



Birth order, allergies and lymphoma risk: Results of the European collaborative research project Epilymph

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Abstract

Lymphomas are a heterogeneous group of malignancies of the immune system. Recent studies suggest that immunological conditions which are modulated by lifestyle-dependent environmental determinants might affect lymphoma risk. We used data from Epilymph, a European multi-centric case–control study with 2480 cases and 2540 controls, to analyse the relationship between lifestyle-dependent immunological determinants and risk of lymphomas. We found an inverse relationship between risk of lymphoma and allergies, mainly respiratory (OR = 0.86, CI = 0.89–1.01) and food allergies (OR = 0.67, CI = 0.52–0.85), a slightly elevated lymphoma risk for first-born children (OR = 1.17, CI = 0.99–1.39) and only children (OR = 1.10, CI = 0.86–1.39). The inverse relationship between atopic disorders and risk of lymphomas is consistent with earlier observations. Our findings on birth order and lymphoma increase the inconsistency of findings across studies and suggest a critical reappraisal of potential underlying mechanisms.

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1. Introduction

Lymphomas are a heterogeneous group of malignant diseases of cells of the immune system. The best established risk factors are those related to down-regulation of immune function, e.g. genetically determined or acquired immune deficiencies including HIV infection or iatrogenically induced immune suppression after transplantation.

Recent studies suggest that risk might additionally be affected by immunological conditions, themselves modulated by lifestyle or culturally determined (e.g., family size, hygienic circumstances, outlined in the so called “hygiene hypothesis, for summary see [1]). Epidemiologically testable indicators of this hypothesis include birth order, assumed to be an indicator for variation in early-life exposure to infection, and a history of allergies as an indicator for lifestyle-related altered immune responsiveness.

Although this hypothesis is conceptually striking, current evidence supporting it appears inconclusive. While several

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studies have found increasing adulthood lymphoma risk with increasing sibship size or birth order [1–4], others have found no association [5–7] or opposite results [8,9].

The association to allergic disorders appears more conclusive: several studies have shown a statistically significantly reduced risk, some an insignificantly decreased risk or null result, but none have reported an elevated lymphoma risk associated with allergies (for details see [1]).

A limitation of many studies was the comparatively small study size largely preventing detailed analyses of different lymphoma entities, which would be appropriate given the heterogeneity of the disease. Here, we present results on the relationship between birth order and allergies and lymphoma risk in Epilymph. This large European collaborative research effort with about 2500 lymphoma cases and 2500 hospital or population controls allows for the analysis of entity-specific associations.

2. Materials and methods

Epilymph comprises case–control data from seven European countries (Czech Republic, Finland, France, Germany, Ireland, Italy, and Spain) based on a common core protocol and conducted between 1998 and 2004. In two of the studies, recruitment was population-based (Germany and Italy) and cases were identified and approached in hospitals and with office-based haematologists (Germany) from the

respective study areas. In the other countries recruitment was hospital-based, and all consecutive lymphoma cases in the participating hospitals were approached. Inclusion criteria were a pathologically verified lymphoma diagnosis according to the WHO classification [10]. Copies of pathology reports were collected for all enrolled cases. The average participation rate of cases was 87.7% (Table 1).

In the population-based studies, selection of controls was accomplished by drawing a random sample from population registers. In hospital-based studies, patients with diseases other than lymphoma were identified from the same hospitals from which the cases were recruited. Controlling for selection bias was attempted by excluding patients hospitalised due to cancer, organ transplantation, or a systemic infection. The average participation rate of control subjects was 68.5% (81.1% for hospital controls and 51.3% for population controls, $p < 0.0001$). Further details are in Fortuny et al. [25] or Besson et al. [26].

The original study comprised 2480 cases and 2540 controls. For the present analyses, data from Finland were excluded due to incompleteness at time of evaluation. Furthermore, seven controls who were hospitalized due to asthma were excluded from the control group leaving 2362 cases and 2458 controls for subsequent analyses.

The self-reported medical history of atopic disorders was obtained directly from study participants. The questionnaire asked ‘Do you remember if you have suffered more than once from any of the following diseases requiring medical treatment?’ For each positive response, the approximate age of disease onset was collected.

Data analysis was carried out for all lymphoma combined ($n = 2362$), the major subgroups Hodgkin lymphoma (HL, $n = 340$), B-non-Hodgkin lymphoma (B-NHL, $n = 1879$) and T-non-Hodgkin lymphoma (T-NHL, $n = 137$), and the more frequent entities (diffuse large B-cell lymphoma (DLBL, $n = 543$), follicular lymphoma (FL, $n = 251$), chronic lymphocytic leukaemia of B-cell type (B-CLL, $n = 414$) and multiple myeloma (MM, $n = 278$)).

2.1. Statistical analysis

Data analysis was carried out by unconditional logistic regression fitting the matching variables sex, age and country to all models. Relative risk was estimated by odds ratios (OR) and the associated 95% confidence intervals (95% CI) using SAS version 9 (SAS Institute, Inc., Cary, North Car-

Table 1
Basic characteristics of lymphoma patients and controls in Epilymph

	Cases n (%)	Controls n (%)
Number of participants	2362 (100)	2465 (100)
Participation rate (%)	87.7	68.5
Population-based studies (%)	88.9	51.3
Hospital-based studies (%)	86.9	81.1
Gender		
Female	1038 (44)	1143 (46)
Male	1324 (56)	1322 (54)
Age (quintiles)		
<41	487 (21)	510 (21)
41–54	452 (19)	495 (20)
55–63	474 (20)	488 (20)
64–71	527 (22)	529 (21)
71	420 (18)	443 (18)
Missing	2 (0.1)	0 (0.0)
Country		
Germany	710 (30)	710 (29)
Italy	262 (11)	336 (14)
Spain	591 (25)	631 (26)
France	298 (13)	276 (11)
Ireland	208 (9)	208 (8)
Czech Republic	293 (12)	304 (12)
Highest school level		
Secondary school	1084 (46)	1122 (46)
High school	926 (39)	991 (40)
University	331 (14)	338 (14)
Missing	21 (1)	14 (1)

Table 2
Birth order and lymphoma risk in Epilymph

Birth order	Cases/Controls	OR [†]	95% CI
Fourth or later-birth order child	502/548	1	–
Third-born child	348/384	0.98	0.81–1.18
Second-born child	583/677	0.91	0.77–1.08
First-born child	708/639	1.17	0.99–1.38
Only child	199/189	1.10	0.86–1.39

OR adjusted for sex, country, and age (continuously); [†] $p_{\text{Heterogeneity}} = 0.051$.

Table 3

Number of younger and older siblings and risk for lymphoma in Epilymph

Number of younger/older siblings	Younger siblings			Older siblings		
	Cases/Controls	OR [†]	95% CI	Cases/Controls	OR [‡]	95% CI
0	806/869	1	Reference	907/828	1	Reference
1	664/606	1.19*	1.02–1.37	583/677	0.79 [§]	0.68–0.91
2	359/400	0.98	0.82–1.16	348/384	0.85	0.71–1.01
3+	503/556	1.00	0.85–1.17	502/548	0.87	0.74–1.02

OR adjusted for sex, country, and age (continuously); * $p < 0.05$; [§] $p < 0.01$; [†] $p_{\text{Heterogeneity}} = 0.193$; [‡] $p_{\text{Heterogeneity}} = 0.076$.

olina). Tests of statistical significance were two-tailed. A test of heterogeneity of risks across countries was done using the likelihood ratios for interaction terms between the country and the variable of interest.

3. Results

3.1. Results for all lymphomas combined

Overall, the risk for all lymphoma was slightly increased for first-born children (OR = 1.17, $p = 0.056$) but not for only children (OR = 1.10, $p = 0.47$), compared to the reference group of fourth or later-birth order children (Table 2). The relationship was rather heterogeneous on the level of the individual countries ($p_{\text{Heterogeneity}} = 0.051$) ranging from a significant (Ireland) or almost significant (Italy) risk elevation over a null result (Czech Republic) to indications of a decreased risk (Germany). The OR for the second-born children was lower than that for all other children including the reference within whole Epilymph and for the countries with lower average number of children per family (Czech Republic, France and Germany with 2–3.5 children per family), while this was not seen among the countries with a higher average number of children per family (Ireland, Italy, Spain with 3.5–5 children per family). This pattern was consistent for both sexes, though the effects were more pronounced for males than for females (data not shown in tables).

Having one or more older siblings was associated with a decreased risk of lymphoma, while having one or more younger siblings gave an overall increased risk (Table 3). Both results were statistically significant for one older/younger sib (older: OR = 0.79, CI = 0.68–0.91/younger: OR = 1.19, CI = 1.02–1.37).

When dichotomised on one key element of the hygiene hypothesis, that is being an only or first-born child, and assigning all second, third or later born children into the reference group, a rather consistent pattern emerged showing an overall significantly increased OR = 1.21 (CI = 1.08–1.37) and an elevated OR for all individual countries statistically significant for Ireland and Italy (Fig. 1).

Since the condition of being an only or first-born child is a well-established risk factor for atopic disorders, we also explored the association between birth order and allergies among the controls to examine whether the variable

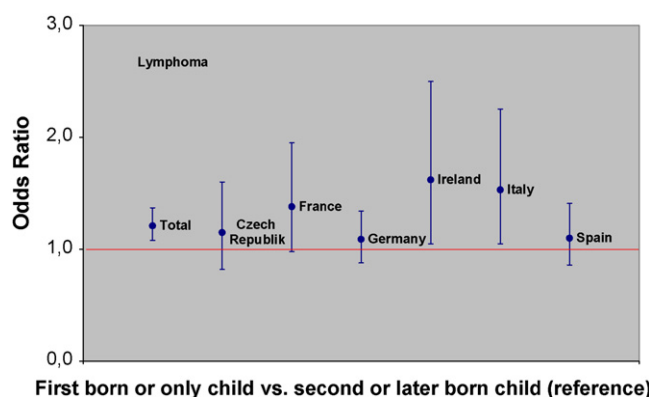


Fig. 1. Association of birth order with risk for lymphoma. Presented are the odds ratio for the comparison of first born or only children vs. second or later born children as reference.

“birth order” performs in the sense as the hygiene hypothesis assumes. Taking ever occurrence of respiratory allergies (hay fever, mite dust allergy, asthma) into account, no association was seen with being the only or first born child, neither overall (OR = 0.95, CI = 0.75–1.21) nor in the individual countries. Even when confined to those respiratory allergies which started at or before the age of 20, an age at which the effect is strongest for atopic disorders, the risk was

Table 4

History of atopic conditions and lymphoma risk in Epilymph

Atopy	Cases/Controls	OR	95% CI
Hay fever			
No	2175/2246	1	–
Yes	146/179	0.82	0.65–1.04, $p_{\text{Heterogeneity}} = 0.28$
Mite/dust allergy			
No	2217/2291	1	–
Yes	102/131	0.80	0.61–1.05, $p_{\text{Heterogeneity}} = 0.847$
Asthma			
No	2190/2228	1	–
Yes	150/212	0.72 [§]	0.58–0.89, $p_{\text{Heterogeneity}} = 0.77$
Food allergy			
No	2217/2253	1	–
Yes	112/171	0.67 [§]	0.52–0.85, $p_{\text{Heterogeneity}} = 0.061$
Respir. allergy ^a			
No	1998/2052	1	–
Yes	316/375	0.86	0.73–1.01, $p_{\text{Heterogeneity}} = 0.19$

OR adjusted for sex, (country), age (continuously); * $p < 0.05$; [§] $p < 0.01$.^a Respir. allergy = Hay fever or mite/dust allergy or asthma.

Table 5

Association of selected characteristics with risk of lymphoma entities

Entities and characteristics	Cases/Controls	OR	95% CI
HL			
First born or only child			
No	192/1609	1	–
Yes	145/828	1.25	0.97–1.62
Shared a bedroom as a child			
No	69/375	1	–
Yes	251/1999	0.78	0.56–1.08
Shared a bed as a child			
No	187/1089	1	–
Yes	69/793	0.93	0.64–1.33
Respiratory allergy			
No	287/2052	1	–
Yes	49/375	0.79	0.56–1.12
Food allergy			
No	320/2253	1	–
Yes	15/171	0.55	0.31–0.99
Med. allergy			
No	285/2096	1	–
Yes	51/322	1.18	0.83–1.68
NHL			
First born or only child			
No	1241/1609	1	–
Yes	762/828	1.21 [§]	1.06–1.37
Shared a bedroom as a child			
No	338/375	1	–
Yes	1617/1999	0.90	0.76–1.07
Shared a bed as a child			
No	812/1089	1	–
Yes	712/793	1.15	0.98–1.34
Respiratory allergy			
No	1711/2052	1	–
Yes	267/375	0.87	0.73–1.03
Food allergy			
No	1897/2253	1	–
Yes	97/171	0.69 [§]	0.53–0.90
Med. allergy			
No	1709/2096	1	–
Yes	287/322	1.10	0.93–1.31
B-NHL			
First born or only child			
No	1149/1609	1	–
Yes	713/828	1.22 [§]	1.07–1.38
Shared a bedroom as a child			
No	309/375	1	–
Yes	1509/1999	0.92	0.78–1.10
Shared a bed as a child			
No	749/1089	1	–
Yes	663/793	1.18*	1.00–1.39
Respiratory allergy			
No	1586/2052	1	–
Yes	252/375	0.89	0.74–1.05
Food allergy			
No	1762/2253	1	–
Yes	91/171	0.70*	0.53–0.91

Table 5 (Continued)

Entities and characteristics	Cases/Controls	OR	95% CI
Med. allergy			
No	1583/2096	1	–
Yes	272/322	1.13	0.94–1.35
DLBL			
First born or only child			
No	323/1609	1	–
Yes	212/828	1.30 [§]	1.07–1.59
Shared a bedroom as a child			
No	93/375	1	–
Yes	426/1999	0.82	0.63–1.06
Shared a bed as a child			
No	230/1089	1	–
Yes	159/793	0.97	0.75–1.25
Respiratory allergy			
No	466/2052	1	–
Yes	65/375	0.78	0.59–1.04
Food allergy			
No	504/2253	1	–
Yes	29/171	0.75	0.49–1.14
Med. allergy			
No	461/2096	1	–
Yes	73/322	1.05	0.79–1.38
FL			
First born or only child			
No	149/1609	1	–
Yes	100/828	1.21	0.92–1.59
Shared a bedroom as a child			
No	28/375	1	–
Yes	212/1999	1.34	0.88–2.04
Shared a bed as a child			
No	105/1089	1	–
Yes	74/793	1.14	0.79–1.62
Respiratory allergy			
No	208/2052	1	–
Yes	36/375	0.85	0.59–1.24
Food allergy			
No	225/2253	1	–
Yes	21/171	0.96	0.59–1.57
Med. allergy			
No	205/2096	1	–
Yes	42/322	1.21	0.85–1.74
MM			
First born or only child			
No	176/1609	1	–
Yes	99/828	1.12	0.85–1.46
Shared a bedroom as a child			
No	44/375	1	–
Yes	227/1999	1.01	0.71–1.44
Shared a bed as a child			
No	100/1089	1	–
Yes	125/793	1.46*	1.06–2.02
Respiratory allergy			
No	246/2052	1	–
Yes	28/375	0.65*	0.43–0.98

Table 5 (Continued)

Entities and characteristics	Cases/Controls	OR	95% CI
Food allergy			
No	266/2253	1	–
Yes	9/171	0.52	0.26–1.04
Med. allergy			
No	240/2096	1	–
Yes	35/322	0.99	0.67–1.44
B-CLL			
First born or only child			
No	259/1609	1	–
Yes	153/828	1.20	0.96–1.51
Shared a bedroom as a child			
No	78/375	1	–
Yes	324/1999	0.86	0.65–1.14
Shared a bed as a child			
No	147/1089	1	–
Yes	161/793	1.37*	1.04–1.81
Respiratory allergy			
No	346/2052	1	–
Yes	60/375	1.01	0.75–1.37
Food allergy			
No	393/2253	1	–
Yes	17/171	0.63	0.37–1.08
Med. allergy			
No	356/2096	1	–
Yes	52/322	0.99	0.72–1.37
Others B-NHL*			
First born or only child			
No	194/1609	1	–
Yes	112/828	1.11	0.86–1.43
Shared a bedroom as a child			
No	56/375	1	–
Yes	246/1999	0.86	0.62–1.19
Shared a bed as a child			
No	132/1089	1	–
Yes	112/793	1.14	0.84–1.54
Respiratory allergy			
No	251/2052	1	–
Yes	51/375	1.10	0.79–1.52
Food allergy			
No	292/2253	1	–
Yes	13/171	0.60	0.34–1.08
Med. allergy			
No	249/2096	1	–
Yes	56/322	1.49*	1.08–2.04
T-NHL			
First born or only child			
No	90/1609	1	–
Yes	46/828	1.06	0.73–1.54
Shared a bedroom as a child			
No	29/375	1	–
Yes	103/1999	0.68	0.44–1.06
Shared a bed as a child			
No	61/1089	1	–
Yes	47/793	0.83	0.53–1.31

Table 5 (Continued)

Entities and characteristics	Cases/Controls	OR	95% CI
Respiratory allergy			
No	120/2052	1	–
Yes	15/375	0.67	0.39–1.17
Food allergy			
No	130/2253	1	–
Yes	6/171	0.69	0.30–1.61
Med. allergy			
No	123/2096	1	–
Yes	13/322	0.74	0.41–1.33

Single models for each characteristics; OR adjusted for sex, country, age (continuously), and educational level; * $p < 0.05$; § $p < 0.01$; *including precursor-B-NHL lymphoplasmacytic lymphoma, mantel cell lymphoma, marginal zone lymphoma and hairy cell lymphoma.

not materially elevated (OR = 1.12, CI = 0.76–1.65). An analysis of the relationship of birth order to food allergies showed similar results (data not shown).

Odds ratios for association between lymphomas and respiratory allergies (hay fever, mite/dust allergy, and asthma) or food allergies were statistically significantly decreased for asthma and food allergies (Table 4). The relationship with food allergies was rather consistent across the countries with the exception of Ireland, while that with respiratory allergies was less pronounced and was not seen in the Czech Republic (OR = 1.6) and France (OR = 0.98).

3.2. Entity-specific results

Being an only child or the first born child was consistently associated with an increased risk for most major lymphoma entities (HL, DLBL, FL, B-CLL, other B-NHL), though the OR was not statistically significant in each instance (Table 5). No increase was observed for MM and T-NHL.

Sharing a bedroom during childhood was not associated with risk of any lymphoma entity. However, sharing the bed during childhood increased the OR for B-NHL, especially MM and B-CLL. For respiratory and food allergies, the ORs were decreased across entities with the exception of food allergies in FL, and respiratory allergies in CLL and “others” among the B-NHL. Again, many of the inverse associations were not statistically significant. Allergies to medications did not fit into this pattern of inverse relationships: ORs were either largely unchanged or slightly increased without reaching statistical significance with the exception of “other” B-cell lymphomas (OR = 1.47, CI = 1.07–2.02).

4. Discussion

The main results of this analysis were an inverse relationship between lymphoma risk and allergies, mainly respiratory and food allergies, and a slightly elevated lymphoma risk for first-born children, and, correspondingly, a decreased risk for having older siblings. The results were rather consis-

tent across countries and, with few exceptions, the different lymphoma entities.

4.1. Atopic conditions and lymphoma

The strongest finding was the decreased risk for subjects with a medical history of atopic conditions. This observation is consistent with reports from other parts of the world including data from the U.S. [4] and Australia [1] and speaks in favour of a true effect.

An underlying causal mechanism could be an effect of histamine released in large quantities in the course of an acute allergic reaction, as already proposed by Holly et al. [4]. Histamine has been found to counteract oxygen radical formation-induced dysfunction and apoptosis of T-cells and NK-cells [11] and might thus contribute to increased NK cell-based anti-tumour activity [12]. Another mechanism could be a general increase of cell-mediated immune responsiveness based on the observation that under atopic conditions Th2 and Th1-mediated immune reactions might be elevated [13]. A further view interprets the association with atopic disorders as indicative for a shift of the Th1/Th2 balance towards the Th2 direction assuming that Th2 dominance may reduce the risk of lymphoma.

4.2. Birth order and atopic conditions

In allergy research, birth order has consistently been found to be inversely related to the prevalence of atopic conditions, especially among children and adolescents, but also in young adults (see e.g., [14]). Both the number of younger and older siblings have shown the same inverse relationship. In terms of the hygiene hypothesis, low birth order (i.e., only child or first-born child) stands for fewer or later infectious contacts compared to sibs with higher birth order who may have acquired infections at an earlier age.

In the present study we found that birth order was only weakly related to atopic conditions, independent of whether age at onset of any of these conditions was unrestricted or restricted to childhood or adolescence. This observation suggests that the variable “birth order” may not have the same effect as that in allergy research. Further lymphoma studies addressing birth order should include examination of the effect of this variable on *atopic conditions* to evaluate whether it performs as assumed by the “hygiene hypothesis”.

4.3. Birth order and lymphoma

A further confusing finding was the relationship of the variable “birth order” with risk of lymphoma. In terms of the hygiene hypothesis, atopic disorders are promoted by delayed exposure to infectious agents early in life, and this is related to low birth order. Thus, the observed decreased risk for lymphomas among atopic subjects would be consistent with an association of a decreased lymphoma risk with low birth order. In this analysis, we found an *increased* risk for

lymphoma with low birth order. Though the effect was weak, it appeared consistent across the countries studied and the major lymphoma entities.

The data of Table 2 indicate a non-linear relationships which may be described best by a kind of U-shaped curve. Taking birth order as ungrouped variable and modelling its relationship to risk of lymphoma, incorporation of birth order as linear term led to an only small reduction of the log-likelihood of the model ($p=0.164$, negative sign of the coefficient), while adding the weakly non-linear term (birth order)^{1.05} led to a stronger reduction ($p=0.069$, positive sign of the coefficient). Together, these two terms constitute a parabolic (as a special case of U-shaped) curvature with elevated ORs for low and high birth orders and a minimum for second-born children ($p=0.046$ for the entire model) indicating a mixture of factors acting in opposite directions.

A non-linear association was also found in studies on birth order and atopic conditions [15]. For lymphoma, the present study agrees with observations of an increased risk in first-born or only-children [8,9], whereas, the recent Australian study and several previous studies found a strictly positive association of lymphoma risk with birth order [1–4].

Consistent with the elevated risk among first-born children was a decreased risk for having one or more *older* siblings which was also found specifically for HL by other authors [16,17].

Having older siblings is frequently considered indicative for earlier exposure to common infections. Correspondingly, observations of a decreased risk for having older siblings would suggest a beneficial effect of *early* exposure to common infection on lymphoma risk. In contrast, the results of Paffenbarger et al. [2], Holly et al. [3,4] and Grulich et al. [1] would indicate a beneficial effect of *delayed* exposure to common infections on lymphoma risk.

Since information on birth order is unlikely to be susceptible to recall bias, the inconsistent effects across studies may point to different underlying exposure conditions and might thus provide clues for a better understanding of the potentially heterogeneous conditions affecting the variable “birth order”. Country-specific results might thus be more instructive than pooling existing data within large-scale analyses.

4.4. Explanatory models

An immunology-related explanation for the conflicting findings on birth order and lymphoma risk might be that in atopic conditions to some extent exposure to *any* infection might be beneficial, while in lymphoma the *specificity* of infections might play a role and might differ across countries [18].

An alternative view calls the immunological interpretability of the variable birth order into question. Its use as an indicator for patterns of contact to immunogenic agents in early childhood is based on the assumption of uniformity of social contacts, hygienic conditions, usage of day care, etc. among families with few children and families with many

children. This is unlikely to be true taking the large range of average number of children per family into account (4.5 in Ireland, 2 in Germany). Rather, it may be more likely that living conditions in countries with small family size might be substantially different from those with large family size thus imprinting different effects on the variable “birth order”.

Furthermore, it has to be taken into account that to date even in allergy research the explanatory model for the birth order—allergy relationship based on delayed early life infection and impaired Th1/Th2 balance have not been consistently verified: recent research has failed to relate any measure of exposure to infection in childhood directly to birth order [19]; even alternative explanatory models (e.g., in utero programming hypothesis, pollution hypothesis) could not be ruled out by the available data (for details see [14]).

The current status of lymphoma research is similar allergy research in that the available data would not be sufficient even to reject the pollution hypothesis which refers to environmental pollution of the child by organochlorines mediated by breastfeeding: it would fit the present association of birth order with lymphoma risk, since organochlorines (a) were frequently found in breast milk in the past decades (e.g., [20]), (b) are candidate risk factors for lymphomas [21], (c) have been shown experimentally to be at highest levels in first-born children and decrease with increasing birth order (e.g., [22,23]), and (d) are found in human milk at different levels in different countries [20]. However, this issue could be resolved by evaluating specifically precursor B-cell lymphoma which arise from B-cells which have not yet had antigen contact but may have been exposed to chemical carcinogens circulating in the blood.

4.5. Limitations of study

A limitation of Epilymph is that the majority of the national studies are hospital-based (see Table 1), and in the two population-based studies the participation rate within the control group is comparatively low. In the hospital-based studies, appropriate criteria of eligibility have been defined to exclude subjects who were hospitalized due to acute infectious or immunological conditions. If this led to an underrepresentation of immunological disorders in the control group compared to the general population, it implied a shift of OR towards unity when decreased risks were investigated (e.g., atopic conditions). Internal comparisons between low and high birth order are unlikely to be affected by potential selection bias in the control group or potential selection bias by low participation rates in the population-based studies. The country-specific results and heterogeneity tests indicate that no systematic differences of findings between population-based and hospital-based studies occurred.

A further limitation is the questionnaire-based determination of atopic status of study participants. However, we only asked for atopic disorders which required medical treatment. Furthermore, we could show in a previous prospective study that there is a high degree of agreement between a reported

physician diagnosis and determination of the atopic status by IgE measurement in stored blood samples, and relative risks did not materially change by taking the one or the other mode of definition for atopy [24].

5. Conclusions

The observed inverse relationship between atopic disorders and risk of lymphomas is consistent with earlier observations. The findings on birth order and lymphoma risk increases the overall inconsistency of previous reports. A critical reappraisal of potential underlying mechanisms appears to be necessary. Further studies of birth order and lymphoma risk should also consider the effect of birth order on allergies when assessing the value of this variable as an indicator for potential underlying immunological mechanisms.

Conflict of interests statement

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