with age as the primary time variable, and Breslow's method to handle ties. The time at study entry was the age at recruitment, while the exit time was defined as the age at cancer diagnosis, death, loss to, or end of follow-up, whichever occurred first. All models were stratified by country,[9] age at recruitment in 1-year categories and sex.

The HLI was modelled as a continuous variable to compute HR estimates for a one-standard deviation (SD) corresponding to approximately 3 units in the score, and in quartiles using the second quartile as reference to avoid extreme comparisons within the HLI range. Models were systematically adjusted for education level (no degree/primary school, secondary/technical or professional school, longer education including university degree, unknown (4%)), height (cm, continuous), and energy intake from non-alcohol sources (kcal/day, continuous).

Overall tests for statistical significance of HRs were determined by comparing Wald-test statistics to a χ^2 distribution with three degrees of freedom (dof) for HLI in categories (p_{Wald}) and one dof in continuous (p_{trend}). The assumption of proportional hazards (PH) was evaluated through the Schoenfeld's residuals.[10]

Potential departure from linearity in the association between HLI and HL risk was evaluated using restricted cubic splines[11] and comparing the difference in log-likelihood of models with and without non-linear terms to a χ^2 distribution with two degrees of freedom.

Sensitivity analyses were carried out by excluding, in turn, each factor from the HLI scores to identify factors mostly driving associations with each lymphoma subtype. The excluded component was used as a confounder in the model. Relationships between the HLI and lymphoma risks (HL and NHL) were examined by, in turn, sex, European region (North: Denmark, Norway, Sweden; Central: United Kingdom, The Netherlands, Germany; South: France, Greece, Italy, and Spain), and age at recruitment (<50, 50–60, ≥60 years old). Heterogeneity was evaluated by comparing the difference in log-likelihood of models with and without interaction terms between the HLI (continuous) and, in turn, sex, European region and age categories, to a χ^2 distribution with dof equal to the total number of interaction terms minus one. Heterogeneity of associations across BCL subtypes was evaluated through data-

augmentation by comparing the difference in log-likelihood of models with and without an interaction term between the HLI and an indicator variable for BCL subtypes to a χ^2 distribution with four dof.[12] To address potential reverse causation, analyses were carried out excluding the first 2 and 5 years of follow-up.

Two-sided p-values were determined with nominal statistical significance set to 5%. Analyses were performed using Stata version 14.[13]

Data availability. Information to access EPIC data and/or biospecimens can be found at http://epic.iarc.fr/access/gain_access.php.

Results

Study participants without lifestyle or dietary information (n=6,902), with a ratio of estimated energy intake to energy requirement in the top or bottom 1% (n=10,241), with self-reported prevalent cancer (n=24,221), with missing follow-up information (n=3,800) and with missing smoking status (n=15,685) or physical activity (n=8,824) were excluded. From a total of 453,808 participants followed-up over 15 years (median), with a total of 6,328,639 person-years, 2,999 incident lymphoma cases were diagnosed, including 2,746 NHL, 132 HL and 121 lymphomas NOS (**Table 1)**. The HLI components and the confounding variables are described in **Table 2**. HLI was positively related to level of education and showed higher values in women than men.

No association was observed between the HLI and the overall risk of lymphoma (**Table 3**). However, a 1-SD increase of HLI was inversely associated with HL risk (HR=0.78, 95%CI: 0.66, 0.94; p_{trend}= 7.3e-03). The HRs for HL risk comparing the first, third and fourth quartile to the second quartile were 1.21 (0.78, 1.86), 0.64 (0.37, 1.09), and 0.64 (0.37, 1.10), respectively, with a significant trend across categories (p_{Wald}=0.03). The HLI was not associated with the risk of the major NHL subtypes (**Table 3**). The PH assumption was satisfied in each lymphoma subtype model.

The HLI and HL risk dose-response relationship using restricted cubic splines presented limited evidence of departure from linearity ($p_{non\text{-}linearity}$= 0.42) **(Online Supplementary Figure 1)**.

Sensitivity analyses indicated that exclusion of smoking or diet from the HLI resulted in HL HRs for a 1-SD increase equal to 0.88 (95%CI: 0.71,1.10; p_{trend}=0.27) and 0.85 (0.69,1.04;

p_{trend}=0.12), respectively (**Online Supplementary Table 1)**. HRs for the other NHL subtypes were not altered after exclusion of, in turn, each lifestyle factors of the HLI.

The associations between the HLI and lymphoma risk did not show evidence of heterogeneity by sex, European region and age at recruitment (results not shown). No evidence for heterogeneity was found across BCL subtypes ($p_{heterogeneity}$=0.20). Exclusion of the first 2 and 5 years of follow-up did not materially alter HR estimates (**Online Supplementary Table 2**).

Discussion

In a large European prospective study, a score combining five lifestyle factors was not associated with the risk of NHL. An inverse relationship was observed for HL, where smoking and, to a lesser extent, diet were the main drivers of the association.

This study is one of the first attempts to investigate the risk of lymphoma with respect to modifiable lifestyle factors combined into a score. Within the NIH-AARP study, a score based on the American Cancer Society recommendations including physical activity, diet, BMI, alcohol, but not smoking, yielded an inverse association between adherence to recommendations and HL risk. A 43% (95%CI: 2%,67%) lower risk of HL was observed when comparing the healthiest with the least healthy score category in an analysis including 113 HL cases, suggesting that lifestyle factors other than smoking may affect HL etiology, while no association was observed with NHL risk, consistently with findings in our study.[14]

Smoking has been consistently positively associated with HL risk,[15] with chronic exposure to cigarette smoking believed to promote and support lymphogenic microenvironment and affect immune cells through the impairment of T cells, natural killer cells, B cells and macrophages.[16] In our work, a comprehensive evaluation of the association between HLI and HL was undertaken via sensitivity analyses where each component of the lifestyle score was, in turn, removed from the HLI. Exclusion of smoking from HLI resulted in a null association suggesting that smoking was largely driving the association between lifestyle factors and HL risk.

Although diet has been inconsistently related to HL,[17] recent EPIC studies showed that dietary patterns reflecting Mediterranean and anti-inflammatory potential of diet were inversely associated with HL risk.[18,19] In our sensitivity analysis a null association was consistently observed after the exclusion of diet from the HLI score, suggesting that diet could be involved in the HLI-HL relationship. Plausible biological mechanisms relating HL pathology to diet may

involve inflammation pathways, possibly reflecting, among other factors, a diet rich in saturated fat, refined grains, red and processed meat, and high glycemic load.[17,20]

Cumulative evidence points towards a positive relationship between obesity and HL[21] which could be the consequence of an alteration of the immune response and stimulate low-grade chronic inflammation in adipose tissue.[5] Alcohol intake has been repeatedly inversely associated with risks of HL and NHL, particularly with DLBCL, CLL and FL subtypes,[6] a result that was partially attributed to reverse causation, as early symptoms of lymphomas may lead individuals to either quit or reduce their alcohol intake.[22]

Current evidence suggests a role of lifestyle factors with respect to several NHL subtype risks. While smoking has been positively related to T-cell NHL,[15] obesity has been related to an increase in diffuse large B-cell lymphoma (DLBC) and multiple myeloma (MM) risks,[5] and a pro-inflammatory diet was positively associated with mature B-cell NHL.[18] In this study, HLI was not associated with the risk of NHL, either overall or within any of the NHL subtypes. Although HLI was inversely associated with the group of 'other BCL' (HR for a 1-SD increase in the HLI: 0.88; 95%CI: 0.79,1.00; p_{trend}=0.04), the associations of HLI across BCL subtypes was not heterogeneous ($p_{heterogeneity}$=0.20). Despite the large size of the EPIC cohort, our study was possibly underpowered to detect likely weak associations of lifestyle habits with respect to lymphoma subtypes. Our results were not altered in sensitivity analyses that excluded, in turn, each lifestyle factor from the score.

The strength of the current study relies on its prospective multi-country design, which included study populations with heterogeneous lifestyle habits. Among the limitations, we note that EPIC participants represent a healthy proportion of the general population and that risk estimates in our study were likely attenuated. In addition, our analyses did not account for potential changes in lifestyle habits during follow-up, potentially introducing bias in association estimates. These changes may have been the result of incident morbid conditions in ageing study population. Reverse causation could have biased some of our findings, by inducing changes of lifestyle behaviors before recruitment as a result of early symptoms. To partially address this, associations were minimally affected after exclusion of the first two and five years of follow-up. Furthermore, as pathological techniques for lymphoma ascertainment have developed continuously over the last decades, some of the cases of lymphoma subtypes may have been misclassified or simply missed. However, the most recent recommendations for lymphoma ascertainment were used in our study.[1,23] Education was used as a proxy for socio-economic status in the adjustment of the models, which may introduce residual confounding.

Furthermore, the HLI score considered a selected list of lifestyle factors, each of which was given an equal weight. Information on occupation, pesticide exposure, history of participants' infectious diseases (e.g. Human Immunodeficiency Virus, Epstein-Barr virus, and hepatitis viruses), which are known risk factors of lymphoma,[24,25] would provide more informative insights of lymphoma etiology. However, information on these factors was available for a limited proportion of the EPIC cohort.

In summary, in a large prospective study of European adults, adherence to a combination of healthy lifestyle habits was not associated with the risk of NHL and was inversely related to the risk of HL, with smoking largely driving this association. These findings suggest a limited role of lifestyle factors in the etiology of lymphoma subtypes. However, the HLI accounts for five lifestyle habits, and other environmental factors like pesticides and occupational exposures might be relevant to lymphoma etiology.

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Conflict of interest

None to declare.

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Table 1. Country-specific distribution of study participants, lymphoma cases and the Healthy Lifestyle Index (HLI) in the EPIC cohort.

				Lymphoma subgroups[2]		NHL subgroups[2]		BCL subgroups[2]				
	Participants	PY	FUP[1]	Overall	**NHL**	**HL**	**BCL**	**MT/NK**	**DLBCL**	**FL**	**CLL /SLL**	**MM /PCN**	HLI[3]
Denmark	53,577	794,546	16	613	569	28	493	23	119	74	115	122	11 (9-14)
France	64,086	829,048	15	219	207	11	196	8	39	41	43	42	13 (11-15)
Germany	48,002	498,396	12	227	211	13	168	11	29	20	39	55	12 (10-14)
Greece	24,687	266,336	11	60	56	3	36	2	2	3	12	15	11 (9-13)
Italy	44,274	627,018	15	296	272	15	216	11	37	32	44	73	11 (9-13)
Norway	29,689	395,178	14	146	141	5	115	14	22	27	23	23	13 (12-15)
Spain	39,855	635,751	17	239	220	14	192	10	33	27	51	51	12 (10-14)
Sweden	47,536	782,458	18	504	436	13	333	20	56	47	72	128	12 (10-14)
The Netherlands	30,555	430,017	15	167	160	6	143	8	37	24	29	38	13 (11-15)
United Kingdom	71,547	1,069,891	16	528	474	24	398	18	87	68	81	106	13 (11-15)
Total	453,808	6,328,639	15	2,999	2,746	132	2,290	125	461	363	509	653	12 (10-14)

Abbreviations: PY, person-years; FUP, follow-up (years); HLI, healthy lifestyle index; NL, The Netherlands; PY, person-years; UK: United Kingdoms; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; BCL, mature B-cell lymphoma; MT/NK, Mature T and natural killer-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia, small lymphocytic leukemia and prolymphocytic lymphocytic leukemia ; MM/PCN, plasma cell neoplasm and multiple myeloma.

[1] Median values;

[2] The groups of overall number of lymphoma, NHL and BCL also included lymphomas not otherwise specified (n=121), other NHL subtypes (n=331) and other BCL subtypes (n=304), respectively;

[3] Means (25^{th}-75^{th} percentiles).

Table 2. Baseline characteristics[1] of the EPIC participants by quartiles of Healthy Lifestyle Index (HLI).

	Total cohort	HLI			
		Q1 [1 - 10]	Q2 [11 - 12]	Q3 [13 - 14]	Q4 [15 - 20]
Total participants (n)	453,808	129,429	111,358	110,730	102,291
Lymphoma cases (n)	2,999	937	734	718	610
Index components					
Smoking (% never)	45	15	40	56	74
Alcohol intake (g/day)	5 (1 - 15)	13 (3 - 30)	6 (1 - 15)	4 (1 - 11)	3 (0 - 7)
BMI (kg/m²)	25 (22 - 28)	27 (24 - 30)	26 (22 - 28)	24 (22 - 27)	23 (22 - 25)
Diet score (units)	27 (23 - 32)	23 (20 - 27)	26 (22 - 30)	28 (24 - 33)	32 (28 - 36)
Physical activity (% active)	18	9	14	19	34
Covariates					
Sex (% women)	70	56	71	77	80
Age at recruitment (years)	52 (45 - 58)	52 (46 - 59)	52 (46 - 59)	51 (45 - 58)	50 (44 - 57)
Energy intake from food (kcal/day)	1,921 (1,572 - 2,339)	1,964 (1,597 - 2,401)	1,918 (1,568 - 2,337)	1,901 (1,559 - 2,308)	1,896 (1,565 - 2,296)
Height (cm)	165 (160 - 172)	167 (160 - 174)	165 (159 - 171)	165 (159 - 171)	165 (160 - 171)
Educational level (% higher education)	24	20	22	25	30

[1] Medians (25^{th} - 75^{th} percentiles) are presented for continuous variables, percentages for categorical variables.

Table 3. Hazard ratio estimates[1] for associations between the Healthy Lifestyle Index (HLI) (in quartiles and in continuous for a 1-SD increase[2]) and risks of lymphoma subtypes in the EPIC study.

	HLI						
	Q1 [1 - 10]	Q2 [11 - 12]	Q3 [13 - 14]	Q4 [15 - 20]	p_{Wald}[3]	1-SD increase	p_{trend}[3]
All lymphomas (n=2,999)							
n	937	734	718	610			
HR (95% CI)	1.04 (0.94 - 1.14)	1.00 (Ref)	1.02 (0.92 - 1.13)	0.97 (0.87 - 1.08)	0.68	0.98 (0.94 - 1.01)	0.23
HL (n=132)							
n	53	36	22	21			
HR (95% CI)	1.21 (0.78 - 1.86)	1.00 (Ref)	0.64 (0.37 - 1.09)	0.64 (0.37 - 1.10)	0.03	0.78 (0.66 - 0.94)	7.3E-03
NHL (n=2,746)							
n	846	669	668	563			
HR (95% CI)	1.02 (0.92 - 1.14)	1.00 (Ref)	1.04 (0.93 - 1.16)	0.98 (0.88 - 1.10)	0.78	0.99 (0.95 - 1.03)	0.50
MT/NK (n=125)							
n	42	25	24	34			
HR (95% CI)	1.77 (0.62 - 5.01)	1.00 (Ref)	0.75 (0.49 - 1.14)	1.44 (0.85 - 2.44)	0.29	1.04 (0.86 - 1.26)	0.68
BCL (n=2,290)							
n	692	564	565	469			
HR (95% CI)	1.00 (0.89 - 1.11)	1.00 (Ref)	1.04 (0.93 - 1.17)	0.97 (0.85 - 1.09)	0.69	0.99 (0.95 - 1.04)	0.81
DLBCL (n=461)							
n	140	117	103	101			
HR (95% CI)	0.98 (0.76 - 1.25)	1.00 (Ref)	0.91 (0.7 - 1.19)	0.98 (0.75 - 1.28)	0.91	0.99 (0.90 - 1.09)	0.84
FL (n=363)							
n	88	92	97	86			
HR (95% CI)	0.82 (0.61 - 1.10)	1.00 (Ref)	1.04 (0.78 - 1.38)	0.98 (0.73 - 1.32)	0.44	1.04 (0.93 - 1.16)	0.49
CLL/SLL (n=509)							
n	171	100	127	111			
HR (95% CI)	1.33 (1.04 - 1.71)	1.00 (Ref)	1.35 (1.04 - 1.75)	1.34 (1.02 - 1.77)	0.08	1.05 (0.96 - 1.15)	0.28
MM/PCN (n=653)							
n	190	169	179	115			
HR (95% CI)	0.91 (0.74 - 1.13)	1.00 (Ref)	1.12 (0.91 - 1.38)	0.83 (0.65 - 1.05)	0.06	0.99 (0.91 - 1.07)	0.73
Other BCL[4] (n=304)							
n	103	86	59	56			
HR (95% CI)	0.96 (0.72 - 1.29)	1.00 (Ref)	0.71 (0.51 - 0.99)	0.75 (0.53 - 1.06)	0.12	0.88 (0.79 - 1.00)	0.04

Abbreviations: HLI, Healthy Lifestyle Index; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; MT/NK, Mature T and natural killer-cell lymphoma; BCL, mature B-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia, small lymphocytic leukemia and prolymphocytic lymphocytic leukemia ; MM/PCN, plasma cell neoplasm and multiple myeloma.

[1] Models were adjusted for education level, height, and non-alcohol energy intakes, and stratified by country, age in 1-year category, and sex;

[2] One standard deviation corresponded to 3 units in the HLI score;

[3] P-values were determined using a Wald test for overall significance, according to a χ^2 distribution with three degrees of freedom for evaluation by quartiles, and one degree of freedom for evaluation in continuous.

[4] Other BCL includes Burkitt lymphoma, hairy cell leukemia, lymphoplasmacytic lymphoma, Mantle cell lymphoma, marginal zone lymphoma, primary effusion lymphoma and prolymphocytic leukemia subtypes.

Healthy lifestyle and the risk of lymphoma in the EPIC study

(IJC-19-2849)

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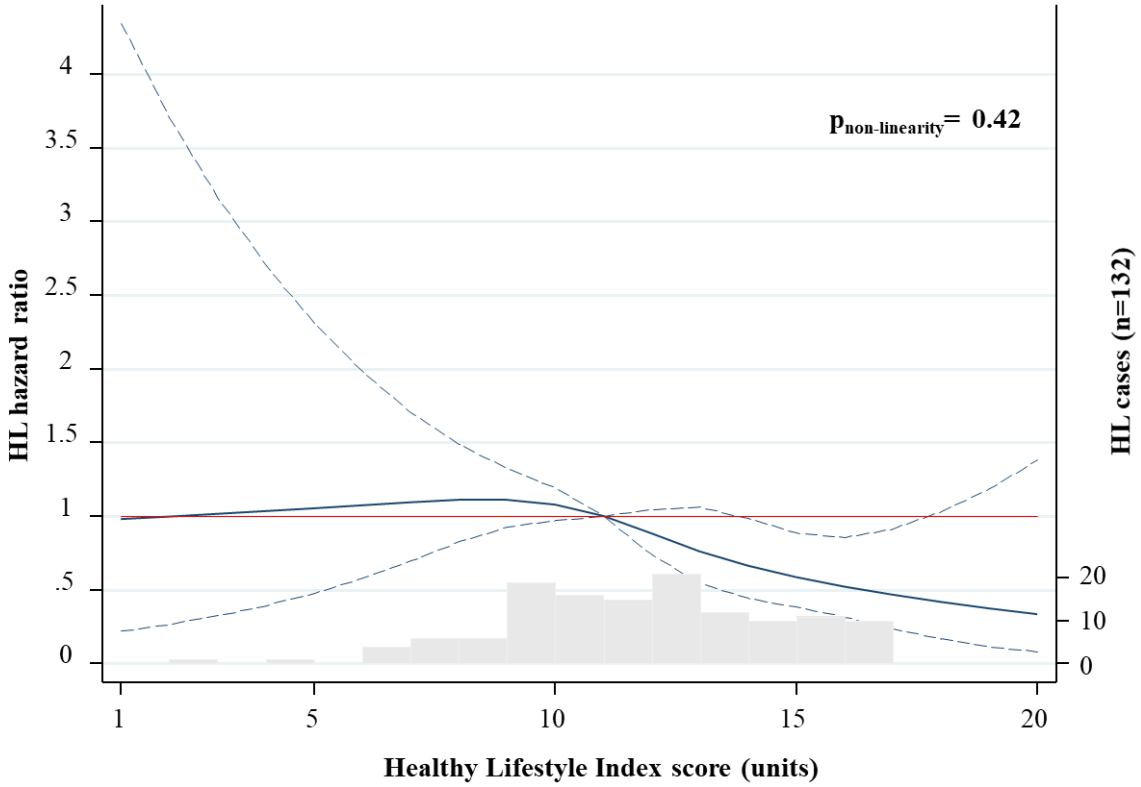
Table of content for online supplementary material

Online Supplementary Figure 1. Hodgkin lymphoma (HL) hazard ratios (solid line) and corresponding 95% confidence interval (dashed line) as a function of the healthy lifestyle index (HLI) score and the risk of Hodgkin lymphoma (HL)[1]



[1] Hazard ratios estimated in Cox models including restricted cubic splines with four internal knots placed at HLI score values of 7, 11, 13 and 17. Departure from linearity was evaluated by comparing the difference in log-likelihood of models with and without non-linear terms to a χ^2 distribution with two degrees of freedom.

Online Supplementary Table 1. Hazard ratio estimates for the associations between a 1-SD increment of Healthy Lifestyle Index (HLI)[1] and the risks of Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) after excluding, in turn, each lifestyle factor from the HLI

	HR[2]	(95% CI)	p_{trend}[3]		HR[2]	(95% CI)	p_{trend}[3]
All lymphoma (n=2,999)				**DLBCL (n=461)**			
HLI without Smoking	0.98	(0.93 - 1.02)	0.30	HLI without Smoking	0.98	(0.87 - 1.10)	0.70
HLI without Alcohol	0.97	(0.93 - 1.01)	0.18	HLI without Alcohol	0.95	(0.85 - 1.05)	0.30
HLI without BMI	0.98	(0.94 - 1.03)	0.44	HLI without BMI	1.02	(0.92 - 1.14)	0.69
HLI without Diet	0.98	(0.94 - 1.02)	0.38	HLI without Diet	1.03	(0.92 - 1.15)	0.59
HLI without Physical activity	0.97	(0.93 - 1.02)	0.21	HLI without Physical activity	0.99	(0.89 - 1.10)	0.84
HL (n=132)				**FL (n=363)**			
HLI without Smoking	0.88	(0.71 - 1.10)	0.27	HLI without Smoking	1.03	(0.9 - 1.18)	0.64
HLI without Alcohol	0.70	(0.58 - 0.85)	3.50E-04	HLI without Alcohol	1.05	(0.94 - 1.19)	0.39
HLI without BMI	0.80	(0.65 - 0.97)	0.02	HLI without BMI	1.04	(0.92 - 1.17)	0.57
HLI without Diet	0.85	(0.69 - 1.04)	0.12	HLI without Diet	1.03	(0.90 - 1.17)	0.68
HLI without Physical activity	0.75	(0.62 - 0.91)	3.60E-03	HLI without Physical activity	1.04	(0.92 - 1.17)	0.56
NHL (n=2,746)				**CLL/SLL (n=509)**			
HLI without Smoking	0.97	(0.93 - 1.02)	0.29	HLI without Smoking	1.05	(0.94 - 1.17)	0.37
HLI without Alcohol	0.98	(0.94 - 1.03)	0.44	HLI without Alcohol	1.07	(0.97 - 1.18)	0.20
HLI without BMI	0.99	(0.95 - 1.04)	0.78	HLI without BMI	1.05	(0.94 - 1.16)	0.40
HLI without Diet	0.99	(0.95 - 1.04)	0.75	HLI without Diet	1.06	(0.95 - 1.18)	0.28
HLI without Physical activity	0.99	(0.94 - 1.03)	0.50	HLI without Physical activity	1.03	(0.93 - 1.14)	0.58
MT / NK cell (n=125)				**PCN/MM (n=653)**			
HLI without Smoking	1.03	(0.83 - 1.29)	0.77	HLI without Smoking	0.94	(0.85 - 1.04)	0.21
HLI without Alcohol	1.07	(0.87 - 1.31)	0.52	HLI without Alcohol	0.98	(0.89 - 1.06)	0.58
HLI without BMI	0.93	(0.75 - 1.14)	0.48	HLI without BMI	1.04	(0.95 - 1.14)	0.44
HLI without Diet	0.95	(0.76 - 1.17)	0.61	HLI without Diet	0.98	(0.89 - 1.08)	0.74
HLI without Physical activity	0.94	(0.77 - 1.15)	0.55	HLI without Physical activity	0.98	(0.90 - 1.08)	0.71
BCL (n=2,290)				**Other BCL[4] (n=304)**			
HLI without Smoking	0.98	(0.93 - 1.03)	0.39	HLI without Smoking	0.88	(0.77 - 1.02)	0.09
HLI without Alcohol	0.99	(0.94 - 1.03)	0.58	HLI without Alcohol	0.88	(0.77 – 1.00)	0.05
HLI without BMI	1.01	(0.96 - 1.06)	0.64	HLI without BMI	0.87	(0.76 – 1.00)	0.04
HLI without Diet	1.00	(0.95 - 1.06)	0.87	HLI without Diet	0.90	(0.78 - 1.03)	0.12
HLI without Physical activity	0.99	(0.94 - 1.04)	0.67	HLI without Physical activity	0.89	(0.78 - 1.02)	0.08

Abbreviations: HLI, Healthy Lifestyle Index; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; MT/NK, Mature T and natural killer-cell lymphoma; BCL, mature B-cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; CLL/SLL, chronic lymphocytic leukemia, small lymphocytic leukemia and prolymphocytic lymphocytic leukemia ; MM/PCN, plasma cell neoplasm and multiple myeloma.

[1] One Standard deviation corresponded to 3 points of HLI;

[2] Models evaluating associations between the HLI and risks of lymphoma were adjusted for education level, non-alcohol energy intakes, height, and the index components currently excluded from the calculation of the HLI, and stratified by study center, age and sex;

[3] *P*-values for trend were determined using a Wald test for overall significance, according to a χ^2 distribution with one degree of freedom.

[4] Other BCL includes Burkitt lymphoma, hairy cell leukemia, lymphoplasmacytic lymphoma, Mantle cell lymphoma, marginal zone lymphoma, primary effusion lymphoma and prolymphocytic leukemia subtypes.

Online Supplementary Table 2. Hodgkin Lymphoma (HL) and non-Hodgkin Lymphoma (NHL) hazard ratio estimates for a 1-SD increase in the Healthy Lifestyle Index (HLI) after exclusion of the first 2 and 5 years of follow-up.

	HL				NHL			
	Cases	**HR**	**(95% CI)**	**p_{trend}**	**Cases**	**HR**	**(95% CI)**	**p_{trend}**
Excluding the first 2 years of follow-up	112	0.75	(0.57 - 0.98)	0.04	2,532	1.00	(0.95 - 1.05)	0.91
Excluding the first 5 years of follow-up	86	0.76	(0.55 - 1.04)	0.09	2,084	0.99	(0.93 - 1.05)	0.74