

Birth Order, Atopy, and Risk of Non-Hodgkin Lymphoma

Andrew Edwin Grulich, Claire Melissa Vajdic, John Martin Kaldor, Ann Maree Hughes, Anne Kricker, Lin Fritschi, Jennifer Jane Turner, Sam Milliken, Geza Benke, Bruce Konrad Armstrong

Background: Immune deficiency is a strong risk factor for non-Hodgkin lymphoma (NHL), but whether or not other forms of immune dysregulation are associated with NHL risk is unknown. We investigated associations between atopy, which is associated with a Th2-dominant immune response, and NHL risk. Because late birth order and childhood crowding are inversely associated with atopy, we also investigated their associations with NHL risk. **Methods:** We carried out a population-based case-control study among adults aged 20–74 years in New South Wales and the Australian Capital Territory, Australia. NHL patients without clinically apparent immune deficiency (N = 704) were selected from a cancer registry, and control subjects (N = 694) were randomly selected from state electoral rolls and frequency-matched to case patients by age, sex, and area of residence. Birth order, childhood crowding, and history of atopic conditions (hay fever, asthma, eczema, and specific allergies) were assessed by questionnaire and interview. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from logistic regression models that included the matching variables as covariates. **Results:** The odds ratios for developing NHL were 0.52 (95% CI = 0.32 to 0.84) for only children, 0.55 (95% CI = 0.40 to 0.75) for first-born children, 0.70 (95% CI = 0.51 to 0.96) for second-born children, and 0.81 (0.57 to 1.14) for third-born children (all compared with fourth- or later-born children) ($P_{\text{trend}} < .001$). Indicators of crowding in later childhood, such as sharing a bed or bedroom, were not associated with NHL risk. A history of atopic conditions was associated with a reduced risk of NHL; this reduction was statistically significant for hay fever (OR = 0.65, 95% CI = 0.52 to 0.82) and food allergies (OR = 0.29, 95% CI = 0.20 to 0.42). **Conclusions:** Early birth order and its immunologic consequence, a Th2-dominated immune response, as reflected by a history of atopic disease, are associated with a reduced risk of NHL. [J Natl Cancer Inst 2005;97:587–94]

Critical characteristics of the adult immune system are believed to be shaped by environmental exposures in early life. For example, there is a well-described inverse relationship between the risk of atopic conditions, which are associated with a Th2-dominant immune response, and indicators of early-life exposure to infections, such as later birth order or sibship size, early attendance at day care, and early exposure to pets or other animals (1). The “hygiene hypothesis” offers one explanation for how early-life exposure to antigens might decrease the risk of atopy (1,2). In utero, the fetus has a predominant Th2 response, which is necessary for the immunotolerance of gestation. The hypothesis suggests that exposure very early in life to commensal

and pathogenic microbes or their products, such as lipopolysaccharide, stimulates the switch to protective Th1-based immunity. According to the hygiene hypothesis, a delay in this type of exposure leads to a persistent Th2-dominant immune response and the subsequent development of atopic conditions (1,2). More recently, it has been hypothesized that infection or colonization with microbial agents very early in life leads to a decreased incidence of atopy, not through a switch to a Th1-dominant response but rather through the production of interleukin-10 and other T-cell regulatory factors that strongly suppress both Th2-based allergic responses and Th1-based autoimmune responses (3).

Non-Hodgkin lymphoma (NHL) arises from cells of the immune system. Rates of NHL in people with congenital or acquired immune deficiency are at least 50 times higher than population rates (4–6). However, it is not known whether other forms of immune dysregulation are associated with risk of NHL. Existing evidence regarding the relationship between atopic conditions and NHL risk is inconsistent (7–18), although the majority of studies have found that atopy is associated with a reduced risk of NHL. Few studies have investigated the association between early-life exposure to infectious agents and risk of NHL.

To examine the association between early development of the immune system and risk of NHL, we carried out a population-based case-control study in Australia. We examined whether measures of childhood household size and structure that might indicate risk of childhood infection and history of atopic conditions were associated with risk of NHL.

SUBJECTS AND METHODS

Participants

The study recruitment methods, including subject characteristics and exclusions, have been described in detail elsewhere (19). Case patients were newly diagnosed with NHL between January 2000 and August 2001, aged 20 to 74 years, and resident in New South

Affiliations of authors: National Centre in HIV Epidemiology and Clinical Research, University of NSW, Sydney, Australia (AEG, CMV, JMK); School of Public Health, The University of Sydney, Sydney, Australia (AMH, AK, BKA); School of Population Health, The University of Western Australia, Perth, Australia (LF); St. Vincent's Hospital, Sydney, Australia (JJT, SM); Department of Epidemiology and Biostatistics, Monash University, Melbourne, Australia (GB).

Correspondence to: Andrew Grulich, MBBS, MSc, PhD, Head, HIV Epidemiology and Prevention Program, National Centre in HIV Epidemiology and Clinical Research, University of NSW, Level 2, 376 Victoria Street, Darlinghurst, NSW 2010, Australia (e-mail: agrulich@ncheer.unsw.edu.au).

See “Notes” following “References.”

DOI: 10.1093/jnci/dji098

Journal of the National Cancer Institute, Vol. 97, No. 8, © Oxford University Press 2005, all rights reserved.

Wales (NSW) or the Australian Capital Territory (ACT). They were identified from the population-based NSW Central Cancer Registry. Control subjects were randomly selected from NSW and ACT electoral rolls (enrollment to vote is compulsory for adult Australian citizens) and were frequency matched to case patients by age, sex, and state of residence at diagnosis. We intended to enroll equal numbers of case patients and control subjects; given the lower response rate in control subjects, extra potential control subjects were therefore identified. Written informed consent was obtained from each participant, and the study was approved by the human research ethics committee at each participating institution.

Patients with a diagnosis of chronic lymphocytic leukemia, plasma cell myeloma, precursor B or T cell lymphoblastic leukemia, and lymphomatoid granulomatosis grades 1 and 2 were excluded. Because the study was designed to examine risk factors for NHL in people without obvious clinical immune deficiency, patients were excluded if they had a history of transplantation or human immunodeficiency virus (HIV) infection. We also excluded potential case patients and control subjects who were dead, had an illness or disability that prevented a 60-minute telephone interview, or had poor English language skills. Pathology reports were reviewed by an anatomical pathologist with a particular interest in hematopathology (Dr. J. Turner, St. Vincent's Hospital, Sydney) to assess confidence in the diagnosis of NHL and to assign, where possible, a cell phenotype and WHO (ICD-03) code (19).

Data Collection

Case patients and control subjects were approached in the same manner, and the data collection procedures were identical for both groups (19). Potential participants were sent a letter and an information leaflet inviting them to participate in a research project about the effects of the environment on the development of NHL, and written informed consent was obtained from those who agreed to participate. Participants completed a self-administered mailed questionnaire and were interviewed by telephone using a computer-assisted questionnaire. Socioeconomic status was assigned to each subject based on his or her address at the time of the interview using a published index constructed from 1996 census data (20).

Data on subjects' self-reported history of medical conditions were ascertained from the telephone interview. Interviews were conducted from March 2000 through May 2002 by experienced interviewers who were blinded to the case and control status of subjects and who interviewed equal numbers of case patients and control subjects. Participants were asked to report their birth order, the total number of other children living in their household when they were a child (defined as the first 10 years of life), whether they usually shared a bed or a bedroom, and the duration (in years) of such sharing. Participants were also asked about their history of atopic conditions, including hay fever, asthma, and eczema during their childhood, teenage years, adulthood, and lifetime. Finally, participants were asked whether they had allergies to any foods or medicines and whether they had ever experienced an allergic reaction severe enough to require urgent medical attention.

Statistical Methods

Continuous variables were categorized into approximate quartiles or tertiles of the exposure distribution among control

subjects. The primary analyses included all case patients. The analyses were also repeated for the case patients with the two most common NHL subtypes, follicular lymphoma ($n = 239$) and diffuse large-B-cell lymphoma ($n = 225$).

Unconditional logistic regression models were adjusted for age, sex, and area of residence (i.e., NSW or ACT). Each model also included ethnicity as a covariate because fewer control subjects were born outside Australia than expected based on the 2001 Australian Census (19). To further exclude the possibility that any observed association was due to selection bias by country of birth in control subjects, we also estimated associations among Australian- and New Zealand-born subjects only. Measures of birth order and childhood crowding were included in models with and without adjustment for socioeconomic status at interview because of the known association between lower socioeconomic status and large household size in Australia (21) and because there is some (albeit inconsistent) evidence of a positive association between higher socioeconomic status and risk of NHL (18).

Variables that were statistically significantly associated with NHL risk in univariate analyses were included in a multivariable model of NHL risk. Birth order was included as a covariate in separate models with key atopy variables, i.e., lifetime history of hay fever, asthma, eczema, or food allergy. We also constructed a model containing all of these variables. Because other analyses of the subjects in this study showed that people with high sun exposure had statistically significantly lower risks of NHL (22), we also included sun exposure as a covariate. Total lifetime sun exposure was derived from measured outdoor hours on working and non-working days and vacations at 10, 20, 30, 40, 50, and 60 years of age (22). In the final model, odds ratios (ORs) were adjusted for quartile of socioeconomic status and quartile of sun exposure.

All analyses were done using STATA software (version 8.0; Stata Corporation, College Station, TX). Tests for linear trend were done by fitting ordered categories of a variable as a single ordinal variable in the logistic regression models; P values for trends were based on the Wald test. All P values presented are two-sided, and the statistical significance level for hypothesis testing was set at 0.05.

RESULTS

A total of 1217 case patients were initially ascertained for the study, 28 of whom were subsequently found to be ineligible due to prior organ transplantation or HIV infection. Of the remaining 1189 eligible case patients, 144 had died, 96 were too ill to participate, 73 had inadequate English skills, and 34 could not be contacted, leaving 842 case patients who were approached for interview. Of these, 717 actually agreed to be interviewed, for an overall response rate of 60% among eligible case patients and a cooperation rate of 85%. Of the 717 interview patients, 13 were excluded after pathology report review because of low confidence in the diagnosis of NHL, leaving 704 case patients for analysis. The majority ($n = 652$, 93%) of NHL cases were of the B-cell phenotype, 4% ($n = 31$) were of the T-cell phenotype, and the remainder were indeterminate ($n = 21$, 3%). The two most common World Health Organization-defined (23) NHL subtypes were follicular lymphoma ($n = 239$, 34%) and diffuse large B-cell lymphoma ($n = 225$, 32%).

Of the 1687 potential control subjects who were initially randomly selected for the study, five had died, 71 were too ill to

participate, 74 had inadequate English, and 401 could not be contacted, leaving 1136 control subjects approached to participate. Of these, 694 were interviewed, corresponding to a response rate of 41% and a cooperation rate of 61%. Participating case patients and control subjects had a similar socioeconomic status, and similar proportions of case patients and control subjects resided in a rural locality at interview (19).

Being an only child or a first-born child of a multi-child family (hereafter referred to as an other first-born child) was strongly inversely associated with risk of NHL; the odds ratio was 0.52 (95% confidence interval [CI] = 0.32 to 0.84) for an only child compared with a fourth-born or later-birth order child and 0.55 (95% CI = 0.40 to 0.75) for an other first-born child (Table 1). The odd ratios for second- and third-born children were 0.70 and 0.81, respectively ($P_{\text{trend}} < .001$). The associations between birth order and risk of NHL were almost identical in men and women (data not shown). There was also a statistically significant trend of decreasing NHL risk with decreasing number of other children who lived in the household during the participant's childhood ($P_{\text{trend}} = .04$, Table 1). However, usually sharing a bedroom or a bed as a child was not associated with risk of NHL (Table 1).

In the analysis of associations with atopic disease, having hay fever at any age or as an adult were both strongly inversely associated with risk of NHL (Table 2). There was no statistically significant association between with history of asthma or eczema and risk of NHL, although the odds ratios for both associations

were less than 1.0 in all the life periods examined and approached statistical significance ($P = .09$) for having eczema as an adult (Table 2).

We observed a strong inverse association between being allergic to one or more foods and NHL risk (Table 3). We examined associations with each of the three most commonly reported food allergies (seafood, preservatives, and dairy foods) individually; risks of NHL were statistically significantly reduced in people with allergies to seafood or to dairy foods (Table 3). Risks were not reduced in those with allergies to preservatives, but only very small numbers of case patients and control subjects reported such allergies, resulting in very wide confidence intervals. Risk of NHL was not statistically significantly associated with a history of allergy to any medicines (including vaccinations) or a history of allergy to any of the four medicine categories (antibiotics, penicillin, sulfa drugs, and analgesics) most commonly reported to cause allergic reactions (Table 3). Having had a severe allergic reaction requiring urgent medical attention was not statistically significantly associated with NHL risk estimates (OR = 1.01, 95% CI = 0.66 to 1.54), regardless of whether the reaction was caused by a food (OR = 0.56, 95% CI = 0.21 to 1.49), medicine (OR = 1.17, 95% CI = 0.71 to 1.91), insect bite (OR = 1.17, 95% CI = 0.33 to 4.22), or other or unknown exposure (OR = 1.09, 95% CI = 0.42 to 2.84).

Including potentially confounding exposures such as total lifetime sun exposure and socioeconomic status at interview in the statistical models did not alter the risk estimates, nor did restricting

Table 1. Birth order and measures of childhood crowding and risk of non-Hodgkin lymphoma*

Variable	Case patients (N = 704)	Control subjects (N = 694)	Adjusted OR†	95% CI	P	$P_{\text{trend}}‡$
Birth order						
Fourth or later-birth order child	167	115	1.00	Referent		
Third-born child	138	120	0.81	0.57 to 1.14	.22	
Second-born child	184	183	0.70	0.51 to 0.96	.03	
First-born child	178	226	0.55	0.40 to 0.75	<.001	
Only child	37	50	0.52	0.32 to 0.84	.008	<.001
No. of other children who lived in household in participant's childhood						
Three or more	346	309	1.00			
Two	173	170	0.91	0.70 to 1.19	.49	
One	149	166	0.82	0.63 to 1.08	.16	
None	36	49	0.66	0.42 to 1.04	.08	.04
Usually shared a bedroom as a child						
Yes	505	489	1.00	Referent		
No	197	199	0.98	0.77 to 1.24	.85	
Don't know	2	6				
No. of years shared a bedroom as a child						
Never shared	197	201	1.00	Referent		
1-7 years	104	122	0.87	0.62 to 1.20	.39	
8-9 years	183	161	1.14	0.85 to 1.52	.39	
10 years	213	200	1.05	0.80 to 1.39	.71	.44
Don't know	7	10				
Usually shared a bed as a child						
No	557	570	1.00	Referent		
Yes	147	124	1.15	0.87 to 1.52	.45	
No. of years shared a bed as a child						
Never shared	557	570	1.00	Referent		
1-6 years	53	40	1.34	0.87 to 2.06	.19	
7-9 years	60	51	1.13	0.75 to 1.69	.55	
10 years	31	28	1.00	0.59 to 1.73	.97	.52
Don't know	3	5				

*Childhood was defined as 10 years of age or younger. OR = odds ratio; CI = confidence interval.

†Adjusted for the matching variables (age as a continuous variable, sex, and state) and ethnicity; OR calculations excluded subjects with "Don't know" responses.

‡ P_{trend} (two-sided) from Wald test.

Table 2. History of hay fever, asthma, and eczema and risk of non-Hodgkin lymphoma (NHL)*

Variable	Case patients (N = 704)	Control subjects (N = 694)	Adjusted OR†	95% CI	P‡
Hay fever during lifetime					
Never	452	377	1.00	Referent	
Ever	241	310	0.65	0.52–0.82	<.001
Don't know	11	7			
Hay fever in childhood§					
Never	613	596	1.00	Referent	
Ever	66	73	0.88	0.61–1.25	.47
Don't know	25	25			
Hay fever in teenage years					
Never	582	548	1.00	Referent	
Ever	106	129	0.79	0.59–1.05	.10
Don't know	16	17			
Hay fever as an adult					
Never	468	394	1.00	Referent	
Ever	224	292	0.65	0.52–0.82	<.001
Don't know	12	8			
Asthma during lifetime					
Never	586	565	1.00	Referent	
Ever	113	126	0.88	0.67–1.17	.39
Don't know	5	3			
Asthma in childhood§					
Never	646	635	1.00	Referent	
Ever	51	54	0.94	0.63–1.41	.77
Don't know	7	5			
Asthma in teenage years					
Never	656	643	1.00	Referent	
Ever	41	48	0.86	0.56–1.33	.49
Don't know	7	3			
Asthma as an adult					
Never	610	594	1.00	Referent	
Ever	88	97	0.90	0.66–1.24	.53
Don't know	6	3			
Eczema during lifetime					
Never	619	589	1.00	Referent	
Ever	74	91	0.79	0.57–1.10	.17
Don't know	11	14			
Eczema in childhood§					
Never	662	646	1.00	Referent	
Ever	30	34	0.90	0.54–1.50	.70
Don't know	12	14			
Eczema in teenage years					
Never	668	651	1.00	Referent	
Ever	25	28	0.88	0.51–1.53	.66
Don't know	11	15			
Eczema as an adult					
Never	643	612	1.00	Referent	
Ever	50	68	0.72	0.49–1.05	.09
Don't know	11	14			

*History of any of these conditions as reported at least 1 year prior to NHL diagnosis (for case patients) or selection as a control subject. OR = odds ratio; CI = confidence interval.

†Adjusted for the matching variables (age as a continuous variable, sex, and state) and ethnicity; OR calculations excluded subjects with “Don't know” responses.

‡P value from unconditional logistic regression model.

§Childhood is defined as 10 years of age or younger.

the analysis to subjects born in Australia or New Zealand (data not shown). When birth order and lifetime history of hay fever were entered together in a multivariable model, their associations with NHL were similar to what they were when included in separate models. When birth order and lifetime history of food allergy were entered together in the model, there was a small reduction in the magnitude of the odds ratios associated with birth order. For example, the odds ratio of NHL among only children compared with fourth- or later-born children increased from 0.52 (95% CI = 0.32 to 0.84) to 0.56 (95% CI = 0.34 to 0.93) after adjustment for lifetime history of food allergy, but the trend for increasing risk with increasing birth order remained highly statistically

significant ($P < .001$). When all three variables (birth order, lifetime history of hay fever, and lifetime history of food allergy) were entered together in the model, there was a further small increase in the odds ratios associated with birth order—for example, the odds ratio among only children compared with fourth- or later-born children increased to 0.58 (95% CI = 0.53 to 0.83)—and the statistical significance of the trend was unaltered.

The risk associations for birth order and the atopic conditions were very similar for follicular lymphoma and diffuse large-B-cell lymphoma (data not shown). In addition, there was little evidence of statistical interaction between history of hay fever or allergy and birth order and the risk of NHL (Table 4).

Table 3. Allergy to foods or medicines and risk of non-Hodgkin lymphoma (NHL)*

Type of allergy	Case patients (N = 704)	Control subjects (N = 694)	Adjusted OR†	95% CI	P‡
Allergic to any foods or medicines, including vaccinations					
Never	481	462	1.00	Referent	
Ever	222	228	0.95	0.75–1.19	.30
Don't know	1	4			
Allergic to one or more foods					
Never	662	571	1.00	Referent	
Ever	41	119	0.29	0.20–0.42	<.001
Don't know	1	4			
Allergic to seafood					
Never	695	660	1.00	Referent	
Ever	8	30	0.25	0.12–0.56	<.001
Don't know	1	4			
Allergic to preservatives					
Never	697	684	1.00	Referent	
Ever	6	6	1.04	0.33–3.25	.94
Don't know	1	4			
Allergic to dairy foods					
Never	692	668	1.00	Referent	
Ever	11	22	0.48	0.23–1.00	.04
Don't know	1	4			
Allergic to one or more medicines					
Never	519	512	1.00	Referent	
Ever	184	178	1.03	0.81–1.32	.81
Don't know	1	4			
Allergic to antibiotics					
Never	586	580	1.00	Referent	
Ever	117	110	1.06	0.80–1.42	.67
Don't know	1	4			
Allergic to penicillin					
Never	638	628	1.00	Referent	
Ever	65	62	1.05	0.73–1.52	.78
Don't know	1	4			
Allergic to sulfa drugs					
Never	664	656	1.00	Referent	
Ever	39	34	1.10	0.68–1.78	.69
Don't know	1	4			
Allergic to analgesics					
Never	657	654	1.00	Referent	
Ever	46	36	1.25	0.79–1.97	.34
Don't know	1	4			

*Allergy history as reported at least 1 year prior to NHL diagnosis (for case patients) or selection as a control subject. OR = odds ratio; CI = confidence interval.

†Adjusted for the matching variables (age as a continuous variable, sex, and state) and ethnicity; OR calculations excluded subjects with “Don't know” responses.

‡P value from unconditional logistic regression model.

DISCUSSION

In this case-control study of atopy, birth order, and the risk of NHL, we found that only children and first-born children had an approximately 50% reduction in NHL risk compared with fourth- or later-born children and that NHL risk increased with increasing number of older siblings. However, markers of crowding later in childhood, such as bedroom and bed sharing, were not associated with risk of NHL. Among the atopic conditions, hay fever and food allergies were associated with statistically significant reductions in risk of NHL, whereas asthma and eczema were associated with non-statistically significant risk reductions. Earlier birth order and atopic conditions are associated with delayed exposure to infections in early life. Thus, taken together, these data suggest that delayed exposure to infections—and the consequent persistence of a Th2-dominated immune response—is associated with a reduced risk of NHL.

Previous studies of birth order and sibship size have yielded inconsistent associations with NHL risk. A recent population-

based case-control study in the United States found that risk of NHL increased with increasing sibship size in women and heterosexual men (13); NHL risk was also increased in non-HIV infected homosexual men with five or more siblings (12). A cohort study of male deaths from NHL in the United States (24) found a non-statistically significant reduction in risk associated with only-child status. A large Swedish cohort study (25) found no association between birth order and the combined risk of Hodgkin lymphoma and NHL in people up to 55 years of age; however, in this age group, Hodgkin lymphoma is likely to have made up a large proportion of diagnoses. Among hospital-based case-control studies of NHL, an Italian study (18) found no association with sibship size, whereas a study in England (9) found a statistically significantly increased NHL risk for only children but no association with sibship size. A population-based study in Denmark found increasing risk of Hodgkin lymphoma with increasing birth order and sibship size in children younger than 15 years but the opposite pattern in young adults (15–42 years of age) (26).

Table 4. Interactions between birth order and hay fever and between birth order and food allergy: associations with risk of non-Hodgkin lymphoma

Birth order	Atopic condition						<i>P</i> _{interaction} [†]
	Case patients	Control subjects	OR* (95% CI)	Case patients	Control subjects	OR (95% CI)	
	Hay fever: never			Hay fever: ever			
Fourth- or later-born child	110	61	1.00 (Referent)	52	54	0.55 (0.34–0.91)	
Third-born child	95	66	0.83 (0.53–1.29)	43	52	0.47 (0.28–0.78)	
Second-born child	112	94	0.66 (0.44–1.01)	70	84	0.47 (0.30–0.74)	
First-born or only child	135	156	0.49 (0.33–0.72)	76	120	0.36 (0.23–0.55)	.32
	Food allergy: never			Food allergy: ever			
Third- or later-born child‡	287	195	1.00 (referent)	18	39	0.31 (0.17–0.56)	
Second-born child	176	147	0.82 (0.61–1.09)	8	34	0.15 (0.07–0.34)	
First-born or only child	199	229	0.59 (0.45–0.77)	15	46	0.22 (0.12–0.41)	.16

*Odds ratios (ORs) were adjusted for the matching variables (age as a continuous variable, sex, and state) and ethnicity. Subjects with “Don’t know” responses were excluded from these analyses. CI = confidence interval.

[†]*P*_{interaction} was calculated as a 1 degree of freedom test for trend in the odds ratios.

‡Third-born children were combined with fourth- and later-born children for the analysis of food allergy because of small numbers.

We found that the risk of NHL was reduced by identical proportions in those who were only or other first-born children and that the risk increased linearly with the number of older siblings. There was no evidence, however, that close proximity to siblings and household members by sharing a bed or a bedroom was associated with NHL risk. These data suggest that it is events related to contact with other children in infancy (which should be identical in only and other first-born children), rather than events later in childhood (which are likely to differ between only and other first-born children), that contribute to NHL risk. Because the case patients and control subjects in our study were frequency matched by age, and age was controlled for in the analyses, these associations are unlikely to be confounded by time trends in household size.

Why should being an only child or other first-born child be associated with a reduced risk of NHL? One possibility is that early infection is a risk factor for NHL and that being an only or other first-born child is a surrogate marker of protection from early infection. It is unclear which infectious agents might be involved. The best-studied candidate for an early-life infection that may be related to NHL, Epstein-Barr virus, is believed to be associated with only a small minority of NHL cases, mainly in individuals with severe immune deficiency (27), who were excluded from this study. However, it is possible that early-life infection in general or its immunologic consequences may increase NHL risk through indirect pathways. It is also possible that other, unmeasured correlates of being first born contribute to NHL risk.

Several previous studies have examined the relationship between atopy and risk of NHL, but the methods by which atopy was measured varied widely and few studies reported on individual atopic conditions. Studies that have measured atopy or allergic conditions overall have generally not found either to be statistically significantly associated with NHL risk (9,11,15–17), but in all of these studies the odds ratios were 1.0 or less. Non-statistically significant reductions in NHL risk have also been reported for asthma (9,13,16) and hay fever (7,10,18); no studies have reported increased NHL risk associated with these conditions. Among those with eczema, a wide range of associations with NHL risk have been observed, including statistically significantly decreased risk (7), statistically significantly increased risk (9), and no statistically significant association (10,18).

Among those with allergies to specific substances (i.e., plants, animals, drugs, and foods), both non-statistically significantly (9,16) and statistically significantly (14) reduced risks have been reported, as well as odds ratios around 1.0 (7,8). No study has reported a statistically significant increase in NHL risk associated with allergies to specific substances. One study in the United States that found a reduced NHL risk in people with atopic conditions also found a reduced risk associated with antihistamine use (12). When these findings are taken together with our findings, a reasonably consistent picture of reduced risk associated with atopic disease appears to be emerging for NHL. Two recently reported population-based case-control studies of childhood acute lymphoblastic leukemia, another neoplasm of B lymphocytes, have reported a similar reduced risk in association with atopic disease in childhood (28–29).

The two factors that were statistically significantly associated with a decreased risk of NHL in our study, early birth order and having a history of atopic disease, have been consistently shown to be related to each other in epidemiologic studies (1). A possible mechanism for this relationship, consistent with the hygiene hypothesis, is that less exposure to infection in early life may lead to later-than-normal colonization of the gut by bacteria, thereby reducing the strong stimulus for a change to a Th1-dominant response that is seen with early-life exposure to infection (30). Evidence in support of this possible mechanism comes from the finding that populations with a higher prevalence of organisms transmitted by the fecal-oral route have a lower incidence of atopic diseases (31). In this context, it is interesting to note that the greatest risk reduction we found was for allergies to substances presented to the gut (i.e., for food allergies).

If the association between a Th2-dominant immune response and decreased NHL risk is causal, the mechanism is uncertain. On its face, the relationship between a Th2-dominant response and decreased NHL risk could be interpreted as the opposite of the well-described association between immune deficiency and increased NHL risk. However, in people with HIV-related immune deficiency, markers of a Th2 immune response, including increased levels of total immunoglobulin and B-cell stimulatory cytokines, are associated with increased rather than decreased NHL risk (32,33). Genetic polymorphisms associated with high

expression of the B-cell stimulatory cytokine interleukin-10 are also associated with NHL risk in HIV-positive people (34). It may be that, in immune-deficient individuals, the absence of effective Th1 function to control the Th2 response explains the positive association with risk of NHL. In our study of non-immune deficient people, we documented an opposite relationship of NHL risk with markers of Th2 function.

This study has several strengths. It was population based and had a low refusal rate among case patients. The most common reasons for case patients not participating were death prior to interview or illness preventing an interview; consequently, patients with the most severe disease may have been underrepresented (19). However, there is no reason to believe that severity of illness would be related to family size or atopic disease. The study also has limitations. As is seen with most population-based case-control studies, the participation rate among control subjects was less than that among case patients, raising the possibility that selection bias may have influenced our results. However, of two important factors known to influence family size, ethnicity and socioeconomic status, neither adjustment for both factors in a multivariable model nor restriction of analyses to those born in Australia and New Zealand materially altered the associations. Although this result weighs against bias caused by major known social determinants of family size, we cannot exclude the possibility that other, unmeasured determinants of family size or of history of atopy influenced study participation. We specifically excluded case patients who had HIV infection or were receiving immune-suppressive therapy after organ transplantation. Therefore, the results may be generalizable only to NHL patients without obvious severe immune deficiency. Control subjects were not asked specifically about their HIV status because of privacy concerns, but because the prevalence of HIV in Australian adults aged 15–49 years is estimated to be 0.1% (35) the presence of HIV-infected control subjects is unlikely to have caused bias.

Another possible limitation is that the data were provided by self-reporting. It seems reasonable to expect that self-report data on birth order and household size should be accurate. The data on atopic conditions were also self-reported and were not confirmed using medical records. However, for relatively mild conditions such as hay fever and eczema, self-report data may be more accurate than medical records because participants may not have sought medical attention. Recall bias is also possible, but it is difficult to conceive of a reason why control subjects should be more likely than case patients to recall these mild conditions, especially given that recall bias usually acts in the opposite direction. If the error in recall of atopic diseases were nondifferential between case patients and control subjects, then it is likely that we have underestimated the strength of association with atopic conditions.

In the multivariable models, associations with the main risk variables—birth order, hay fever, and food allergy—were attenuated only slightly after mutual adjustment for birth order and each atopic condition. In addition, there was little evidence of interactions between atopic conditions and birth order. Thus, it appears that the pathways by which atopy and birth order might mediate decreased NHL risk, assuming that they are causal, are at least partially independent.

Taken together, our findings suggest that reduced exposure to infection in early life and its immunological consequence of a Th2-dominated immune response are associated with a reduced risk of NHL. It should be noted, however, that our findings cannot explain the increasing incidence of NHL seen in industrialized

countries (36), in which household size is decreasing and the incidence of atopic conditions is increasing (1). One possible explanation for this observation is that early-life exposure to infection may have increased recently despite decreasing household size, due to the increasing use of day care for children. The incidence of Th1 diseases such as multiple sclerosis and type I diabetes is also increasing (3). It may be that all diseases that are associated with immune dysregulation are increasing in incidence and that NHL is another such condition.

Further epidemiologic studies are needed to confirm the link between birth order (or more specific measures of exposure to infection in early life), atopy, and reduced risk of NHL. Such studies, in addition to measuring other early-life environmental exposures relating to crowding and potential for infection, should measure biomarkers of Th2 response and T-cell regulation. Although data from case-control studies of genetic determinants of immune regulation may provide some information, data from cohort studies will also be required because the origin of NHL in the immune system will almost certainly frustrate retrospective assessment of these biomarkers in case-control studies.

REFERENCES

- (1) Strachan DP. Family size, infection and atopy: the first decade of the "hygiene hypothesis." *Thorax* 2000;55(1 Suppl):S2–S10.
- (2) Strachan DP. Hay fever, hygiene, and household size. *BMJ* 1989;299:1259–60.
- (3) Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: revisiting the hygiene hypothesis. *Nat Rev Immunol* 2001;1:69–75.
- (4) Beral V, Peterman T, Berkelman R, Jaffe H. AIDS-associated non-Hodgkin lymphoma. *Lancet* 1991;337:805–9.
- (5) Filipovich AH, Mathur A, Kamat D, Shapiro RS. Primary immunodeficiencies: genetic risk factors for lymphoma. *Cancer Res* 1992;52(19 Suppl):5465s–7s.
- (6) Kinlen LJ, Sheil AGR, Peto J, Doll R. Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. *Br Med J* 1979;1461–6.
- (7) Bernstein L, Ross RK. Prior medication use and health history as risk factors for non-Hodgkin's lymphoma: preliminary results from a case-control study in Los Angeles County. *Cancer Res* 1992;52(19 Suppl):5510s–5s.
- (8) Briggs NC, Levine RS, Brann EA. Allergies and risk of non-Hodgkin's lymphoma by subtype. *Cancer Epidemiol Biomarkers Prev* 2002;11:401–7.
- (9) Cartwright RA, McKinney PA, O'Brien C, Richards ID, Roberts B, Lauder I, et al. Non-Hodgkin's lymphoma: case control epidemiological study in Yorkshire. *Leuk Res* 1988;12:81–8.
- (10) Doody MM, Linet MS, Glass AG, Friedman GD, Pottern LM, Boice JD Jr, Fraumeni JF Jr. Leukemia, lymphoma, and multiple myeloma following selected medical conditions. *Cancer Causes Control* 1992;3:449–56.
- (11) Franceschi S, Serraino D, Bidoli E, Talamini R, Tirelli U, Carbone A, La Vecchia C. The epidemiology of non-Hodgkin's lymphoma in the north-east of Italy: a hospital-based case-control study. *Leuk Res* 1989;13:465–72.
- (12) Holly EA, Lele C. Non-Hodgkin's lymphoma in HIV-positive and HIV-negative homosexual men in the San Francisco Bay Area: allergies, prior medication use, and sexual practices. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997;15:211–22.
- (13) Holly EA, Lele C, Bracci PM, McGrath MS. Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. *Am J Epidemiol* 1999;150:375–89.
- (14) Holly EA, Bracci PM. Population-based study of non-Hodgkin lymphoma, histology, and medical history among human immunodeficiency virus-negative participants in San Francisco. *Am J Epidemiol* 2003;158:316–27.
- (15) La Vecchia C, Negri E, Franceschi S. Medical history and the risk of non-Hodgkin's lymphomas. *Cancer Epidemiol Biomarkers Prev* 1992;1:533–6.
- (16) Tavani A, La Vecchia C, Franceschi S, Serraino D, Carbone A. Medical history and risk of Hodgkin's and non-Hodgkin's lymphomas. *Eur J Cancer Prev* 2000;9:59–64.

- (17) Tielsch JM, Linet MS, Szklo M. Acquired disorders affecting the immune system and non-Hodgkin's lymphoma. *Prev Med* 1987;16:96-106.
- (18) Vineis P, Miligi L, Crosignani P, Fontana A, Masala G, Nanni O, et al. Delayed infection, family size and malignant lymphomas. *J Epidemiol Community Health* 2000;54:907-11.
- (19) Hughes AM, Armstrong BK, Vajdic C, Turner J, Grulich A, Fritschi L, et al. Pigmentary characteristics, sun-sensitivity and non-Hodgkin lymphoma. *Int J Cancer* 2004;110:429-434.
- (20) Australian Bureau of Statistics. Socio-economic indexes for areas, Australia. ABS catalog no. 2039. 0. Canberra (Commonwealth of Australia): Australian Bureau of Statistics; 1998.
- (21) Hugo G. Recent trends in fertility differentials in Australia. *People Place* 1993;1:1-5.
- (22) Hughes AM, Armstrong BK, Vajdic CM, Turner J, Grulich A, Fritschi L, et al. Sun exposure may protect against non-Hodgkin lymphoma: a case-control study. *Int J Cancer* 2004;112:865-71.
- (23) Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. Pathology and genetics of tumours of haematopoietic and lymphoid tissues. World Health Organization classification of tumours. Lyon (France): IARC Press; 2001.
- (24) Paffenbarger RS Jr, Wing AL, Hyde RT. Characteristics in youth predictive of adult-onset malignant lymphomas, melanomas, and leukemias: brief communication. *J Natl Cancer Inst* 1978;60:89-92.
- (25) Hemminki K, Mutanen P. Birth order, family size, and the risk of cancer in young and middle-aged adults. *Br J Cancer* 2001;84:1466-71.
- (26) Westergaard T, Melbye M, Pedersen JB, Frisch M, Olsen JH, Andersen PK. Birth order, sibship size and risk of Hodgkin's disease in children and young adults: a population-based study of 31 million person-years. *Int J Cancer* 1997;72:977-81.
- (27) Thorley-Lawson DA, Gross A. Persistence of the Epstein-Barr virus and the origins of associated lymphomas. *New Engl J Med* 2004;350:1328-37.
- (28) Schuz J, Morgan G, Bohler E, Kaatsch P, Michaelis J. Atopic disease and childhood acute lymphoblastic leukemia. *Int J Cancer* 2003;105:255-60.
- (29) Wen W, Shu XO, Linet MS, Neglia JP, Potter JD, Trigg ME, Robison LL. Allergic disorders and the risk of childhood acute lymphoblastic leukemia (United States). *Cancer Causes Control* 2000;11:303-7.
- (30) Wold AE. The hygiene hypothesis revised: is the rising frequency of allergy due to changes in the intestinal flora? *Allergy* 1998;53(46 Suppl):20-5.
- (31) Kay AB. Allergy and allergic diseases. *N Eng J Med* 2001;344:30-7.
- (32) Grulich AE, Wan X, Law MG, Milliken ST, Lewis CR, Garsia RJ, et al. B-cell stimulation and prolonged immune deficiency are risk factors for non-Hodgkin's lymphoma in people with AIDS. *AIDS* 2000;14:133-40.
- (33) Schroeder JR, Saah AJ, Hoover DR, Margolick JB, Ambinder RF, Martinez-Maza O, et al. Serum soluble CD23 level correlates with subsequent development of AIDS-related non-Hodgkin's lymphoma. *Cancer Epidemiol Biomarkers Prev* 1999;8:979-84.
- (34) Breen EC, Boscardin WJ, Detels R, Jacobson LP, Smith MW, O'Brien SJ, et al. Non-Hodgkin's B cell lymphoma in persons with acquired immunodeficiency syndrome is associated with increased serum levels of IL10, or the IL10 promoter -592 C/C genotype. *Clin Immunol* 2003;109:119-29.
- (35) UNAIDS. Report on the global HIV/AIDS epidemic 2002. Geneva (Switzerland): UNAIDS; 2002.
- (36) Hartge P, Devesa SS, Fraumeni JF Jr. Hodgkin's and non-Hodgkin's lymphomas. *Cancer Surv* 1994;19:423-53.

NOTES

This study was funded by the National Health and Medical Research Council of Australia, The Cancer Council NSW, and The University of Sydney Medical Foundation. Claire Vajdic has a Postdoctoral Research Fellowship of the National Health and Medical Research Council. Ann Maree Hughes has an Australian Postgraduate Award and a Faculty of Medicine Postgraduate Award through The University of Sydney. Lin Fritschi is supported by a NHMRC career development award. Bruce Armstrong's research is supported by a University of Sydney Medical Foundation program grant. The National Centre in HIV Epidemiology and Clinical Research is funded by the Australian Government Department of Health and Aging.

We gratefully acknowledge the individuals who participated in the research, the clinicians who gave permission for us to approach their patients, and staff at the NSW Central Cancer Registry and the Hunter Valley Research Foundation. Special thanks to Melissa Litchfield, Maria Agaliotis, and Chris Goumas for data collection and data entry and to Jackie Turner for telephone follow-up. We also thank Sean Riminton and Michael Boyle, who made important comments on an earlier draft of the manuscript.

Manuscript received July 19, 2004; revised January 20, 2005; accepted February 14, 2005.