

The effect of atopy, childhood crowding, and other immune-related factors on non-Hodgkin lymphoma risk

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Abstract

Objective Since adult immune responsiveness is influenced by early childhood exposures, we examined the role of family size, history of atopic disease, and other

childhood immune-related exposures in a multi-center case-control study of NHL.

Methods Interviews were completed with 1,321 cases ascertained from population-based cancer registries in Seattle, Detroit, Los Angeles and Iowa, and with 1,057 frequency-matched controls, selected by random-digit dialing and from the Medicare files database. Multivariable logistic regression was used to estimate risk.

Results A history of any allergy (excluding drug allergies), decreased risk of all NHL (Odds Ratio [OR] = 0.7, 95% Confidence Interval [CI] = 0.6–1.0), diffuse large B-cell lymphoma [DLBCL] (OR = 0.6, 95% CI = 0.4–0.9), and follicular NHL (OR = 0.7, 95% CI = 0.5, 1.0). A similar effect was observed for hay fever. A history of eczema was associated with an increased risk of follicular lymphoma (OR = 1.9, 95% CI = 1.1–3.4), but not DLBCL (OR = 1.1, 95% CI = 0.6–2.0). Asthma did not affect risk. Youngest compared to oldest siblings had a 90% increased risk of DLBCL (95% CI = 1.2–3.1; *p* for trend with increasing birth order = 0.006), but not follicular lymphoma (OR = 1.1, 95% CI = 0.6–1.8).

Conclusions We infer that some childhood and immune-related factors may alter NHL risk.

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Introduction

The incidence rate of non-Hodgkin lymphoma (NHL) has been increasing world-wide for the past 50 years. Although little is known about the reasons for the increase, HIV-associated and iatrogenically induced severe immune

suppression increased during the same period and are the most well-accepted and consistently demonstrated risk factors [1]. It is possible that NHL risk also reflects more subtle differences in immune system responsiveness. The role of childhood exposures in shaping the adult immune system has been explored over the last few decades, particularly in relation to the occurrence of allergy and asthma. Normal immune development may require early exposure to infections; absence of such exposures may lead to an immune system skewed towards a T-helper 2 (Th2) type of immune response, which in turn promotes allergy and other atopic disease [2]. Interestingly, all twelve NHL case-control studies conducted since 1990 that examined atopy reported a reduction in risk of NHL associated with either a history of allergy in general or of a specific type of allergy [3–14]. There has been inconsistency with respect to the type of allergy associated, and only the most recent studies reported NHL histology-specific associations [11, 12, 14, 15].

Allergy, asthma, and eczema are atopic conditions with some clinical and immunological factors in common, and all have been linked to small family size and less crowded childhood conditions [16, 17]. These surrogate measures of childhood isolation or crowding have been associated with some hematologic neoplasms, but the direction of the association varies depending on the specific cancer. Youngest children in large families have a reduced risk of young adult Hodgkin lymphoma [18, 19] and possibly childhood leukemia [20]. Grulich and colleagues recently reported that being an only or first-born child significantly protected against NHL [11], and Bracci and colleagues found that being the youngest of many siblings increased risk [12], however three other studies did not observe an association between NHL and either sibship size or birth order [21–23].

To explore these hypotheses further, especially for NHL subtype-specific risk, we examined surrogate measures of childhood exposure to infections and other immune-related childhood exposures on the risk of developing NHL in a multi-center case-control study.

Methods

Case selection

We conducted this study in four areas with Surveillance, Epidemiology, and End Results (SEER) cancer registries [24]: the Detroit metropolitan area; northwestern Washington state; the state of Iowa; and Los Angeles County. The study was approved by the Institutional Review Board at each of the participating sites and at the National Cancer Institute. Residents of these geographic areas aged

20–74 years (inclusive) and had a first primary diagnosis of NHL between 1 July 1998 and 30 June 2000 were reported to study personnel using a rapid identification and reporting system at each registry (developed to reduce losses to follow-up through illness and death). In Iowa and Seattle, all consecutive cases were eligible, while in Los Angeles and Detroit all African American cases and only a random sample of non-African American cases were considered eligible for recruitment. HIV-positive cases were excluded. All cases were histologically confirmed, and cases were coded at each SEER registry according to the International Classification of Diseases-Oncology, 2nd Edition [25] updated to the 3rd edition [26]. For this report, we evaluated all NHL (9591, 9670–9723) and follicular (morphology codes 9690–9698) and diffuse large B-cell (DLBCL) (morphology codes 9680–9683), as coded by the SEER Program without central review.

Once patients were identified, letters were sent to their physicians explaining the study and eligibility criteria. Of 2,248 eligible cases, 320 (14%) died before we could conduct an interview, 127 (6%) could not be located, 16 (1%) had moved out of the area, and 57 (3%) had physician refusals. We attempted to contact the remaining 1,728, but 274 (16%) declined to be interviewed, and 133 (8%) never responded or were not interviewed because of illness, impairment or other reasons. This left 1,321 eligible cases who were enrolled into the study, for a participation rate of 76% of the cases we attempted to contact and an overall response rate of 59% based on all living and deceased cases presumed to be eligible. Approximately 60% of the cases were interviewed within six months of their diagnosis, and 84% were interviewed within one year of their diagnosis. Response rates were highest in Iowa (68%), among women (62%), among white subjects (77%) and at ages 45–54 (64%). Response rates were also higher for patients with follicular (67%) than DLBCL) (51%) NHL.

Control selection

Population-based controls were selected from area residents aged 20–74 years (inclusive), and were frequency matched to the case age within five years and sex distribution. Controls with a prior history of NHL or HIV infection were excluded. To select controls below 65 years of age, we used one-step list-assisted random digit dialing (RDD) [27]. In total, 42,640 telephone numbers were dialed over three time periods, and 78.5% of contacts provided a roster consisting of name, age, sex, and race (for Detroit and Los Angeles) of each household member. Subjects were then selected at random from these household rosters, stratified on geographic area, sex, age, and race. Controls aged 65–74 years were randomly selected from Center for Medicare and Medicaid Services files of residents eligible

for Medicare, also stratified on geographic area, sex, age, and race.

Of the 2,409 controls selected, 28 (1%) died before contact, 311 (13%) could not be located, and 24 (1%) had moved out of the geographic area. We attempted to contact a total of 2,046, but 839 (41%) declined to be interviewed and 150 (6%) failed to complete an interview because of illness, impairment or other reason. Thus, a total of 1,057 eligible controls were interviewed, for a participation rate of 52% of the controls that we attempted to contact, and of 44% among all presumed eligible controls.

Data collection

We obtained written informed consent from each participant prior to interview. To accommodate a large number of questions, we used a split-sample design, with a core set of questions given to all respondents and the remainder given to participants in either Group A (all African American and 50% of non-African American participants) or Group B (50% of non-African American participants, e.g., the non-African American patients were randomly assigned to Group A or Group B). During the interview, the interviewer administered a computer-assisted personal interview (CAPI) that included demographics, height and weight, occupational history, pesticide exposure and hair dye use, as well as number of siblings and birth order. The Group A CAPI also included an extended medical history, including childhood conditions such as asthma and eczema, and surgeries such as tonsillectomy and appendectomy. All items required an ever/never dichotomous response as well as a date of the onset or procedure. The Group B CAPI contained an abbreviated medical history but detailed questions including those about specific types of allergy.

Data analysis

Odds ratios were calculated using unconditional logistic regression, adjusting for reference age (<45 years old, 45–64 years old, and >65 years), race (white vs. other), education (<12 years, 12–15 years, and >16 years) and study site (Iowa, Seattle, Detroit, Los Angeles). Analyses were further stratified by the two most common NHL histological types, DLBCL, and follicular lymphoma. Tests for trends across sibship size and birth order were calculated using logistic regression, assuming linearity of the categories.

Distributions of age of onset of childhood conditions and procedures were examined in controls and appropriate cut-offs based on the distributions were made such that risk could be assessed for both childhood and adult exposures. The reference group for analyses of sibship size consisted of only children, but the reference group for birth order

consisted of first-born children with only children excluded. We also examined sibship size and birth order associations with NHL separately by gender to evaluate heterogeneity by this variable.

To examine possible confounding, we evaluated the risk of tonsillectomy, birth order, asthma, eczema, hay fever, and any allergy excluding medications by education level (3 categories, as above), among controls, by estimating odds ratios using unconditional logistic regression adjusted for study center, race/ethnicity, age, and gender. We did not adjust CI's or *p* values for multiple comparisons.

Results

Cases and controls were generally similar with respect to demographic characteristics (Table 1). As described above, African American cases and controls were assigned exclusively to the Group A CAPI version of the questionnaire and thus did not answer questions about history of allergy.

Atopic and childhood conditions

Hay fever was associated with a reduced risk of NHL, DLBCL, and follicular lymphoma (Table 2). Allergy to medications was associated with statistically significant increased risk of all NHL combined and DLBCL. The 95% confidence intervals (CIs) for the risk estimates for all other types of allergies did not exclude 1.0, but most odds ratios were between 0.6 and 0.8 for each type of NHL examined. A history of any allergy, excluding allergy to medications, was associated with an odds ratio (OR) of 0.7 for all NHL combined and for follicular lymphoma, and with an OR of 0.6 for DLBCL. Age of onset of the allergy did not affect the risk estimates (data not shown).

Asthma was not associated with NHL risk overall or with risk of DLBCL or follicular lymphoma (Table 3). The risk of NHL associated eczema varied by subgroup (Table 3). Eczema was associated with an increased risk of follicular lymphoma (OR = 1.9, 95% CI = 1.1–3.4), but not with all NHL combined or DLBCL.

Childhood crowding and family structure

There was no clear trend in NHL risk by maternal age, although being born to a mother who was 35 years or older at the index birth conferred a 1.6-fold marginally significant increased risk of all NHL combined (95% CI = 1.0–2.4) (Table 4). Neither the number of siblings, birth order, nor the length of the interval between births of siblings contributed to the risk of all NHL combined or follicular

Table 1 Demographic characteristics of cases and controls

Category	All subjects		Subjects who responded to Questionnaire A		Subjects who responded to Questionnaire B	
	Cases (n = 1321)	Controls (n = 1057)	Cases (n = 759)	Controls (n = 589)	Cases (n = 551)	Controls (n = 462)
<i>Sex, n (%)</i>						
Male	711 (53.8)	546 (51.7)	410 (54.0)	304 (51.6)	294 (53.4)	239 (51.7)
Female	610 (46.2)	511 (48.3)	349 (46.0)	285 (48.4)	257 (46.6)	223 (48.3)
<i>Age at diagnosis or selection, years, n (%)</i>						
20–34	81 (6.1)	58 (5.5)	43 (5.7)	41 (7.0)	37 (6.7)	16 (3.5)
35–44	166 (12.6)	104 (9.8)	89 (11.7)	64 (10.9)	74 (13.4)	39 (8.4)
45–54	289 (21.9)	196 (18.5)	168 (22.1)	125 (21.2)	118 (21.4)	69 (14.9)
55–64	350 (26.5)	253 (23.9)	206 (27.1)	135 (22.9)	143 (26.0)	118 (25.5)
65–74	435 (32.9)	446 (42.2)	253 (33.3)	224 (38.0)	179 (32.5)	220 (47.6)
Mean age (standard deviation)	56.4 (12.6)	58.1 (12.4)	56.6 (12.4)	56.9 (12.7)	56.2 (12.8)	59.9(11.6)
<i>Race, n (%)</i>						
White	1123 (85.0)	843 (79.8)	604 (79.6)	407 (69.1)	519 (94.2)	436 (94.4)
African American*	110 (8.3)	151 (14.3)	100 (13.2)	145 (24.6)	–	–
Other	88 (6.7)	63 (6.0)	55 (7.3)	37 (6.3)	26 (5.6)	32 (5.8)
<i>Center, n (%)</i>						
Detroit	319 (24.2)	214 (20.3)	238 (31.4)	138 (23.4)	80 (14.5)	75 (16.2)
Iowa	361 (27.3)	276 (26.1)	170 (22.4)	124 (21.1)	188 (34.1)	149 (32.3)
Los Angeles	319 (24.2)	273 (25.8)	187 (24.6)	172 (29.2)	132 (24.0)	101 (21.9)
Seattle	322 (24.4)	294 (27.8)	164 (21.6)	155 (26.3)	151 (27.4)	137 (29.7)
<i>Education, years, n (%)^a</i>						
0–11	128 (9.7)	111 (10.5)	85 (11.2)	61 (10.4)	42 (7.6)	50 (10.8)
12–15	815 (61.7)	616 (58.3)	471 (62.1)	361 (61.3)	337 (61.2)	252 (54.6)
16 or more	377 (28.6)	330 (31.2)	202 (26.7)	167 (28.4)	172 (31.2)	160 (34.6)
<i>Histology</i>						
Follicular	319 (24.2)	–	172 (22.7)	–	145 (26.3)	–
DLBCL	417 (31.6)	–	224 (29.5)	–	189 (34.3)	–
T-cell	82 (6.2)	–	54 (7.1)	–	28 (5.1)	–
Other	459 (34.8)	–	282 (37.2)	–	172 (31.2)	–
Unknown	44 (3.3)	–	27 (3.6)	–	17 (3.1)	–

^a Information on education was missing for one case

lymphoma (Tables 4 and 5). However, among subjects with at least three siblings, there was a borderline significant trend between increasing birth order and risk of all NHL combined ($p = 0.05$) (Table 4). The association was stronger when DLBCL was considered separately. Youngest children had a 1.9-fold increase in risk of DLBCL compared to first-born children (95% CI = 1.2–3.1; p for trend = 0.006) (Table 5). There was no association between sibship size or birth interval and risk of DLBCL, or between family structure and follicular lymphoma risk.

We observed slightly different effects in men and women for DLBCL risk and birth order. Compared to first-born women, last-born women had more than twice the risk of DLBCL (OR = 2.2, 95% CI = 1.1–4.0); by contrast, the

effect among men was weaker and the CIs included 1.0 (OR = 1.3, 95% CI = 0.7–2.5).

Sharing a bedroom as a child was associated with a non-significant increased risk of all NHL combined, DLBCL, and follicular NHL (Table 6). The number of different childhood residences prior to age 10 was not related to risk (5+ residences vs. 1 residence OR = 0.9, 95% CI = 0.6–1.3).

When the reference group was 4 or more siblings, we observed little difference in risk among those with fewer siblings (OR for 4+ vs. 3 siblings = 1.0; OR for 4+ vs. 2 siblings = 1.0; OR for 4+ vs. 1 or 0 siblings = 0.8, p for trend 0.85). First-born children had no excess risk compared to children born second or later (OR = 1.0, 95% CI = 0.7–1.2).

Table 2 History of allergy and risk of all non-Hodgkin lymphoma combined (All NHL); diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (Follicular)

	Controls	All NHL cases		DLBCL Cases		Follicular	
	<i>n</i>	<i>n</i>	OR ^a (95% CI ^b)	<i>n</i>	OR ^a (95% CI ^b)	<i>n</i>	OR ^a (95% CI ^b)
<i>Type of allergy</i>							
<i>Hay fever</i>							
No	305	401	Ref.	142	Ref.	107	Ref.
Yes	155	149	0.7 (0.5–0.9)	46	0.6 (0.4–0.9)	38	0.7 (0.5–1.1)
<i>Food allergies</i>							
No	379	473	Ref.	160	Ref.	126	Ref.
Yes	82	78	0.8 (0.5–1.1)	29	0.8 (0.5–1.4)	19	0.7 (0.4–1.3)
<i>Animal allergies</i>							
No	398	477	Ref.	168	Ref.	126	Ref.
Yes	63	74	0.9 (0.6–1.3)	21	0.7 (0.4–1.2)	19	0.9 (0.5–1.6)
<i>Insect allergies</i>							
No	419	501	Ref.	174	Ref.	136	Ref.
Yes	42	48	0.9 (0.6–1.4)	13	0.7 (0.3–1.3)	9	0.6 (0.3–1.3)
<i>Dust allergies</i>							
No	357	429	Ref.	152	Ref.	114	Ref.
Yes	105	119	0.9 (0.7–1.2)	36	0.7 (0.5–1.1)	30	0.8 (0.5–1.3)
<i>Allergies to Medications</i>							
No	320	358	Ref.	120	Ref.	96	Ref.
Yes	141	193	1.4 (1.1–1.8)	69	1.6 (1.1–2.4)	46	1.3 (0.7–1.2)
<i>Any allergy</i>							
No	162	207	Ref.	73	Ref.	58	Ref.
Yes	298	343	0.9 (0.7–1.2)	116	0.9 (0.6–1.3)	86	0.8 (0.5–1.2)
<i>Any allergy (Excluding allergy to medications)</i>							
No	285	260	Ref.	104	Ref.	78	Ref.
Yes	210	252	0.7 (0.6–1.0)	85	0.6 (0.4–0.9)	67	0.7 (0.5–1.0)

^a Odds ratio calculated using multivariable logistic regression adjusted for study center, age, gender, race, and education^b 95% Confidence Interval**Table 3** Childhood/adolescent medical conditions and surgeries and risk non-Hodgkin lymphoma combined (All NHL); diffuse large B-cell lymphoma (DLBCL), and follicular lymphoma (Follicular)

	Controls	All NHL Cases		DLBCL Cases		Follicular	
	<i>n</i>	<i>n</i>	OR ^a (95% CI ^b)	<i>N</i>	OR ^a (95% CI ^b)	<i>n</i>	OR ^a (95% CI ^b)
<i>Asthma</i>							
No	416	544	Ref.	168	Ref.	118	Ref.
Yes	48	60	1.0 (0.7–1.5)	17	0.9 (0.5–1.6)	19	1.5 (0.8–2.7)
<i>Eczema</i>							
No	429	552	Ref.	174	Ref.	116	Ref.
Yes	35	52	1.2 (0.8–1.9)	11	0.9 (0.4–1.8)	21	2.3 (1.1–4.2)
<i>Tonsillectomy</i>							
No	262	337	Ref.	116	Ref.	66	Ref.
Yes	202	267	1.0 (0.8–1.3)	69	0.8 (0.5–1.2)	71	0.8 (0.5–1.2)

^a Odds ratio calculated using multivariable logistic regression adjusted for study center, age, gender, race, birth order, and, education^b 95% Confidence Interval

Table 4 Maternal age, family structure, and risk of all non-Hodgkin's lymphoma combined

Family structure	Category	All NHL		
		Cases/Controls	OR ^a	95% CI ^b
Maternal age at birth	Under 26	305/222	1.2	0.9–1.5
	26–35	260/212	Ref.	–
	Over 35	71/36	1.6	1.0–2.4
	<i>p</i> for trend			0.13
Number of Siblings	0 or 1	53/52	Ref.	-
	2	165/124	1.2	0.7–1.8
	3	156/109	1.2	0.8–2.0
	4	90/89	0.9	0.6–1.5
	5	71/48	1.4	0.8–2.3
	6	39/29	1.2	0.6–2.3
	7+	107/74	1.5	0.9–2.4
	<i>p</i> for trend			0.45
Birth Order ^c	First-born	195/144	Ref.	-
	Middle-born	207/183	0.9	0.6–1.2
	Last-born	173/105	1.2	0.9–1.7
	<i>p</i> for trend			0.11
Interval separating births	>4 years apart	447/344	Ref.	-
	≤4 years apart	125/86	1.1	0.8–1.5
≤3 Siblings	First-born	143/106	Ref.	-
Birth order ³	Middle-born	45/37	0.9	0.5–1.4
	Last-born	118/78	1.1	0.7–1.6
	<i>P</i> for trend			0.72
Interval separating births	>4 years apart	91/61	Ref.	-
	≤4 years apart	212/157	0.9	0.6–1.4
>3 Siblings	First-born	52 /39	Ref.	-
Birth order ^c	Middle-born	162 /145	0.9	0.5–1.5
	Last-born	55 /27	1.7	0.9–3.4
	<i>P</i> for trend			0.05
Interval separating births	>4 years apart	34 /25	Ref.	-
	≤4 years apart	235 /186	0.9	0.5–1.7

^a Odds ratio adjusted for study center, gender, race, age, and education^b 95% confidence interval^c Excluding only children

Relationship between education and childhood exposures in controls

Among controls, increasing education level was associated with increasing risk of tonsillectomy and all of the childhood atopic conditions except asthma (Table 7), although only the trend for any allergy excluding medication allergies was statistically significant. No association was observed between birth order and education; however the reference group contained only 8 exposed subjects.

Discussion

Overall, a history of allergies was associated with a decreased risk of all NHL combined and NHL subtypes. In other studies, hay fever is the type of allergy most often associated with protection, with odds ratios ranging from 0.5 [5, 6] to 0.7 [7, 11, 12] and 0.8 [14], consistent with our results. Additional evidence supporting a link was demonstrated in a hospital-based NHL case-control study in which persons with high occupational exposure to allergens had a significantly decreased risk, especially for DLBCL

Table 5 Maternal age, family structure, and risk of diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (Follicular)

Family structure	Category	DLBCL			Follicular		
		Cases/Controls	OR ^a	95% CI ^b	Cases/Controls	OR ^a	95% CI ^b
Number of Siblings	0–2	112/285	Ref.	–	95/285	Ref.	–
	3+	85/240	1.0	0.7–1.4	76/240	1.0	0.7–1.4
Birth order ^c	First-born	47/144	Ref.	–	47/144	Ref.	–
	Middle-born	57/183	1.0	0.6–1.6	53/183	0.9	0.6–1.5
	Last-born	64/105	1.9	1.2–3.1	36/105	1.1	0.6–1.8
	<i>p</i> for trend			0.006			0.9
Interval separating births	>4 years apart	131/344	Ref.	–	107/344	Ref.	–
	≤4 years apart	36/86	1.0	0.6–1.6	29/86	1.0	0.6–1.7

^a Odds ratio adjusted for study center, gender, race, age, and education^b 95% confidence interval^c Excluding only children**Table 6** Number of other children who slept in the bedroom and risk of NHL by subtype

No. Children In Bedroom	NHL combined		DLBCL		Follicular	
	Ca ^a /Co ^b	OR ^c (95% CI ^d)	Ca ^a /Co ^b	OR ^c (95% CI ^d)	Ca ^a /Co ^b	OR ^c (95% CI ^d)
None	265/221	1.0 (ref)	83/221	1.0 (ref)	55/221	1.0 (ref)
1	315/234	1.1 (0.9–1.5)	85/234	1.0 (0.7–1.4)	84/234	1.5 (1.0–2.2)
2+	177/133	1.2 (0.9–1.7)	55/133	1.3 (0.9–2.1)	33/133	1.2 (0.7–2.0)
Total	758/589	<i>p</i> for trend = 0.36	224/589	<i>p</i> for trend = 0.33	172/589	<i>P</i> for trend = 0.14

^a Cases^b Controls^c Odds Ratio calculated using multivariable logistic regression, adjusted for study center, age, race/ethnicity, gender, and education^d Confidence Interval

(OR = 0.5, 95% CI = 0.2–1.1) [28]. Most cohort studies have not found a similar protective association between NHL and allergy [29–35], however these studies were generally based on relatively young persons and thus very few cases to be meaningfully interpreted.

Results from previous studies examining asthma and eczema in association with NHL risk have been mixed [3, 15, 29, 34, 35]. There is no clear, consistent, and internationally recognized definition for asthma. The phenotype consists of a heterogeneous group of subtypes, and not all subtypes have an allergic component. Furthermore, the majority of the subjects reported asthma onset as adults, which has a less clear relationship to childhood exposures. Eczema is a condition that has both an allergic and an inflammatory component which may explain the increased risk observed here.

In this study, youngest children from large families had an increased risk of NHL, especially of DLBCL, but not of follicular lymphoma. Birth order was more strongly related to risk than the total number of siblings or other surrogates for childhood crowding. Two studies reported similar associations between birth order and risk of all NHL

combined; one reported a stronger effect of birth order compared to sibship size [11] and there was an equally strong effect of number of siblings and birth order in the other [12]. Three European case–control studies reported no association with family structure [21–23] although one reported a weak positive association between sharing a bedroom as a child and increased NHL risk [23].

Of the eight pathogens that have been implicated as etiologic factors for NHL [36, 37], only *H. pylori* infection is positively associated with late birth order and large family size [38], therefore other factors may explain the birth order effect. The maternal immune responses to the fetus can be affected by previous pregnancies [39], and this maternal response may modulate the immune system environment that subsequently develops in these last-born children. Another possibility is that the reduced risk associated with allergy could be the true underlying risk factor that explains the birth order effect, since allergy is generally inversely associated with late birth order. It is possible that IgE-mediated anti-tumor responses may be directly involved in protection from the development and/or growth of NHL. Therefore, an enhanced ability to mount

Table 7 Association between childhood exposure variables and education^a within controls

Education ^a (years)	Condition (Yes/No)	OR ^c (95% CI ^d)
<i>Tonsillectomy</i>		
<12 ^b	19/42	1.0
12–15	141/220	1.3 (0.7–2.4)
16+	77/90	1.7 (0.9–3.4)
<i>p</i> for trend ^e		0.08
<i>Eczema</i>		
<12 ^b	2/59	1.0
12–15	25/336	1.8 (0.4–7.9)
16+	14/153	2.4 (0.5–11.8)
<i>p</i> for trend ^e		0.21
<i>Asthma</i>		
<12 ^b	7/54	1.0
12–15	46/315	1.1 (0.4–2.6)
16+	13/154	0.5 (0.2–1.5)
<i>p</i> for trend ^e		0.08
<i>Hay fever</i>		
<12 ^b	11/39	1.0
12–15	76/174	1.5 (0.7–3.2)
16+	67/93	1.9 (0.9–4.2)
<i>p</i> for trend ^e		0.08
<i>Any allergy^f</i>		
<12 ^b	19/31	1.0
12–15	128/124	1.5 (0.7–2.7)
16+	105/55	2.3 (1.2–4.6)
<i>p</i> for trend ^e		0.008
<i>Last-born</i>		
<12 ^b	8/28	1.0
12–15	63/199	1.0 (0.4–2.4)
16+	34/98	0.9 (0.4–2.3)
<i>p</i> for trend ^e		0.8

^a Education considered as a categorical variable (<12 years, 12–15 years, 16+ years)

^b Reference group

^c Odds ratio for per unit increase in category

^d 95% Confidence Interval

^e *p*-value for linear trend calculated from chi-square using unconditional logistic regression with 1 degree of freedom, adjusting for age, gender, race/ethnicity, and study center

^f Any allergy excluding allergies to medications

IgE-mediated immune responses, which would be expected to be associated with an elevated incidence of atopy, may protect from the development of NHL.

Alternatively, the birth order effect could be explained by exposure to some general aspect of infection, or the reaction to it, rather than by a specific pathogen. Younger children from large families are exposed earlier to pathogens transmitted by the fecal-oral route, than children from smaller families [40]. Components of these pathogens,

such as endotoxin, may act through the innate immune system to downregulate the Th2 immune response in early childhood [2]. In fact, endotoxin exposure links many of the risk factors. Exposure to farming has long been recognized as a risk factor for NHL [1] and as a protective factor for allergy [41]. Children of farmers have greater exposure to endotoxin than children of non-farmers [42] and they also have increased expression of toll-like receptors (innate immune receptors that recognize bacterial components, including endotoxin) [43]. Within the last two years, polymorphisms in toll-like receptor genes have been linked to NHL risk [44, 45].

Alternative explanations for our findings might include selection bias, recall bias, confounding and chance. The response rates for both cases and controls were relatively low and thus it is possible that certain groups were under- or over-represented, affecting the results. This would be especially true if cases or controls from lower socioeconomic (SES) groups preferentially participated, since larger family size is associated with poorer education. In fact, both cases and controls were less likely to come from lower SES groups (Shen, submitted). Therefore, although lower SES groups may be under-represented in this study, there was no differential response based on SES between the cases and controls. Also, we generally observed the expected correlations between education and the childhood exposures examined within controls, suggesting that the controls were representative with respect to the exposures of interest in spite of the low response rate.

To evaluate the possibility of non-response bias further, we examined the main associations within subgroups of study center, race/ethnicity, and education. When restricted to the study center with the highest response rate (Iowa), the associations were unchanged and remained statistically significant. In fact, the associations remained unchanged across all strata with sufficient numbers. This somewhat lessens concerns regarding selection bias or confounding impacting our results, although there could be unmeasured confounders strongly related to both atopy and disease risk. The consistency of the ORs for most types of allergy in this study and in others suggests that our observations are not the result of chance.

Since recall bias usually involves over-reporting of a condition by a case, and therefore a positive association with the disease, this seems an unlikely explanation for the deficit of most allergies in cases compared to controls. The significantly increased risk associated with drug allergies that we observed may be due to recall bias, since patients may inadvertently include reactions to chemotherapy. However, if NHL itself causes a suppression of the allergic response, patients may confuse early symptoms with distant medical history. There has been one hospital case series reporting that NHL patients may experience a

decrease in allergic symptoms as a result of developing NHL [46].

More recently, Melbye and colleagues demonstrated that IgE levels did not differ between NHL cases and controls, all women, in samples collected during a pregnancy years prior to diagnosis, and that pre-diagnostic antigen-specific IgE reactivity decreased as the time of diagnosis approached [14]. Interpretation of these results is complicated, because pregnancy, parity [40] and smoking [47] all can affect IgE levels, and IgE levels are not completely correlated with atopy. Furthermore, the number of NHL cases identified in the pregnancy cohort through registry linkage was relatively small. Therefore, although this work raises questions about the nature of the association between atopy and NHL risk, the results are not conclusive and do not negate the possibility of an etiologic role for atopy.

Because our observations of allergy and birth order associations with NHL are consistent with those of other published studies, and because the relationship of these risk factors to each other are internally consistent, we conclude that the association of NHL risk and both birth order and allergy are supportive of an etiologic association. One possible model for one NHL risk pathway consistent with our observations is shown in Fig. 1. Late birth order, increased numbers of siblings, and exposure to farming all result in greater exposure to endotoxin or other bacterial components at an early age. These exposures could result in an alteration of the immune response leading to increased susceptibility to NHL. Conversely, the lack of these early risk factors increases the risk of atopy, which is

associated with an increased Th2 immune response and a deficit of NHL.

Since family size is decreasing [48] and atopy is increasing [49] in developed countries, these risk factors cannot explain the increasing incidence rates of NHL over the last century. Nevertheless, they may offer clues to causal factors. Case-control studies now under way are evaluating genetic and environmental interactions that can identify mechanistic pathways by which atopy and birth order affect risk, and larger pooled studies could confirm the histology-specific associations we observed for childhood crowding. Given a large sample size, appropriate biological samples, and sufficient length of the follow-up, cohort studies could more definitively assess the role of atopy. We have previously compared the unaffected identical twins of Hodgkin lymphoma case to unrelated controls to link interleukin-6 to disease susceptibility [50], and such a design might be used to identify links between NHL and childhood experiences.

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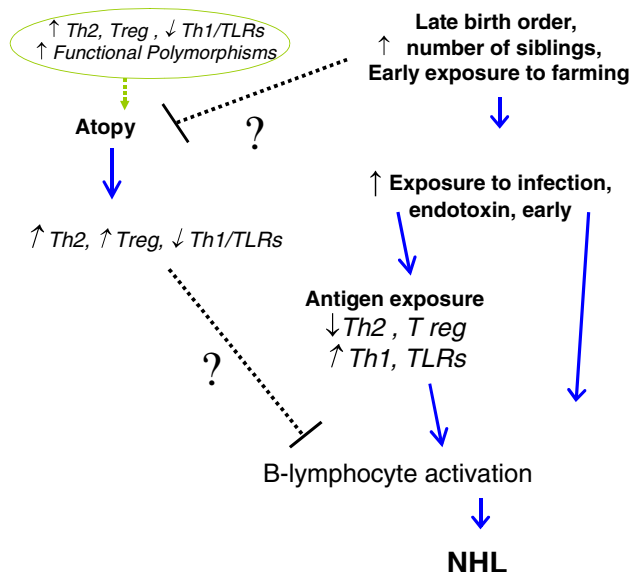


Fig. 1 Possible etiologic pathway involving the immune response to early childhood exposures

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