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Occupational exposure to immunologically active agents and risk for lymphoma: The European Epilymph case–control study

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ABSTRACT

Objectives: Allergies and asthma may be protective for the development of lymphoma. We evaluated whether occupational allergens that provoke immune reactivity and asthma through an IgE-mediated pathway are protective for lymphoma.

Methods: The Epilymph study includes histologically or cytologically confirmed Hodgkin, B-cell, and T-cell lymphoma cases from six European countries (Spain, France, Germany, Italy, Ireland, and Czech Republic) recruited in 1998–2004. Controls were frequency matched to cases by age, gender, and study centre. Lifetime occupational exposure to seven high molecular weight

(HMW) agents was evaluated through an asthma-specific job-exposure matrix. 2205 lymphoma cases and 2296 controls with complete occupational history could be included in the analysis. Associations between HMW exposures and lymphoma were evaluated using pooled unconditional logistic regression analyses.

Results: Individuals exposed to HMW agents had a non-statistically significant decreased risk of any lymphoma (OR, 0.88; 95% CI, 0.74–1.05) and of B-cell lymphoma (OR, 0.91; 95% CI, 0.76–1.09), and a significantly decreased risk for Hodgkin lymphoma (OR, 0.62; 95% CI, 0.40–0.98). A decrease in risk for lymphoma was found for exposure to latex (OR, 0.74; 95% CI, 0.55–0.99).

Conclusions: Further epidemiologic and mechanistic research is needed to confirm that occupational exposure to HMW agents predisposing to asthma can reduce the risk of lymphoma.

1. INTRODUCTION

The role of the immune system in the aetiology of non-Hodgkin lymphoma (NHL) has been demonstrated by the excess risk among immunosuppressed patients and also in situations of chronic immunostimulation, due to bacterial and viral infections^[1]. A decreased risk of haematological malignancies has been observed among asthma patients in several studies suggesting an immunological link between both diseases^{[2], [3], [4], [5], [6], [7] and [8]}. Atopic asthma is typically associated with a deregulated Th2-biased immune response including the production of B cell-stimulatory cytokines, such as IL-4 and IL-13^{[9] and [10]}. Asthma is associated with high IgE levels. Interestingly, total and specific IgE to common aeroallergens have been shown to be inversely associated with risk of lymphoma in some studies^[11]. However, the fact that in a small prospective study this association was observed close to the time of diagnosis, was interpreted as a possible reverse causality in which NHL suppresses the immunologic response to allergens^[12]. Some case-control studies have suggested a link between asthma and lymphoma, but the potential concern in these studies is that the onset of the disease may change IgE levels.

In a preliminary analysis of the Spanish arm of the international Epilymph case-control study on lymphoma, we evaluated whether occupational exposure to high molecular weight (HMW) agents that are associated with asthma^[13] and that act predominantly through an IgE-dependent allergic mechanism^[14], were also associated with risk for specific NHL types^[15]. That analysis showed that exposure to HMW agents may lead to a decreased risk of all lymphomas, particularly B-cell lymphoma, and to an increased risk for Hodgkin lymphoma. In 2009, a large case-control study in Italy using a similar approach also identified a reduced risk of lymphoma associated with exposure to agents related to occupational asthma^[16]. In this analysis we incorporate data from studies in six countries participating in the international Epilymph consortium following the same protocol. We evaluated

whether lifetime occupational exposure to HMW agents capable of inducing IgE-mediated allergic sensitization is associated with the risk of specific lymphoma subtypes^[17], aiming to reduce with this analysis the potential effect of a reverse causality mechanism.

2. MATERIALS AND METHODS

2.1. Study design and participants

The Epilymph study is a multicenter case–control study including populations from 6 European countries (Germany, Italy, Spain, Ireland, France and Czech Republic). Newly diagnosed cases of lymphoid neoplasms and controls were recruited from 1998 to 2004 using a common core protocol and interview in all countries. The diagnosis of lymphoma was verified by histology and 99% of them were supplemented by immunohistochemistry test and flow cytometry. Cases were categorized according to the WHO Classification for Neoplastic Diseases of the Lymphoid Tissues^[18]. Subjects with a diagnosis of uncertain malignant potential such as post-transplant lymphoproliferative disorder or monoclonal gammopathies of undetermined significance were excluded. Controls were identified at same time as the diagnosis of the cases and were sampled from the general population based on census lists in Italy and Germany matched by age and sex. In the other 4 countries, controls were recruited from the same hospital as the cases and were frequency matched to cases by age, gender, and hospital. Individuals with organ transplantation, HIV or a diagnosis of a systemic infection were excluded by protocol [19] and [20]; for our study, controls hospitalized due to respiratory diseases were also excluded. We further excluded subjects who reported to have never worked. Finally, the study includes 2205 lymphoma cases and 2296 controls with complete information of the exposure and adjustment variables (Fig. 1). Informed consent was obtained from all participants in accordance to guidelines from the institutional review boards of the participating institutes.

[FIGURE 1]

2.2. Questionnaire and occupational history

Information was requested through a structured face-to-face interview. The same structured questionnaire was used and translated into the local language in each country. Questions collected information on socio-demographic factors, reproductive, familial and medical history including allergies and asthma, residence, tobacco, alcohol and drugs consumption, use of hair dyes, sunlight exposure and complete occupational history. Lifetime occupational history was recorded including all jobs held for at least one year including a job and industry description and start and end years.

2.3. Occupational exposure assessment

Occupations were coded in each country using the 1968 International Labour Office International Standard Classification of Occupations (ISCO-68)^[21]. ISCO-68 uses a five-digit hierarchical system that classifies jobs into 1506 occupational titles and is

published in English, French, and Spanish. Codes of all jobs for each participant were linked to an asthma-specific job exposure matrix (OAJEM) that had been adapted to the ISCO-68 coding system^[15]. The OAJEM includes protein exposures such as latex, flour, biological enzymes and mites that are known to produce asthma through an IgE mediated mechanism^[13]. In addition, the OAJEM also assigns exposure to other recognized occupational risk factors for asthma. Each matrix cell contains a yes or no indication of exposure, favouring specificity over sensitivity as jobs are classified as exposed only if the probability of exposure is expected to be high for a considerable number of subjects in that job. Seven of the protein-derived HMW included in the OAJEM are agents causing sensitization through an IgE-mediated mechanism. These agents are classified in a hierarchical scheme with some specific allergens nested in the larger groups: latex, flour, other plant antigens (derived from plants); rodents and livestock, fish and shellfish (derived from animals); arthropods or mites; and bioaerosols. These agents are known to produce asthma through an IgE mediated mechanism. The OAJEM also evaluates low molecular weight agents that include a variety of organic and inorganic compounds that have not been consistently associated with an IgE-mediated mechanism such as isocyanates, metal fumes and wood dusts, bioaerosols including moulds and endotoxins and four mixed environments that have been associated with asthma (metal working fluids, textile and agricultural settings). Finally, the OAJEM includes three wide groups of (mainly irritating) agents that may be considered low risk factors for (occupational) asthma.

Estimates of exposure to asthma causing agents were derived for each job held by study subjects and individual indices of exposure were created by integration over the whole occupational history of each case and control. Exposed individuals were defined taking into account 5 years of lag for high molecular weight exposures; for cases, exposures occurring in the last 5 years before the diagnosis were not considered, for controls, the lag was based on the interview date. We calculated the duration of occupational exposure using the total time of exposure among jobs excluding the 5 years previous to the date of diagnosis/interview. A five-year exposure lag was applied under the assumption that very recent exposures cannot be the causes of the lymphoma.

2.4. Statistical analysis

Unconditional logistic regression was used to assess the risk of lymphoma in relation to ever exposure to high molecular weight agents. Odds ratios (OR) and the corresponding 95% confidence intervals (CI) for all lymphomas and lymphoma subtypes were estimated adjusting for age (in quartiles), sex and study centre. Alternative analysis was done with further adjustment for potential confounders, we estimated the risk of lymphoma including educational level (as marker of socioeconomic status), smoking, and also other occupational exposures evaluated by the matrix (low risk exposures and other high risk exposures as low molecular weight, mixed exposures, bioaerosols, drugs, and irritants). Specific allergens exposure was evaluated for all lymphomas and B-cell lymphoma and Hodgkin lymphoma. In order to assess the duration-response relationship, we evaluated cumulative years of exposure to high molecular weight agents during occupational history. Generalized additive models (GAM) were applied to exposed individuals to examine the linearity of the duration-response effect; since the

relationship was non-linear, we analyzed duration of exposure using years of exposure dichotomized at the median (8 years) for exposed individuals. Several sensitivity analyses were done. To ensure that the estimates were not affected by excluding exposures occurred in the last 5 years, we performed an additional analysis excluding those individuals that had been exposed only in the 5 previous years to diagnosis or interview. We also estimated the risk of lymphoma without taking into account the 5 year lag assumption, and additionally we tested a ten-year exposure lag. For Hodgkin lymphoma, we randomized a 1:1 matched case-control and applied conditional logistic regression to assess the impact of the unequal distribution of age between Hodgkin lymphoma cases and controls; for this analysis, controls were matched to Hodgkin cases by centre, age and sex. To make sure that the risk estimates were robust and not dependent on a specific country, we evaluated the risk of lymphoma excluding the countries one by one. Furthermore, we tested the interaction between country and exposure to HMW agents through likelihood-ratio test and evaluated also the heterogeneity between country-specific estimates using I-squared measure^[22]. As countries did not present heterogeneity, neither interaction between country and exposure was found, we present the results of the pooled analyses. Effect modification by asthma was assessed through a stratified analysis by asthma status and also using likelihood-ratio test comparing models with additive and interaction terms.

The level of significance was set at 0.05 and all tests were two-sided. All analyses were performed using statistical package Stata version 12.1 (StataCorp LP, Texas, USA).

3. RESULTS

Table 1 describes the characteristics of the study population by case/control status and major lymphoma subtypes. Controls and all lymphoma cases were similar concerning age, sex and educational level. Hodgkin lymphoma cases were significantly ($p < 0.0001$) younger (mean = 39 years, sd = 15.3) than controls (mean = 56 years, sd = 15.7) and had higher educational level ($p < 0.0001$). Controls were more likely to have self-reported asthma (8% and 6% of controls and cases, respectively). Concerning other occupational exposures, Hodgkin lymphoma cases were less often exposed to low risk exposures and other high risk exposures ($p = 0.008$ and $p < 0.0001$, respectively).

Odds ratios for all lymphoma and major lymphoma subtypes related to occupational exposure to high molecular weight agents are shown in ^{Table 2}. Subjects exposed to HMW agents had a risk of the order of 0.9 for most types of lymphoma, although conventional levels of statistical significance were only reached for Hodgkin lymphoma. A 12% decreased risk was found for all lymphoma (OR, 0.88; 95% CI, 0.74–1.05) and a similar estimation was found for B-cell lymphoma category (OR, 0.91; 95% CI, 0.76–1.09), while lower risk was observed for Hodgkin lymphoma (OR, 0.62; 95% CI, 0.40–0.98). Additional adjustment for other potential confounders did not change the observed risk estimates for high molecular weight agents. The analysis by country did not show any significant association (Fig. 2), although the direction was consistent across countries except for Germany, that

showed a positive OR for all lymphoma and B-cell lymphoma; and for Spain, that showed a positive OR for Hodgkin lymphoma, being consistent with the preliminary analysis of the Spanish part of the Epilymph study^[15].

[TABLE 2]

An evaluation of duration of exposure did not show differences in risk when examining exposures in two groups classified by the median (Table 3) or when evaluating tertiles of exposure (not shown). Evaluation of age at first exposure did not show differences in risk of lymphoma. Results for specific allergens are also shown in Table 3. Only one B-cell lymphoma case and no controls had occupational exposure to fish enzymes and this category was excluded from the table. We evaluated separate associations for the six remaining HMW agents and ORs were consistent with the results for exposure to any allergens, except for exposure to plant antigens where a non-significant increased risk was assessed for all lymphoma (OR, 1.85; 95% CI, 0.77–4.43) and for B-cell lymphoma (OR, 1.81; 95% CI, 0.72–4.54). Exposure to latex antigens showed a statistically significant decreased risk for lymphoma (OR, 0.74; 95% CI, 0.55–0.99) and stronger inverse risk was obtained for the association between latex exposure and Hodgkin lymphoma (OR, 0.32; 95% CI, 0.15–0.69).

[TABLE 3]

Occupational exposure to HMW agents showed a non-significant increased risk of asthma (OR, 1.15; 95% CI, 0.85–1.57) and asthmatics individuals showed a significantly decreased risk of lymphoma (OR, 0.74; 95% CI, 0.59–0.93). We performed sensitivity analyses excluding asthmatics individuals and results were consistent, for all lymphoma we observed a non-significant decreased risk of 13% in exposed individuals (OR, 0.87; 95% CI, 0.73–1.04), and the significance for Hodgkin lymphoma remained when asthmatic individuals were excluded (OR, 0.63; 95% CI, 0.40–0.99).

Only 10 cases and 12 controls were excluded when we performed sensitivity analysis to ensure that exposures occurring in the 5 previous years to the diagnostic/interview did not affect to the estimates, and results remained the same. Similar results were also obtained when the lag period was extended to 10 years. Results for Hodgkin lymphoma risk were similar when we conducted an age and sex matched case–control, showing a stronger risk reduction (OR, 0.46; 95% CI, 0.28–0.77). As we had seen in the country-specific estimates, exposure to HMW agents showed opposite direction of risk for all lymphoma and B-cell lymphoma in Germany, while an increased OR was observed in Spain for Hodgkin lymphoma. In the sensitivity analysis excluding the centres one by one, we obtained a significant risk reduction for all lymphoma when Germany was excluded (OR, 0.78; 95% CI, 0.63–0.96), and similarly for B-cell lymphoma (OR, 0.79; 95% CI, 0.63–0.99). For Hodgkin

lymphoma, a stronger risk reduction was obtained when we excluded Spain from the pooled analysis (OR, 0.46; 95% CI, 0.27–0.80).

4. DISCUSSION

Our results suggest that exposure to HMW agents may moderately modulate the risk of lymphoma, being consistent with previous findings in the literature showing a lower risk among individuals with a medical history of allergies and allergic asthma and among those with high IgE levels at the time of diagnosis^[2] and^[11]. Our data based on lifetime occupational exposure are in agreement with a temporal relationship as exposures occurred at least 5 years before diagnosis. We did not observe a trend of lower lymphoma risks with increasing number of years exposed; the reduced risk was mainly seen among those exposed less than 8 years. Almost all lymphoma subtypes showed an OR less than one but were only statistically significant for Hodgkin lymphoma and for B-cell lymphoma among those exposed less than 8 years in a consistent manner across the different countries. Focusing on the HMW specific allergens, this risk reduction of lymphoma in exposed individuals was mostly due to exposure to animal antigens, flour-associated antigens, and latex antigens and was statistically significant for exposure to latex for all lymphoma and for Hodgkin lymphoma.

Several potential limitations of our study should be discussed. The study is based in hospital and population controls depending on the country and we found a low response rate in the population based studies. Hospital case–control studies are more likely to show a lower OR associated to medical conditions. To address a potential selection bias due to the inclusion of hospital controls that could be more likely to suffer asthma than cases, we excluded controls who were hospitalized due to respiratory diseases. Further, there were no major differences in the analysis when hospital and population based studies were compared. For Hodgkin lymphoma, which is our main finding, results were comparable in hospital-based and population-based centres. Results were mostly consistent between countries; differences were observed for B-cell lymphoma in Germany and for Hodgkin lymphoma in Spain. These differences could not be explained by a variation in the age distribution of the cases between countries, nor by a variation in the prevalence of exposure. Finally, the small numbers of some specific lymphoma types do not allow making inferences for some specific types.

HMW agents that are known to stimulate the immune system through an IgE mediated pathway were associated with a moderately decreased risk for B-cell lymphoma. The mechanism of antibody-dependent hypersensitivity and asthma is complex. HMW agents are complete antigens and cross-link with surface-bound IgE, leading to a cascade of events and eventually to an inflammatory response. Several inflammatory mediators, e.g. IL3, IL4 and IL5 cytokines, β -chemokines, are involved in this process. The mechanism underlying the association between exposure to HMW agents and lymphoma may be directly related to the nature of Th2 type responses. The fact that the potential protective effect of several IgE related exposures (i.e. asthma, atopy, occupational exposures or IgE levels) is seen in a wide range of lymphoma subtypes irrespective of aggressivity of the subtype and prior to

treatment, could be interpreted as a generic trigger linked to the Th1/2 equilibrium rather than a result of a biased approach of the epidemiological studies. Epidemiological evidence indicates that IgE mediated conditions such as asthma and allergy are inversely associated with lymphoma risk. In the pooled analysis of InterLymph Consortia, including over 13,000 cases of NHL and over 16,000 controls, a significant reduction of NHL risk was observed for history of allergy (OR, 0.80; 95% CI, 0.68–0.94). In this study the protective effect of asthma was largely explained by the joint presentation of other allergic conditions ^[2].

Breen et al. ^[23] evaluated several B-stimulatory cytokines and markers of Immune activation including IgE levels in HIV patients prior to NHL development. The authors identified increased levels of IL-6, sCD27 and sCD30 more than 3 years before the diagnosis of systemic NHL. No variations were observed however for IgE and sCD23, the low affinity receptor for IgE, suggesting that these latter ones were not in the pathway of HIV-related NHL.

Assessment of occupational exposures using a job exposure matrix (JEM) has been applied in many community-based epidemiological studies to assign cumulative exposure to workers. Since variability in exposure within job categories is typically not accounted for, this has been shown to lead frequently to an underestimation of the risk due to non-differential exposure misclassification. In addition, the validity of exposure assessment depends on the quality of the underlying information on occupational histories derived from interviews. The application of the specific occupational asthma JEM has been shown in large cohort studies to predict occurrence of asthma risk among exposed workers ^[24]. The advantage of using this matrix is the evaluation of a group of agents that occur in a variety of jobs. Data collection of lifetime history provided in the face to face interview and the posterior assignment of the job codes and of the specific exposure using the matrix is complex. The use of a labour-intensive expert assessment by industrial hygienists to re-evaluate specific exposures may lead to more valid exposure assignments with a higher specificity.

The association of lymphoma risk with IgE or other immunoglobulin levels as well as the association with clinical conditions such as allergy or asthma could alternatively be due to reverse causation through suppression of the immunologic response to allergens among lymphoma patients. In this respect it has been proposed that allergy and lymphoma could develop in parallel through similar immune-related mechanisms ^[25]. The approach followed in this study overcomes this problem since the evaluation of immune response is done through the estimation of lifetime exposure to known occupational chemical agents that affect this response and that are associated with asthma. The application of a 5-year lag in the evaluation of exposure further minimizes the potential for any reverse association of disease on the exposure. However, we cannot rule out misclassification of the exposure. This should not have a biased effect but could have resulted in attenuation of the exposure-response relationships and hence a lower power to detect a true association. Fig. 3 depicts in a very simplified manner the interrelationship of the potential mechanisms that may lead to lower risk of lymphoma and the potential alternative explanations as counterpart.

[FIGURE 3]

In conclusion, we observed a moderately reduced risk between occupational exposure to HMW agents and lymphoma risk, this reduction was found for most lymphoma subtypes, although statistical significance was reached only for Hodgkin lymphoma. This finding is plausible when interpreted in the light of the role of immunological factors in lymphomagenesis. Some inconsistencies in results, the small number of exposed cases, and the retrospective nature of the investigation prevent drawing conclusions on the causal nature of the association. We expect our results to stimulate further epidemiologic and mechanistic research in this field.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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TABLES AND FIGURES

Fig. 1. :Study population flow diagram.

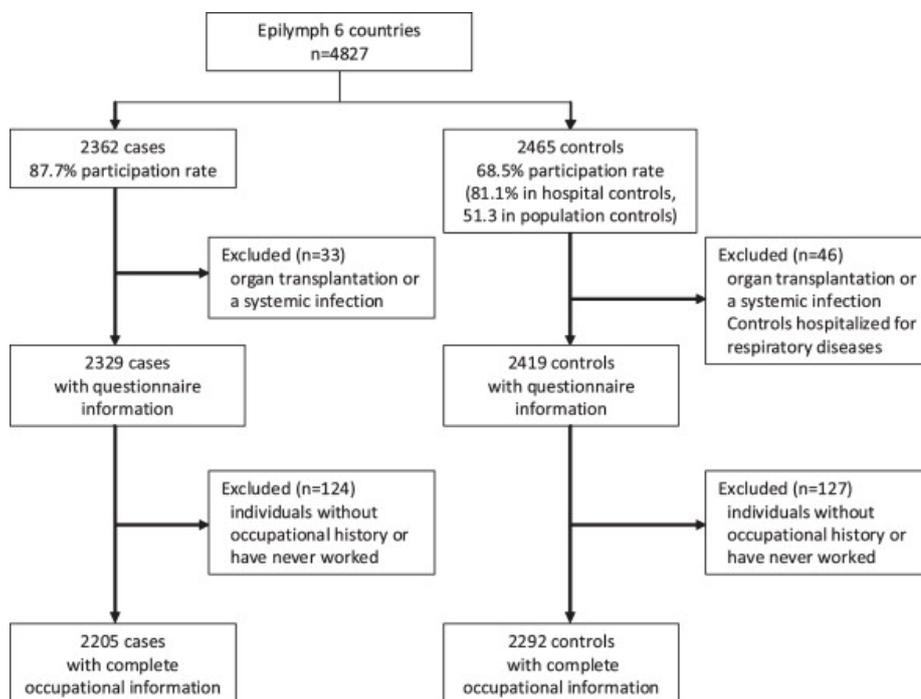


Table 1. Characteristics of the study population.

	Controls (n = 2296)	All lymphoma (n = 2205)	B-cell lymphoma (n = 1696)	Hodgkin lymphoma (n = 299)	T-cell lymphoma (n = 125)
Country					
Spain	546 (23.8)	534 (24.2)	424 (25.0)	56 (18.7)	42 (33.6)
France	253 (11.0)	281 (12.7)	227 (13.4)	30 (10.0)	16 (12.8)
Germany	694 (30.2)	681 (30.9)	524 (30.9)	100 (33.4)	34 (27.2)
Italy	297 (12.9)	228 (10.3)	190 (11.2)	22 (7.4)	12 (9.6)
Ireland	204 (8.9)	196 (8.9)	134 (7.9)	33 (11.0)	11 (8.8)
Czech Republic	302 (13.2)	285 (12.9)	197 (11.6)	58 (19.4)	10 (8.0)
Sex					
Female	1026 (44.7)	946 (42.9)	730 (43.0)	135 (45.2)	48 (38.4)
Age, mean (sd)	56 (15.7)	57 (15.7)	60 (13.6)	39 (15.3)	55 (15.0)
Educational level					
Low	1023 (44.6)	998 (45.3)	816 (48.1)	81 (27.1)	66 (52.8)

	Controls (n = 2296)	All lymphoma (n = 2205)	B-cell lymphoma (n = 1696)	Hodgkin lymphoma (n = 299)	T-cell lymphoma (n = 125)
Medium	952 (41.5)	885 (40.1)	647 (38.1)	157 (52.5)	44 (35.2)
High	321 (14.0)	322 (14.6)	233 (13.7)	61 (20.4)	15 (12.0)
Ever asthma diagnosis					
Yes	192 (8.4)	143 (6.5)	113 (6.7)	18 (6.0)	7 (5.6)
High molecular weight exposure					
Exposed	354 (15.4)	304 (13.8)	248 (14.6)	26 (8.7)	18 (14.4)
Other asthma high risk exposures					
Exposed	1126 (49.0)	1067 (48.4)	846 (49.9)	114 (38.1)	70 (56.0)
Asthma low risk exposures					
Exposed	1081 (47.1)	1067 (48.4)	854 (50.4)	116 (38.8)	58 (46.4)

Numbers (%) are given, unless otherwise indicated.

Table 2: Associations between exposure to high molecular weigh agents and lymphoma risk in the Epilymph study. Odds ratios (OR) and 95% confidence intervals (CI).

	n	n (%) Exposed	OR (95% CI)^a
Controls	2296	354 (15.4%)	1 (Reference)
All lymphoma	2205	304 (13.8%)	0.88 (0.74, 1.05)
B-cell lymphoma	1696	248 (14.6%)	0.91 (0.76, 1.09)
DLBCL and similar NHL	501	75 (15.0%)	0.93 (0.70, 1.23)
B CLL-SLL and similar NHL	395	60 (15.2%)	1.03 (0.75, 1.41)
Multiple myeloma	265	37 (14.0%)	0.86 (0.59, 1.26)
Follicular NHL	239	37 (15.5%)	0.89 (0.60, 1.30)
Marginal zone B-cell lymphoma	98	16 (16.3%)	0.95 (0.54, 1.68)
Mantle cell lymphoma	65	5 (7.7%)	0.58 (0.23, 1.51)
LPL and similar NHL	43	6 (14.0%)	0.83 (0.34, 2.04)
Splenic marginal zone B-cell lymphoma	38	8 (21.1%)	1.08 (0.48, 2.46)
Precursor B NHL	37	4 (10.8%)	0.71 (0.24, 2.09)
Hairy cell leukaemia	15	0 (0.0%)	n.e.
Hodgkin lymphoma	299	26 (8.7%)	0.62 (0.40, 0.98)
Classical HL	275	23 (8.4%)	0.58 (0.36, 0.94)
Non-classical HL	24	3 (12.5%)	1.34 (0.37, 4.87)
T-cell lymphoma	125	18 (14.4%)	0.97 (0.57, 1.66)
Mycosis T-cell NHL	35	9 (25.7%)	1.83 (0.81, 4.12)
Other T-cell NHL ^b	90	9 (10.0%)	0.64 (0.31, 1.31)

NHL: non-Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; CLL: chronic lymphocytic leukaemia; SLL: small lymphocytic lymphoma; LPL: lymphoplasmacytic lymphoma; n.e.: non-estimable.

^A Odds ratio and 95% confidence interval adjusted for age (categorical), sex and country.

^B Includes: precursor T-cell NHL, cutaneous T-cell NHL and other T-cell NHL.

Fig. 2: Country-specific associations and pooled estimates between exposure to high molecular weight agents and risk of lymphoma; ^aB-cell lymphoma includes: DLBCL and similar NHL, B CLL-SLL and similar NHL, multiple myeloma, follicular NHL, marginal zone B-cell lymphoma, mantle cell lymphoma, LPL and similar NHL, splenic marginal zone B-cell lymphoma, precursor B NHL, hairy cell leukaemia; ^bT-cell lymphoma includes: precursor T-cell NHL, mycosis T-cell NHL, cutaneous T-cell NHL and other T-cell NHL.

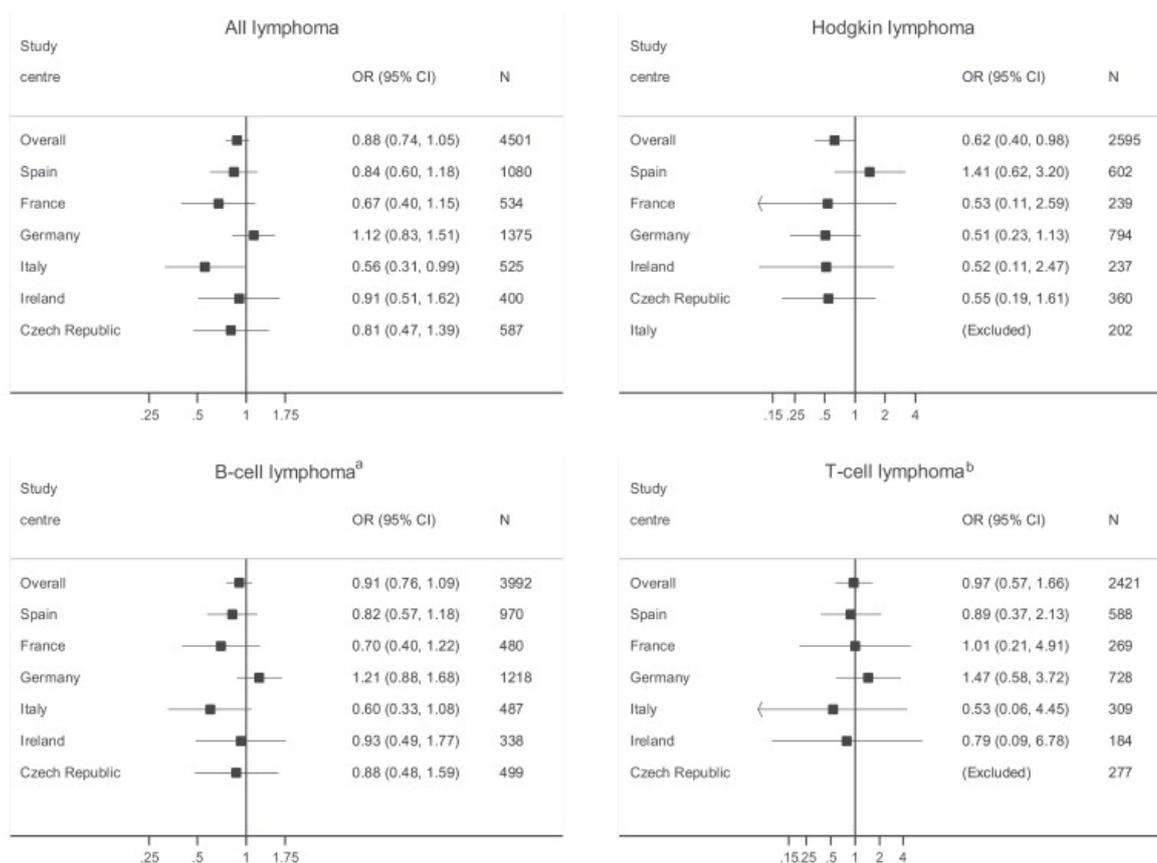


Table 3: Associations between duration and specific type of exposure to high molecular weight (HMW) agents and lymphoma.

	Controls		All lymphoma		B-cell lymphomaa		Hodgkin lymphoma	
	n (%)	n (%)	OR (95% CI) ^b	n (%)	OR (95% CI) ^b	n (%)	OR (95% CI) ^b	
Non-exposed ^c	1942	1901	1 (Reference)	1448	1 (Reference)	273	1 (Reference)	
Years of HMW exposure								
≤8 years	209 (9.1%)	152 (6.9%)	0.75 (0.60, 0.93)	118 (7.0%)	0.75 (0.59, 0.96)	17 (5.7%)	0.53 (0.31, 0.92)	
>8 years	145 (6.3%)	152 (6.9%)	1.08 (0.85, 1.38)	130 (7.7%)	1.12 (0.87, 1.45)	9 (3.0%)	0.89 (0.43, 1.85)	
Age at first HMW exposure								
> 18 years	162 (7.1%)	147 (6.7%)	0.95 (0.75, 1.20)	117 (6.9%)	0.98 (0.76, 1.26)	14 (4.7%)	0.60 (0.33, 1.09)	
≤18 years	192 (8.4%)	157 (7.1%)	0.83 (0.66, 1.04)	131 (7.7%)	0.85 (0.67, 1.08)	12 (4.0%)	0.65 (0.35, 1.24)	
HMW agents ^d								
Animal antigens	71 (3.5%)	59 (3.0%)	0.83 (0.58, 1.18)	47 (3.1%)	0.82 (0.56, 1.20)	4 (1.4%)	0.70 (0.24, 2.02)	
Flour-associated antigens	48 (2.4%)	40 (2.1%)	0.85 (0.55, 1.30)	32 (2.2%)	0.82 (0.52, 1.29)	3 (1.1%)	0.84 (0.24, 2.87)	
Plant-associated antigens	8 (0.4%)	14 (0.7%)	1.85 (0.77, 4.43)	11 (0.8%)	1.81 (0.72, 4.54)	2 (0.7%)	2.94 (0.49, 17.47)	
Mite and insect allergens	147 (7.0%)	134 (6.6%)	0.95 (0.73, 1.23)	114 (7.3%)	0.97 (0.74, 1.28)	9 (3.2%)	0.73 (0.35, 1.53)	
Antigenic enzymes	23 (1.2%)	20 (1.0%)	0.88 (0.48, 1.61)	18 (1.2%)	0.94 (0.51, 1.76)	2 (0.7%)	1.21 (0.26, 5.61)	
Latex antigens	116 (5.6%)	81 (4.1%)	0.74 (0.55, 0.99)	64 (4.2%)	0.83 (0.60, 1.14)	8 (2.8%)	0.32 (0.15, 0.69)	

^A B-cell lymphoma includes: DLBCL and similar NHL, B CLL-SLL and similar NHL, multiple myeloma, follicular NHL, marginal zone B-cell lymphoma, mantle cell lymphoma, LPL and similar NHL, splenic marginal zone B-cell lymphoma, precursor B NHL, hairy cell leukaemia.

^B Odds ratio and 95% confidence interval adjusted for age (categorical), sex and country.

^C Reference group for all models.

^D Non-mutually exclusive agents (one subject can be in more than one group).

Fig. 3. : Outline of the potential link between IgE mediated immune response and lymphoma risk and potential biases. IgE mediated conditions such asthma and allergy have been found to be inversely associated with lymphoma risk [11]; this association might be also attributed to a reverse causation when evaluated retrospectively. The evaluation of occupational exposures may be non-differentially misclassified with an attenuation of the observed association [15]. Diagnosis of allergic diseases may condition the selection of an occupation.

