EUROPEAN JOURNAL OF CANCER 47 (2011) 748–760

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Physical activity and lymphoid neoplasms in the European Prospective Investigation into Cancer and nutrition (EPIC)

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0959-8049/$ - see front matter
doi:10.1016/j.ejca.2010.11.010

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ARTICLE INFO

Article history:
Received 14 June 2010
Received in revised form 6 November 2010
Accepted 9 November 2010
Available online 13 December 2010

Keywords:
Lymphoid neoplasm
Hodgkin lymphoma
Non-Hodgkin lymphoma
Multiple myeloma
Lymphocytic leukaemia
Physical activity
Cohort study

ABSTRACT

Background: Lymphoid neoplasms are a heterogeneous group of cancers that originate in the lymphatic cells of the immune system. Several risk factors have been identified or suggested, but they all account for only a small proportion of the lymphoid neoplasm incidence. It has been hypothesised that regular exercise may modulate the immune system and thereby reduce the risk of developing the disease.

Design and methods: The European Investigation into Cancer and Nutrition (EPIC) cohort consists of 521,457 adults, recruited by 23 centres in 10 European countries. The analytical cohort included 343,756 participants, with 778 non-Hodgkin lymphoma (NHL) cases (376 men and 402 women) and 690 B-cell non-Hodgkin lymphoma (B-NHL) cases (326 men and 364 women). Multivariate Cox regression models were used to calculate hazard ratios (HR) for the association between total, recreational, occupational, and household physical activity and NHL and B-NHL risk, as well as the risk for several B-NHL subtypes. Models were stratified by study centre and age at recruitment and adjusted for various potential confounding factors.

Results: We found no evidence of any effect of total physical activity on NHL (adjusted p-trend = 0.76 and 0.30 for men and women, respectively) and B-NHL risk (adjusted p-trend = 0.99 and 0.21 for men and women, respectively) for either men or women. Also no robust results were found for B-NHL subtype analyses among men or women.

Conclusions: This study provided no consistent evidence for an association between various physical activity measures and the risk of lymphoid neoplasms or any of the B-NHL subtypes.

1. Introduction

Lymphoid neoplasms are a heterogeneous group of cancers that originate in the lymphatic cells of the immune system. It includes Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), multiple myeloma (MM) and acute and chronic lymphocytic leukaemia (ALL and CLL).[1] NHL can be divided into B-NHL (including several subtypes) and T-NHL.[2] While the incidence of HL seems rather stable over the last years, the incidence trends of NHL have increased until approximately 1999, after which they levelled off, especially in Northern European Countries.[3–5]

The causes of these trends are largely unknown, as the aetiology of these cancers is still poorly understood. Some suggested risk factors are acquired or inherited immune deficiency, specific infectious agents, and certain occupational exposures.[6–9] NHL is an AIDS defining illness and it is 60 times more frequent among patients with AIDS than in the general population.[10] Dietary factors such as high intake of fat and meat products,[11,12] and anthropometric measures including body mass index and height[11,13–19] have been suggested as factors contributing to the development of lymphomas, although none of these have been clearly established as causal agents. The evidence for the consumption of fruit and vegetables[11,20,21] and lifestyle factors such as alcohol consumption and smoking,[16] as well as personal use of hair dyes[22] is inconsistent. No evidence was found for the role of self-reported diabetes in the aetiology of lymphomas.[23] However, even if these factors were causally related to the disease, they would account for only a small proportion of the lymphoma incidence.

There is some discussion about the classification of multiple myeloma (MM), a malignancy of plasma cells, but it is classified as B-NHL by the InterLymph Consortium.[2] Men are slightly more at risk than women, the incidence increases with age and is highest among African Americans.[24,25] Some studies have found dietary factors, such as low fish consumption[26,27] and low vegetable consumption[28] to play a possible

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role. Others reported an increased incidence of MM with increasing body mass index (BMI) but data on other exposures associated with energy balance are limited.[26,29]

The InterLymph Consortium also classified acute lymphocytic leukaemia (ALL) and chronic lymphocytic leukaemia (CLL) as B-NHL. Recently, the potential relationship between inflammatory and autoimmune conditions and CLL has been investigated but for both leukaemias the aetiology remains largely unknown.[30,31]

Physical activity has been associated with a decreased incidence of several types of cancer, such as colon and breast, and probably lung, and prostate cancer.[32] It has been hypothesised that regular exercise may contribute to modulate the immune system and thereby may lead to a reduced risk of cancers, such as lymphomas.[32–34] Also, physical exercise may play a role in the relationship between energy balance and MM.[25] If physical activity is associated with reduced risks of lymphoid neoplasms, it would be an important target for the prevention of the disease, since it is a modifiable factor.

To date, only a few prospective epidemiological studies have focused on the association between physical activity and risk of lymphomas,[13,15–17,35–37] myelomas[24,38] and leukaemias.[39,40] The results of these investigations are inconsistent, probably due to the lack of reliable, valid and comprehensive measures of physical activity.[32]

The aim of this paper is to address the possible role of various physical activity measures in the development of lymphoid neoplasms, using physical activity variables based on 'metabolic equivalent' (MET) values in a large prospective study.

2. Design and methods

The *European Prospective Investigation into Cancer and Nutrition* (EPIC) is a prospective cohort study aimed at investigating the relationships between nutritional, lifestyle and environmental factors and the risk of cancer and other chronic diseases. At enrolment, baseline information was collected through questionnaires from all participants aged 20 years or above, along with blood samples and anthropometric measurements, between 1992 and 2000.

The EPIC cohort consists of 521,457 volunteers, recruited by 23 centres in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom. All participants were recruited from the general population, with the exception of the French cohort, where the recruitment was based on female participants of a health insurance agency for school and university employees; the Spanish cohort, where most of the participants were blood donors; the Utrecht cohort and Florence cohort, based on women attending breast cancer screening; the Ragusa cohort, based on blood donors and their spouses; and part of the Oxford cohort, which recruited 27,000 vegetarians and vegans.

All eligible subjects who accepted the invitation to participate in the study gave informed consent. The ethical review boards of the International Agency for Research on Cancer (IARC) and of local participating centres approved the study protocol. A more detailed description of the study population, study design and data collection methods is reported elsewhere.[41]

2.1. Study population

Of the total EPIC population (521,457), participants with prevalent cancer at any site at baseline (27,089) were excluded, as well as 6,220 subjects with missing data on dietary factors (4999), non-dietary factors (60), or both (1161). To prevent inclusion of extreme values into the analysis 9674 subjects were excluded because they were in the top or bottom 1% of the ratio of energy intake to estimated energy requirement. Furthermore, because of a lack of data on physical activity, subjects form the Norwegian cohort (35,227) and the Umeå cohort (24,305) were excluded, along with 6779 other participants from other cohorts with missing data on physical activity. Participants in the French cohort (68,050) were also excluded from the study because of incomplete case ascertainment. From the remaining subjects, we excluded 13 cases with an unclear diagnosis. To minimise the possibility of reverse causality we excluded another 344 cases with less than 3 years of follow-up. The final analyses thus included 343,756 participants from 8 European countries.

2.2. Outcome assessment

Incident cases with lymphoid neoplasms were identified through population cancer registries (Denmark, Italy, the Netherlands, Spain, Sweden, and the United Kingdom), and through active follow-up (Germany and Greece). The latter method included using health insurance records, cancer and pathology hospital registries, or direct contacts with participants or next of kin.

Follow-up started at the date of recruitment and ended at either the date of lymphoid neoplasm diagnosis, death or last complete follow-up. Mortality data were obtained from cancer or mortality registries at the regional or national level and coded according to the 10th Revision of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-10). Date of complete follow-up varied between December 1999 and March 2004 between EPIC centres.

Initially, cases with lymphoid neoplasms were classified according to the second revision of the International Classification of Disease for Oncology (ICD-O-2). Later, all cases were recoded using the WHO classification of tumours of hematopoietic and lymphoid tissue, which is based on ICD-O-3.[42] The conversion was made using a program available from the Surveillance Epidemiology and End Results (SEER) webpage (http://www.seer.cancer.gov/) and involved a pathology expert and local expertise from participating EPIC centres (see Appendix I and a publication by Morton and colleagues).[43] In case ICD-O-2 codes could not be translated unequivocally into a lymphoid neoplasm diagnosis according to the WHO classification system, a case was categorised as lymphoid neoplasm unclassified ("nos").

Because the numbers were too small for the HL category, we considered the risk of NHL and B-NHL in the current analyses. NHL included B-NHL, T-NHL, and NHL not specified

(NHLnos). B-NHL included B-cell acute lymphatic leukaemia (BALL); diffuse large B-cell lymphoma (DLBCL); follicular lymphoma (FL); B-cell chronic lymphatic leukaemia (BCLL); lymphoplasmocytic lymphoma/Waldenström's disease (LPL); multiple myeloma/plasmacytoma (MM); marginal zone B-cell lymphoma (ML); Hairy cell leukaemia (HCL); B-cell lymphoma, other (BO); B-cell lymphomas not specified (Bnos).

Separate analyses were performed among the following B-NHL subtypes: DLBCL, FL, BCLL, MM, and Bnos. Other subtypes of B-NHL and T-NHL were not considered because of the small number of cases.

2.3. *Exposure assessment*

Detailed information on lifestyle and environmental factors, and medical history were obtained using self administered or interview-based questionnaires at time of enrolment. The assessment of physical activity measures is described in detail elsewhere.[44,45] A study assessing the validity and reproducibility of the non-occupational physical activity questions showed that it was sufficient for ranking or classifying the subjects, but less appropriate for estimating energy expenditure at an absolute level.[46]

Current occupational physical activity was based on employment status and level of physical activity at current work, which was later coded in categories (sedentary occupation, standing occupation, manual work, heavy manual work, and unemployed). There were few participants with heavy manual work in the cohort (especially among women) and therefore 'manual work' and 'heavy manual work' categories were collapsed. Information on housework, do-it-yourself work, gardening and climbing stairs was combined to estimate the overall amount of household activity. Walking, cycling and sport activities were combined to determine overall recreational activity.

Because only the duration and frequency of recreational and household/do-it-yourself work were directly assessed and no data on the intensity of the activity were recorded, estimates were made for the energy expenditure using metabolic equivalent (MET) values, according to the *Compendium of Physical Activities* (a comprehensive list of all occupational household, recreational and leisure activities).[47] The assigned MET values were 3.0 for walking, 6.0 for cycling, 4.0 for gardening, 6.0 for sports, 4.5 for do-it-yourself work, 3.0 for household work, and 8.0 for flights of stairs climbed daily.

To assess the total impact of physical activity on lymphoid neoplasm risk, we used a 'total physical activity' index that was created by Friedenreich and colleagues.[48] Participants were cross tabulated on the basis of categories of occupational activity with sex-specific quartiles of recreational and household activity (in quartiles of MET-hours/week) which resulted in the categories 'inactive', 'moderately inactive', 'moderately active', and 'active' (see Appendix II).

Participants' height and weight were measured at baseline, except for Norway and Oxford, where self-reported height and weight were obtained via questionnaire. BMI was calculated as weight in kilograms divided by height squared metres. BMI was split into categories using WHO cut-off points (World Health Organisation, BMI classification, 2007)

Table 1 – Frequency of lymphoma cases by country, stratified by sex.

	Men							Women						
				NHL subgroups							NHL subgroups			
	Lymphoid neoplasms	HL	NHL	B-NHL[a]	T-NHL[b]	NHLnos	Lymphoid neoplasms	Lymphoid neoplasms	HL	NHL	B-NHL[a]	T-NHL[b]	NHLnos	Lymphoid neoplasms
Italy	91	4	87	77	7	3	39	52	1	51	46	4	1	52
Spain	85	7	78	70	5	3	47	38	1	37	32	2	3	38
UK	166	4	162	142	3	17	64	102	2	100	93	0	7	102
Netherlands	54	1	53	49	2	2	7	47	0	47	44	1	2	47
Greece	23	1	22	20	1	1	16	7	1	6	5	0	1	7
Germany	76	7	69	64	1	4	48	28	4	24	22	0	2	28
Sweden	143	4	139	112	4	23	73	70	3	67	58	2	7	70
Denmark	178	10	168	156	6	6	104	74	4	70	64	3	3	74
Total	816	38	778	690	29	59	398	418	16	402	364	12	26	418

[a] B-NHL includes BALL: B-cell acute lymphatic leukaemia (incl. ALL); DLBCL: diffuse large B-cell lymphoma (incl. Burkitt); FL: follicular lymphoma (all grades); BCLL: B-cell chronic lymphatic leukaemia (incl. SLL, PLL); LPL: lymphoplasmocytic lymphoma/Waldenström's disease; MM: multiple myeloma/plasmacytoma; ML: marginal zone B-cell lymphoma; HCL: Hairy cell leukaemia; BO: B-cell lymphoma, other; and Bnos: B-cell lymphomas not specified.

[b] T-NHL includes TALL: T-cell ALL (incl. ALL + adult T-leukaemia); SEZ: mycosis fungoides, Sezary syndrome; PTL: peripheral T-cell lymphoma nos; CTL: cutaneous T-cell lymphoma; TO: T-cell lymphoma, other.

as follows: underweight <18.50 kg/m^2, normal 18.50–24.99 kg/m^2, overweight 25–29.99 kg/m^2 and obese $\geqslant$30 kg/m^2.

2.4. Statistical analyses

Hazard ratios (HR) and 95% confidence intervals (95% CI) were estimated for the association between physical activity and lymphoid neoplasms, for men and women separately, using Cox proportional hazard models, where age was the primary time variable in all models. The participant's age at recruitment was used to define the moment at which the subject entered the study and the exit time was either defined as age at diagnosis of lymphoid neoplasm, death, loss to follow-up, or censoring at the end of the follow-up period, whichever came first. All multivariate Cox models were stratified by study centre and age at study recruitment in one-year-categories, to control for differences in questionnaire design, follow-up procedures, and other centre effects. Additionally, the analyses were adjusted for confounding by considering the following potential confounding factors: level of education, smoking status, alcohol consumption, medical history of hypertension, hyperlipidaemia, and diabetes, as well as anthropometric characteristics including BMI, weight, height, waist and hip circumference, and waist-to-hip ratio. Dietary variables such as dairy products, vegetables, and meat were also considered as potential confounding factors. A covariate was considered a confounder if there was at least a 10% change in the risk estimate for the disease, when models were compared with and without the covariate term. Unfortunately it was not possible to adjust for confounding factors in the subtype analyses because the numbers were too small. Participants were excluded from the analyses in case of missing responses for a specific variable.

To calculate p values for trends across categories of physical activity variables, participants were assigned a score, which was entered as a continuous term in the Cox regression models. All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant. We performed our analyses using Stata version 10.0.

3. Results

The results presented here are based on the analyses performed on the cohort excluding the first 3 years of follow up. Results before exclusion are available on request.

The final analytical cohort consisted of 127,353 men and 216,403 women, who contributed to 1,083,717 and 1,867,843 person years, respectively. Mean age at recruitment was 52.9 (sd = 9.8) for men and 51.0 (sd = 10.9) for women. A total of 778 NHL cases (376 men and 402 women) and 690 B-NHL cases (348 men and 380 women) were identified.

The mean MET-hours/week of combined household and recreational physical activity was lower among men (64.9) than women (101.2) and there were large differences between the countries (data not shown). It is noticeable that in southern countries, the MET-hours/week were higher among women than among men, whereas in northern countries differences between men and women were smaller.

Table 2 – Frequency of B-NHL subtypes by country.

	B-NHL subtypes (n = 690)					
	DLBCL	FL	BCLL	MM	Other	Bnos
Italy	7	20	9	20	13	8
Spain	14	12	14	17	10	3
UK	20	17	24	30	22	29
Netherlands	10	12	7	10	4	6
Greece	3	1	7	4	1	4
Germany	3	8	19	18	5	11
Sweden	4	11	16	34	11	36
Denmark	33	17	46	32	16	12
Total	94	98	142	165	82	109

DLBCL: diffuse large B-cell lymphoma (incl. Burkitt); FL: follicular lymphoma (all grades); BCLL: B-cell chronic lymphatic leukaemia (incl. SLL, PLL); MM: multiple myeloma/plasmacytoma; other: other subtypes incl. BALL (B-cell acute lymphatic leukaemia incl. ALL), LPL (lymphoplasmocytic lymphoma/Waldenström's disease), ML (marginal zone B-cell lymphoma), HCL (Hairy cell leukaemia), and BO (B-cell lymphoma, other); and Bnos: B-cell lymphomas not specified.

Frequencies of lymphoid neoplasms by country and by sex can be found in Table 1. Overall 59 subjects were classified as NHL case with an unknown subtype. Table 2 is a description of the frequency of several B-NHL subtypes by country. The most frequent sub-entities were MM (n = 165) and BCLL (n = 142). 109 B-NHLs could not be further specified.

Demographic and lifestyle characteristics of the EPIC study population, stratified by NHL and B-NHL status, are presented in Table 3. Only small differences were observed between cases and non-cases with regard to education, smoking status (more former smokers among both case groups), and alcohol consumption (a higher percentage of cases consumed higher amounts of alcohol per day) (data for the last two variables not shown).

Anthropometric measurements, like weight, height, BMI, waist circumference, hip circumference and waist–hip-ratio were comparable for cases and non-cases. A higher percentage of cases compared to non-cases reported hypertension (27.6%, 27.6% and 21.8% of NHL, B-NHL, and non-cases, respectively) and hyperlipidaemia (25.5%, 25.5% and 19.3% of NHL, B-NHL, and non-cases, respectively), while no major differences were observed for diabetes. The distribution of the cases and non-cases into the quartiles of total physical activity variables (sex specific) were nearly comparable, as well as for occupational physical activity, household activity, and recreational activity.

In Table 4, the crude and multivariate adjusted hazard ratios for NHL cases by type of physical activity are presented, stratified by age at recruitment and study centre. Overall, we found no evidence of an association between total physical activity and NHL risk. There seemed to be an increased risk among women in the active total physical activity category (HR = 2.02, 95% CI = 1.10–3.71) but after adjustment for confounders this apparent effect disappeared.

Table 5 is constructed in the same way as Table 4, but only for B-NHL cases. Again, women in the active total physical activity category appeared to have an increased risk

Table 3 – Demographic and lifestyle characteristics of the EPIC study population stratified by lymphoma status.

Characteristic	NHL cases (*n* = 778)	B-NHL cases (*n* = 690)	Subjects without lymphoma (*n* = 342,940)
Sex (%)			
Men	48.3	47.3	37.0
Women	51.7	52.7	63.0
Age at recruitment (years) (mean, sd)	58.1 (8.4)	57.9 (8.3)	51.7 (10.6)
Education (%)			
None	3.8	3.7	5.6
Primary school	32.7	33.3	26.7
Technical/professional school	29.1	29.3	26.5
Secondary school	14.3	14.7	17.5
University degree	20.1	19.0	23.7
BMI (%)			
Underweight	0.7	0.7	1.1
Normal	39.1	39.1	44.1
Overweight	42.7	43.1	38.7
Obese	17.5	17.1	16.1
Weight (kg) (mean, sd)	74.9 (13.6)	74.8 (13.7)	72.1 (13.7)
Height (cm) (mean, sd)	168.2 (9.0)	168.1 (9.0)	166.4 (9.3)
Waist circumference (cm) (mean, sd)	88.5 (12.5)	88.4 (12.6)	85.7 (13.0)
Hip circumference (cm) (mean, sd)	101.6 (8.1)	101.6 (8.1)	101.1 (8.5)
WHR (cm/cm) (mean, sd)	0.87 (0.1)	0.87 (0.1)	0.85 (0.1)
Hypertension (%)			
Yes	27.6	27.6	21.8
No	72.4	72.4	78.2
Hyperlipidaemia (%)			
Yes	25.5	25.5	19.3
No	74.5	74.5	80.7
Diabetes (%)			
Yes	3.8	3.9	3.1
No	96.2	96.1	96.9
Total physical activity (sex specific) (%)			
Inactive	17.4	17.2	17.5
Moderately inactive	29.0	28.8	29.0
Moderately active	40.2	39.9	42.4
Active	13.4	14.1	11.1
Occupational activity (%)			
Sedentary	25.8	25.6	31.2
Standing	17.5	18.1	20.6
Manual/heavy manual work	15.4	15.6	12.8
Non-worker	41.3	40.7	35.4
Household activity (MET-hours/week) (%)			
<21.02	27.6	27.2	25.3
⩾21.02–<43.6	25.6	25.2	24.7
⩾43.6–<80.1	25.2	25.4	25.0
⩾80.1	21.6	22.2	25.0
Recreational activity (MET-hours/week) (%)			
<14.25	29.2	28.3	25.8
⩾14.25–<27.75	20.9	21.4	24.2
⩾27.75–<45.75	29.2	29.6	26.4
⩾45.75	20.7	20.7	23.6

NHL includes: B-NHL, T-NHL, Bnos.

B-NHL includes: DLBCL: diffuse large B-cell lymphoma (incl. Burkitt); FL: follicular lymphoma (all grades); BCLL: B-cell chronic lymphatic leukaemia (incl. SLL, PLL); MM: multiple myeloma/plasmacytoma; other: other subtypes incl. BALL (B-cell acute lymphatic leukaemia incl. ALL), LPL (lymphoplasmocytic lymphoma/Waldenström's disease), ML (marginal zone B-cell lymphoma), HCL (Hairy cell leukaemia), and BO (B-cell lymphoma, other); and Bnos: B-cell lymphomas not specified.

Table 4 – Crude and multivariate adjusted hazard ratios for male and female NHL cases by type of physical activity, stratified by age at recruitment and centre.

Type of activity	Men (n = 376)			Women (n = 402)		
	Number of cases[a]	Age- and centre-stratified hazard ratio and 95% confidence interval	Multivariate adjusted hazard ratio and 95% confidence interval[b]	Number of cases[a]	Age- and centre-stratified hazard ratio and 95% confidence interval	Multivariate adjusted hazard ratio and 95% confidence interval[b]
Total physical activity						
Inactive	74	1.00	1.00	61	1.00	1.00
Moderately inactive	113	1.17 (0.67–2.01)	1.18 (0.49–2.86)	113	0.74 (0.45–1.21)	0.76 (0.31–1.88)
Moderately active	142	1.39 (0.82–2.35)	1.10 (0.49–2.49)	171	0.82 (0.50–1.34)	1.22 (0.50–2.94)
Active	47	1.13 (0.60–2.11)	0.83 (0.31–2.24)	57	2.02 (1.10–3.71)	1.50 (0.45–5.0)
p-trend		0.45	0.76		0.07	0.30
Occupational activity						
Sedentary	109	1.00	1.00	89	1.00	1.00
Standing	65	1.00 (0.60–1.70)	0.76 (0.34–1.68)	69	0.81 (0.50–1.33)	0.61 (0.25–1.52)
Manual/heavy manual	68	1.15 (0.69–1.89)	1.05 (0.46–2.41)	50	1.61 (0.94–2.79)	2.06 (0.65–6.51)
Non-worker	131	1.58 (0.93–2.69)	1.18 (0.51–2.76)	186	0.75 (0.47–1.19)	1.24 (0.53–2.91)
p-trend[c]		0.08	0.75		0.10	0.41
Household activity (MET-hours/week)						
< 21.02	167	1.00	1.00	48	1.00	1.00
⩾21.02–<43.6	116	0.77 (0.50–1.17)	0.92 (0.49–1.73)	83	1.22 (0.70–2.12)	2.11 (0.73–6.06)
⩾43.6–<80.1	68	1.26 (0.75–2.13)	1.02 (0.41–2.56)	128	1.64 (0.96–2.79)	1.65 (0.60–4.55)
⩾80.1	25	0.80 (0.40–1.60)	0.88 (0.35–2.21)	143	1.70 (0.96–3.03)	1.78 (0.60–5.27)
p-trend		0.93	0.82		0.05	0.49
Recreational activity (MET-hours/week)						
< 14.25		1.00	1.00	114	1.00	1.00
⩾14.25–<27.75	113	1.21 (0.74–1.97)	1.29 (0.58–2.86)	90	0.81 (0.50–1.30)	0.57 (0.21–1.56)
⩾27.75–<45.75	73	1.09 (0.68–1.75)	1.06 (0.49–2.30)	115	1.20 (0.75–1.90)	1.48 (0.58–3.78)
⩾45.75	112	1.05 (0.62–1.76)	1.11 (0.49–2.52)	83	1.07 (0.66–1.73)	1.25 (0.49–3.16)
p-trend	78	0.91	0.91		0.44	0.42

[a] Numbers of cases do not always add up to total number of cases across each physical activity variable due to missing values.

[b] Adjusted for hypertension, hyperlipidaemia, education and diabetes.

[c] The test for trend excludes non-workers

Table 5 – Crude and multivariate adjusted hazard ratios for male and female B-NHL cases by type of physical activity, stratified by age at recruitment and centre.

Type of activity	Men (n = 326)			Women (n = 364)		
	Number of cases[a]	Age- and centre-stratified hazard ratio and 95% confidence interval	Multivariate adjusted hazard ratio and 95% confidence interval[b]	Number of cases[a]	Age- and centre-stratified hazard ratio and 95% confidence interval	Multivariate adjusted hazard ratio and 95% confidence interval[b]
Total physical activity						
Inactive	62	1.00	1.00	57	1.00	1.00
Moderately inactive	97	1.06 (0.59–1.91)	1.17 (0.46–2.98)	102	0.66 (0.40–1.11)	0.66 (0.25–1.70)
Moderately active	124	1.43 (0.81–2.53)	1.24 (0.52–2.95)	151	0.80 (0.48–1.33)	1.27 (0.50–3.27)
Active	43	1.05 (0.55–2.02)	0.89 (0.31–2.54)	54	2.07 (1.10–3.87)	1.80 (0.51–6.39)
p-trend		0.47	0.99		0.05	0.21
Occupational activity						
Sedentary	92	1.00	1.00	82	1.00	1.00
Standing	58	1.07 (0.61–1.86)	0.80 (0.34–1.88)	65	0.90 (0.53–1.50)	0.62 (0.24–1.62)
Manual/heavy manual	61	1.18 (0.70–1.99)	1.52 (0.62–3.70)	45	1.60 (0.91–2.81)	1.99 (0.61–6.46)
Non-worker	113	1.80 (1.01–3.21)	1.77 (0.69–4.52)	164	0.73 (0.45–1.19)	1.31 (0.54–3.18)
p-trend[c]		0.09	0.46		0.09	0.42
Household activity (MET-hours/week)						
<21.02	146	1.00	1.00	42	1.00	1.00
⩾21.02–<43.6	99	0.68 (0.43–1.07)	0.82 (0.41–1.65)	75	1.26 (0.70–2.27)	2.07 (0.67–6.43)
⩾43.6–<80.1	58	1.20 (0.69–2.09)	0.89 (0.34–2.36)	117	1.89 (1.06–3.35)	1.85 (0.64–5.36)
⩾80.1	23	0.71 (0.34–1.48)	0.79 (0.29–2.17)	130	2.10 (1.13–3.87)	2.33 (0.75–7.22)
p-trend		0.68	0.62		0.01	0.21
Recreational activity (MET-hours/week)						
<14.25	91	1.00	1.00	104	1.00	1.00
⩾14.25–<27.75	64	1.37 (0.80–2.35)	1.31 (0.56–3.08)	84	0.82 (0.50–1.35)	0.57 (0.20–1.65)
⩾27.75–<45.75	101	1.24 (0.74–2.08)	1.21 (0.51–2.84)	103	1.26 (0.78–2.06)	1.62 (0.60–4.40)
⩾45.75	70	1.26 (0.72–2.19)	1.14 (0.47–2.75)	73	1.02 (0.62–1.69)	1.25 (0.44–3.58)
p-trend		0.48	0.87		0.53	0.40

[a] Numbers of cases do not always add up to total number of cases across each physical activity variable due to missing values.
[b] Adjusted for hypertension, hyperlipidaemia, education and diabetes.
[c] The test for trend excludes non-workers.

Table 6 – Hazard ratios (HR) and 95% confidence intervals (95% CI) for B-NHL subtypes in different categories of total physical activity.

	DLBCL		FL		BCLL		MM		BNOS	
	N_{cases}	HR (95% CI)	N_{cases}	HR (95% CI)	N_{cases}	HR (95% CI)	N_{cases}	HR (95%CI)	N_{cases}	HR (95% CI)
Men	45		37		83		77		45	
Inactive	6	1.00	8	1.00	18	1.00	15	1.00	10	1.00
Moderately inactive	15	2.20 (0.51–9.43)	9	1.31 (0.21–8.15)	28	0.67 (0.21–2.16)	21	0.55 (0.12–2.50)	13	0.38 (0.07–2.93)
Moderately active	17	2.13 (0.55–8.30)	13	1.61 (0.34–7.78)	26	0.58 (0.17–1.98)	33	0.86 (0.20–3.76)	21	0.93 (0.19–4.66)
Active	7	2.03 (0.38–10.79)	7	2.82 (0.52–15.23)	11	0.76 (0.23–2.53)	8	0.34 (0.05–2.14)	1	0.16 (0.01–1.95)
p-trend		0.44		0.24		0.59		0.64		0.50
Women	49		61		59		88		64	
Inactive	7	1.00	12	1.00	9	1.00	15	1.00	7	1.00
Moderately inactive	9	1.15 (0.30–4.36)	17	0.40 (0.09–1.75)	17	0.83 (0.22–3.07)	20	0.51 (0.18–1.47)	24	1.77 (0.35–9.01)
Moderately active	22	2.74 (0.72–10.46)	20	0.44 (0.11–1.78)	24	1.85 (0.51–6.75)	43	0.68 (0.26–1.77)	25	0.26 (0.05–1.43)
Active	11	5.03 (1.19–21.33)	12	2.59 (0.54–12.38)	9	10.95 (1.55–77.48)	10	0.65 (0.14–3.16)	8	1.60 (0.20–12.52)
p-trend		00.1		0.23		0.01		0.64		0.17

DLBCL: diffuse large B-cell lymphoma (incl. Burkitt); FL: follicular lymphoma (all grades); BCLL: B-cell chronic lymphatic leukaemia (incl. SLL, PLL); MM: multiple myeloma/plasmacytoma; and Bnos: B-cell lymphomas not specified.

(HR = 2.07, 95% CI = 1.10–3.87), as well as women in the 3rd and 4th quartile of household physical activity (HR = 1.89, 95% CI = 1.06–3.35 and HR = 2.10, 95% CI = 1.13–3.87, respectively), but the adjusted HRs did not show a statistically significant association for either men or women for any of the different types of activity.

Table 6 shows the risk estimates for different B-NHL subtypes in different categories of total physical activity. Results for subtypes that contained small numbers are not displayed in the table. In addition, because of the small numbers it was not possible to adjust the risk estimates for confounding factors.

Again among active women, an increased risk for the subtypes diffuse large B-cell lymphoma (DLBCL) (HR = 5.03, 95% CI = 1.19–21.33, *p*-trend = 0.01)) and B-cell chronic lymphatic leukaemia (BCLL) (HR = 10.95, 95% CI = 1.55–77.48, *p*-trend = 0.01) was observed. For other subtypes, or among men, no significant results were found.

4. Discussion

No consistent association was found between physical activity and lymphoid neoplasm risk among men or women in this prospective study. The subtype analyses showed an increased risk of DLBCL and BCLL for active women, with a significant *p*-trend, indicating a dose response effect, while among men no significant associations were found for NHL, B-NHL or any of its subtypes. Before interpreting these results, however, the strengths and weaknesses of the study are discussed.

Strengths include the large, prospective cohort design. The cohort consisted of a heterogeneous population, with considerable variation of physical activity across the EPIC centres. This variation was especially evident for recreational activities in both men and women.[44] Standardised data referring to physical activity and a wide range of other (confounding) variables were used. The relative validity and reproducibility of the physical activity questions were assessed and it was reported that a short version of the complete questionnaire ranks study participants adequately in terms of activity levels.[46] However, some degree of measurement error and misclassification is likely.

This study also benefits from a comprehensive assessment of physical activity, to our knowledge being the first prospective study to assess all different aspects of physical activity in relation to lymphoid neoplasms. This is important because non-occupational activity has been shown to be the most important component of daily activity in modulating immune function.[35] Moreover, sex specific cut-points were used which has not been done by any previous study. Currently, the majority of published papers on physical activity and cancer use the units of MET-hours/week as the standard method for reporting the dose of physical activity performed by the population. Therefore the use of MET-hours/week in this study makes direct comparison with other studies possible.

To minimise the possibility of reverse causality we excluded the first 3 years of follow-up among the cases. This is particularly relevant for some lymphoid neoplasms with long prediagnostic periods during which body functions may be impaired. All results of the analyses that we

performed including the first 3 years of follow up are available on request.

Among female NHL cases, a decreased risk was found for recreational activity between 14.25 and 27.75 MET-hours/week when it was compared to recreational activity of less than 14.25 MET-hours/week (HR = 0.27, 95% CI = 0.11–0.65). Because this association disappeared after excluding the first 3 years of follow up, it is likely that such effects were due to reverse causality. Cases who are suffering from a low grade, undiagnosed lymphoid neoplasm, in the early stages of the disease, are likely to exercise less because of physical impairment.

Although overall we analysed approximately 800 cases with lymphoid neoplasms, a small sample size for less frequently occurring subtypes is a major limitation of the study, making it difficult to draw conclusions. The differences between crude and adjusted HRs in Tables 4 and 5 are probably due to chance, as it is based on fairly small numbers. However, we cannot rule out the possibility that physical activity may affect certain subtypes and not others. Smedby and colleagues confirmed a positive association between certain auto-immune disorders and specific lymphoma subtypes, primarily diffuse large B-cell lymphoma.[49] This study and other studies indicate that the malignancies that are jointly referred to as lymphoid neoplasms are diverse, differing not only in clinical and morphologic appearance but also in their aetiology.[50] Therefore, heterogeneity in the relationship between physical activity and risk of lymphoid neoplasm subtypes is likely.

Another methodological limitation concerns occupational physical activity data which did not include duration and frequency. As a result it was not possible to combine all of the activities done over the past year into one overall variable expressed as MET-hours/week. Instead, an index of activity was used that was based on a cross-classification of occupational activity with the combination of household and recreational activity.

Previous studies examining the association between physical activity and lymphoid neoplasms report inconsistent results. Two studies evaluated the role of occupational physical activity in the development of NHL and observed no association.[35,51] Cerhan and colleagues did not find any evidence for the role of total physical activity in NHL development in their prospective cohort study, where occupational physical activity data were missing and only a small number of NHL cases were identified.[36] Another population-based case-control study found an inverse association between non-occupational physical activity and NHL, but the assessment of physical activity was limited and not validated. There was no dose response effect and the association became weaker after adjustment for confounding factors.[15] Pan and colleagues suggested that higher levels of recreational activity were associated with a lower risk of NHL.[17] However, the retrospective design of the study might have caused information bias. Focussing on HL, Keegan and colleagues used data from a population-based case control study and found an association between strenuous physical activity and the disease among women.[37] However, the summary measure that was created for this type of physical activity appeared to be inexact and the study did not evaluate less strenuous or occupational physical activity.

Few studies evaluating the relationship between physical activity and MM have been published. One cohort study in Japan found walking less than 30 min a day to be associated with an increased risk of MM, but other types or intensities of physical activity were not assessed in this study.[38] Birmann and colleagues performed a more elaborate measurement of physical activity and did not observe a statistically significant association between it and the risk of MM, although they could not rule out a modest inverse association.[24] Concerning CLL, both the above mentioned study by Cerhan and colleagues[36] and a study by Lu and colleagues[39] did not find an association between recreational physical activity and the disease. One population based case-control study that also only assessed recreational activity suggested that higher vigorous activity may decrease the risk of adult leukaemia but the authors themselves note that the results should be interpreted with caution.[40]

In conclusion, we found no consistent evidence for the role of total physical activity on the risk of lymphoid neoplasms in this large prospective study, including approximately 800 cases. The increased risk for the subtypes DLBCL and BCLL for active women compared to inactive women is possibly a chance finding.

Conflict of interest statement

None declared.

Acknowledgments

This work was supported by Europe against Cancer Program of the European Commission (SANCO); Deutsche Krebshilfe, Deutsches Krebsforschungszentrum, German Federal Ministry of Education and Research; Danish Cancer Society; Health Research Fund (FIS) of the Spanish Ministry of Health, Spanish Regional Governments of Andalucia, Asturias, Basque Country, Murcia and Navarra; the ISCIII Network RCESP (C03/09), Spain; Cancer Research UK; Medical Research Council, United Kingdom; Hellenic Ministry of Health; Stavros Niarchos Foundation; Hellenic Health Foundation; Italian Association for Research on Cancer (AIRC); Italian National Research Council, Fondazione-Istituto Banco Napoli, Italy; Compagnia di San Paolo; Dutch Ministry of Public Health, Welfare and Sports; World Cancer Research Fund; Swedish Cancer Society; Swedish Scientific Council; Regional Government of Skåne, Sweden; Norwegian Cancer Society; Research Council of Norway; French League against Cancer (LNCC); National Institute for Health and Medical Research (INSERM), France; Mutuelle Générale de l'Education Nationale (MGEN), France; 3M Co, France; Gustave Roussy Institute (IGR), France; and General Councils of France.

Appendix I. ICD-O-3 codes and lymphoma subtypes

ICD-O-3	Entity	
9650/3, 9651/3, 9652/3, 9653/3, 9654/3, 9655/3, 9659/3, 9663/3, 9664/3, 9665/3, 9667/3	HL	Hodgkin's lymphoma
9590/3	NHL	Non-Hodgkin's lymphoma
9727/3, 9835/3, 9728/3, 9836/3	BALL	B-cell acute lymphatic leukaemia (incl. ALL)
9680/3, 9684/3, 9679/3, 9687/3, 9826/3	DLBCL	Diffuse large B-cell lymphoma (incl. Burkitt)
9675/3, 9690/3, 9691/3, 9695/3, 9698/3	FL	Follicular lymphoma (all grades)
9670/3, 9823/3, 9832/3, 9833/3	CLL	B-cell chronic lymphatic leukaemia (incl. SLL, PLL)
9671/3, 9761/3	LPL	Lymphoplasmocytic lymphoma/Waldenstrom's disease
9731/3, 9732/3, 9734/3	MM	Multiple myeloma/plasmacytoma
9699/3, 9689/3	ML	Marginal zone B-cell lymphoma
9940/3	HCL	Hairy cell leukaemia
9673/3, 9765/1	BO	B-cell lymphoma, other
9591/3	Bnos	B-cell lymphoma, nos
9837/3, 9729/3, 9827/3	TALL	T-cell ALL (incl. ALL + adult T-leukaemia)
9700/3, 9701/3	Sez	Mycosis fungoides, Sezary syndrome
9702/3	PTL	Peripheral T-cell lymphoma nos
9709/3, 9708/3, 9718/3	CTL	Cutaneous T-cell lymphoma
9705/3, 9834/3, 9831/3, 9714/3, 9716/3, 9717/3, 9719/3, 9948/3	TO	T-cell lymphoma, other

Appendix II. Definition of total physical activity by cross tabulating occupational activity with combined recreational and household activity (in MET-hours/week)

Occupational activity	Recreational and household activity (MET-hours/week)			
	Low	Medium	High	Very high
Sedentary	Inactive	Inactive	Moderately inactive	Moderately active
Standing	Moderately inactive	Moderately inactive	Moderately active	Active
Manual	Moderately active	Moderately active	Active	Active
Heavy manual	Moderately active	Moderately active	Active	Active
Unemployed	Moderately inactive	Moderately inactive	Moderately active	Moderately active
Unknown/missing	Inactive	Moderately inactive	Moderately inactive	Moderately active

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