

# Number of Siblings and Risk of Hodgkin's Lymphoma

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## Abstract

**Background:** Epidemiologic evidence indicates that risk of Hodgkin's lymphoma (HL) in young adults is associated with correlates of delayed exposure to infection during childhood. In contrast, HL among children and older adults may be associated with earlier childhood infection. This study examines the associations of HL risk with having older or younger siblings. **Methods:** We conducted a case-control study in Sweden comparing 2,140 HL patients identified from the Swedish Cancer Register with 10,024 controls identified from national population registers. The Swedish Multi-Generation Register was used to link individuals to their parents and siblings. **Results:** Among young adults ages 15 to 39 years, the odds ratios (OR) associated with having one, two, and three or more older siblings, compared with none, were 0.96 [95% con-

fidence interval (CI), 0.82-1.13], 0.88 (95% CI, 0.72-1.09), and 0.72 (95% CI, 0.55-0.93), respectively (*P* value for trend = 0.01). In contrast, number of older siblings was not associated with HL risk among children or older adults. Number of younger or total siblings, mother's age at birth, and father's occupation were not associated with HL at any age. The decreased risk of young-adult HL did not vary appreciably by age difference or sex of older siblings. **Conclusions:** Risk of HL was lower among young adults with multiple older but not younger siblings. Having older siblings is associated with earlier exposure to common childhood pathogens. Pediatric and older-adult HL were not associated with number of siblings, suggesting a different pathogenesis of disease in these age groups. (Cancer Epidemiol Biomarkers Prev 2004;13(7):1236-43)

## Introduction

In most developed nations, the age-specific incidence of Hodgkin's lymphoma (HL) has a bimodal pattern, with an initial peak occurring among young adults ages 15 to 39 years, followed by a second peak among older adults. In developing nations, the first peak occurs earlier, among children under age 15 years (1, 2). HL has long been thought to have an infectious origin (2, 3), with the Epstein-Barr virus (EBV) being the most likely candidate etiologic agent (4). EBV is a typically benign lymphotropic herpesvirus that infects more than 90% of the world's population, usually during childhood (5). A causal role of EBV in HL is supported by findings of elevated levels of EBV antibodies in individuals before HL onset (6-8), as well as by the molecular detection of monoclonal EBV genome and viral products in the malignant cells of one quarter to one half of HL tumors (4, 9, 10).

When EBV infection is delayed from childhood to adolescence, it can cause infectious mononucleosis in about half of infected individuals (11, 12); a history of infectious mononucleosis increases the risk of young-adult HL by about 3-fold (13-23). Correspondingly, factors that influence age at infection with EBV and

other common pathogens also seem to affect HL risk in young adults. For example, late birth order and large family size favor earlier childhood exposure to infectious agents, because younger siblings are often exposed to infections at an early age by older siblings who attend school (24-26). It follows, then, that later-born children and those with many siblings should have a lower risk of young-adult HL (19, 27-30). However, some studies have reported no association between birth order or sibship size and HL risk (31-33). Furthermore, early infection seems to be unrelated to risk of HL in childhood or older adulthood, or may even increase both pediatric and elderly HL risk (28, 34-36), suggesting that the etiology of disease differs by age group (3).

Although previous studies have investigated the association between number of siblings and risk of HL, none have examined older and younger siblings separately, most likely due to limitations in sample size. Differentiating older from younger siblings enables us to distinguish between associations with birth order—that is, number of older siblings—and sibship size. We conducted a register-based case-control study in Sweden to investigate the effect of having older and younger siblings on HL risk by age of diagnosis, as well as re-examine the associations of total sibship size and parental characteristics with HL risk.

## Materials and Methods

**Study Population.** HL cases were identified through the population-based Swedish Cancer Register, which

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was established in 1958, and contains individual data on all newly diagnosed malignant tumors in Sweden (37). Tumors must be reported to the Cancer Register separately by both the diagnosing clinician and the pathologist or cytologist. Nearly 100% of all diagnosed cancers are reported, with histologic verification of 97% of the tumors. Eligible cases were born after 1941 and diagnosed with HL (International Classification of Diseases-7 code: 201; ref. 38) between 1958 and 1998.

Controls were randomly selected from the Swedish Population Register and were frequency matched to the cases on age and district of residence at the time of case diagnosis. Controls were required to be alive and not to have a diagnosis of HL before the time of selection, and had the same restrictions on year of birth as the cases.

The Swedish Multi-Generation Register was used to link cases and controls, based on their unique national registration numbers, with information about first-degree relatives (39). This register is based on index individuals born in 1932 or later and alive in 1961. Information is almost complete for subjects who were alive in 1991 and around 50% complete for those who died between 1961 and 1991. Only cases and controls who could be linked with both parents were included in this analysis. Immigrants and emigrants were excluded, because information is largely incomplete for this group.

Because age at selection was missing for all controls in the data set, we imputed the ages of the controls from year of birth, district of residence, and age at case diagnosis. That is, within a given birth year and residential district, the distribution of age among the controls was imputed to be the same as that among the cases, because cases and controls were originally matched on age and district of residence at the time of case diagnosis. Controls whose year of birth and district of residence did not match that of an eligible case were excluded.

A total of 9,103 HL cases and 33,092 frequency-matched controls were identified overall. Of these, 6,580 cases and 20,963 controls had missing parental data and were, therefore, excluded. We further excluded 98 cases and 244 controls who had migrated to or from Sweden, as well as 285 cases and 1,861 controls born before 1941, when data on older siblings were likely to be incomplete. These exclusion criteria should not have differentiated selectively between HL cases and controls. Our final study population consisted of 2,140 cases and 10,024 controls.

**Measures of Exposure.** Information on family structure included number of older and younger siblings, siblings' age and sex, parents' age, and father's occupation. Numbers of older, younger, and total siblings were categorized into binary variables with categories for none, one, two, and three or more. A separate variable was used to denote whether or not an individual had any siblings. Only siblings within 15 years of age of the index subject were counted as relevant to the childhood environment. Mother's age was divided into a series of binary variables, with categories for under 20 years, 20 to 24 years, 25 to 29 years, 30 to 39 years, and 40 years and above. Residential districts were grouped into those with large cities (Stockholm county, Malmöhus county, and Göteborg and Bohus county) and those without.

Father's occupation was used as a marker of social class during the subject's childhood. Occupation was

coded according to a standard classification scheme, including 10 categories distinguishing between owners and employees in specific industries. These categories were combined into generally "lower social class" occupations (agricultural worker, technical or commercial employee, industrial employee, or service employee) and "higher social class" occupations (agricultural owner, business owner, professional, executive, or military). Occupational data were based only on Censuses conducted in 1960 and 1970, because earlier data were not available and later Censuses would not have been relevant to assessing childhood environment for the majority of subjects. Therefore, analyses using the occupation variable were greatly reduced in statistical power. Because occupation is influenced by age, the father's age at the time of the Census was used to create an additional set of binary variables, with categories for 25 to 33 years, 34 to 41 years, and 42 to 49 years, as well as an interaction term between father's age and occupation. Occupation was excluded for fathers under 25 years of age, because occupation is a less reliable indicator of family circumstances for those under 25 years (40), and for those over 49 years, because most men no longer had young children and infants after that age. Fathers with unknown or unidentified occupation were also excluded. Data on father's occupation were limited to 1,549 cases and 7,138 controls who were analyzed as a subset of the overall population. The subjects with father's occupational data were significantly older (mean: 39.7 years) than those without such data (mean: 36.7 years) ( $P < 0.0001$ ), although the absolute difference in age was only 3 years. The two groups did not differ significantly by sex or total number of siblings.

This study was approved by the Karolinska Institute Ethics Committee.

**Statistical Analysis.** Unconditional logistic regression was used to estimate odds ratios (OR) for HL, and corresponding 95% confidence intervals (CIs), associated with number of younger and older siblings. Analyses were adjusted for age in categorical 10-year intervals, sex, residence in or outside of a large city, total siblings, and mother's age at giving birth. All analyses were repeated with further adjustment for father's occupation and age at the time of Census-taking. The significance of potential confounders was evaluated using prior knowledge, the 10% change-in-estimate method (41), and likelihood ratio tests comparing models with and without additional variables.

Although all covariates listed above were included in the multivariate models for the purpose of minimizing bias, we also tested reduced models, using stepwise selection of only those variables that were significantly associated with HL risk (in addition to age and region of residence, which were case-control matching factors). Using tests of homogeneity, we ensured that the estimates for association with HL did not differ between the full and reduced models.

To detect possible effect modification of ORs by age, case-control comparisons were stratified by age group. Wald  $\chi^2$  tests were done to compare associations with HL risk among individuals below 15 years old (children), 15 to 39 years old (younger adults), and 40 years and above (older adults).

To assess the presence of a period effect, individuals were stratified by decade of diagnosis (1958 to 1968, 1969 to 1978, 1979 to 1988, and 1989 to 1998), and alternatively at the midway point of the diagnostic period (before and after 1979). Statistical analyses were done with the SAS System software, release 8.2 (The SAS Institute, Inc., Cary, NC, 1999-2001).

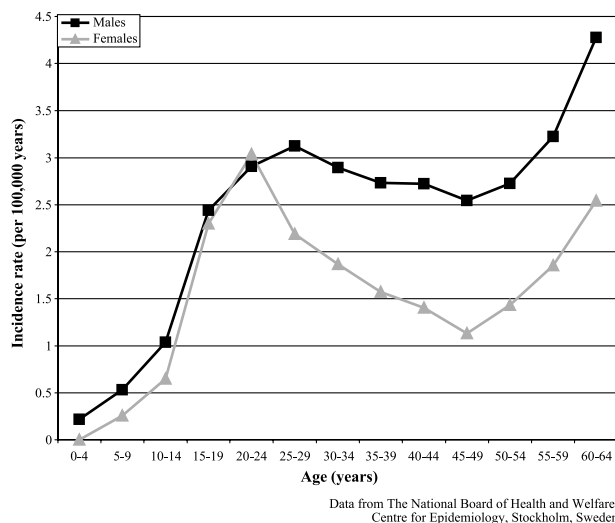
## Results

The age-specific incidence of HL in Sweden from 1970 to 1998 is illustrated in Fig. 1. This curve shows the characteristic bimodality of HL in developed countries, with a first incidence peak among young adults ages 15 to 39 years, and a second peak among older adults more than age 50 years.

**Number of Siblings.** Table 1 shows the distribution of sibship size and other characteristics among HL cases and controls. There was an inverse association between HL risk and having older siblings, compared with having no siblings, adjusting for age, sex, urban residence, number of younger siblings, only-child status, and mother's age at giving birth (full multivariate model). After additionally adjusting for father's occupation (limited to individuals with available data), there was a significant decreasing trend in HL risk with an increasing number of older siblings.

In contrast, there was no apparent association between HL risk and number of younger or total siblings in any model. There was no linear trend between HL risk and number of younger or total siblings.

We evaluated the possibility of a calendar period effect, or a change in risk associations over time, by grouping the cases by year of HL diagnosis, and comparing them to all controls combined. Whether the analyses were stratified by decade of diagnosis (1958 to 1968; 1969 to 1978; 1979 to 1988; and 1989 to 1998) or in two equal time intervals (1958 to 1978 and 1979 to 1998), there were no differences in the association between sibship size and HL risk (data not shown).



**Figure 1.** Age-specific incidence of Hodgkin's lymphoma among males and females in Sweden between 1970 and 1998.

**Other Characteristics.** Males had a significantly higher risk of HL than females in all models. Maternal parity—that is, having had more than one child—was not associated with HL risk. Although the simple adjusted estimates suggested that HL risk was lower among individuals with older mothers, and there was a marginally significant trend toward decreasing HL risk with older maternal age at birth, this association disappeared after adjustment for additional variables (Table 1). Among individuals with information on father's occupation in 1960 and 1970, there was no association between father's occupation and risk of HL.

**Analyses by Age at Diagnosis.** Separate analyses were conducted for cases and controls below age 15 years (children), between ages 15 and 39 years (younger adults), and above age 40 years at diagnosis (older adults) (Table 2). The inverse association between HL risk and number of older siblings was evident only for young-adult cases, with a significant decreasing trend in the OR with increasing number of older siblings, compared with no siblings. In contrast, the OR for having three or more older siblings versus none was statistically non-significant for older adults, and there was no apparent trend in association with number of older siblings. For pediatric cases, the OR was suggestive of an inverse association between number of older siblings and HL risk, although it was based on a small number of cases. A test of heterogeneity among the three age groups found no modification of the OR between number of older siblings and HL risk ( $P$  for heterogeneity = 0.23), but suggested some variation of the trend by age group ( $P$  for heterogeneity = 0.09).

There was no association between number of younger siblings and HL risk at any age, nor was there any evidence of heterogeneity by age group in the associations between HL risk and number of younger siblings, sex, total siblings, or maternal age (data not shown). However, because the trend between HL risk and having older siblings differed somewhat by age group, further analyses were stratified by age at diagnosis.

**Analyses by Number of Other Siblings.** The OR for having three or more older siblings versus having no siblings was inverse regardless of the number of younger siblings, although there was a suggestion of a stronger inverse association among young adults with more younger siblings (Table 2). The OR for having three or more younger siblings versus none also decreased with an increasing number of older siblings, or later birth order. Whereas there was no difference in young-adult HL risk among those with three or more younger but no older siblings, compared with those without any siblings, the relative risk became steadily lower with an increasing number of older siblings. The OR was most strongly inverse for young adults with three or more older and three or more younger siblings, compared with those without siblings. In smaller families with sibships of three or fewer, the risk of young-adult HL was not significantly decreased for any combination of older and younger siblings, although the OR was non-significantly inverse for those with two older and no younger siblings, compared with no siblings at all (OR = 0.88; 95% CI: 0.70-1.10). None of these estimates varied appreciably among older adults and children.

**Table 1. Distribution of siblings and other family characteristics by case status, and association with risk of Hodgkin's lymphoma**

	Cases (%)		Controls (%)		Simple multivariate adjusted*		Full multivariate adjusted†		Full multivariate, also adjusted for father's occupation‡	
	N = 2,140		N = 10,024		OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
					P value for trend		P value for trend		P value for trend	
<b>No. of total siblings<sup>§</sup></b>										
0	366	(17)	1,659	(17)	1.00	—	1.00	—	1.00	—
1	826	(39)	3,927	(39)	0.96	(0.83-1.09)	0.94	(0.82-1.08)	0.94	(0.79-1.11)
2	567	(27)	2,578	(26)	0.99	(0.85-1.14)	0.97	(0.84-1.13)	0.96	(0.80-1.14)
3+	381	(18)	1,860	(19)	0.91	(0.78-1.07)	0.91	(0.78-1.07)	0.91	(0.75-1.11)
					P = 0.37		P = 0.74		P = 0.82	
<b>No. of younger siblings</b>										
0	1,018	(48)	4,950	(49)	1.00	—	1.00	—	1.00	—
1	732	(34)	3,279	(33)	1.08	(0.98-1.20)	1.07	(0.93-1.24)	1.08	(0.91-1.28)
2	256	(12)	1,240	(12)	0.99	(0.85-1.15)	0.98	(0.81-1.18)	0.99	(0.80-1.24)
3+	134	(6)	555	(6)	1.15	(0.94-1.40)	1.14	(0.91-1.43)	1.27	(0.97-1.65)
					P = 0.26		P = 0.57		P = 0.26	
<b>No. of older siblings</b>										
0	1,066	(50)	4,789	(48)	1.00	—	1.00	—	1.00	—
1	678	(32)	3,167	(32)	0.96	(0.86-1.07)	0.99	(0.86-1.14)	0.98	(0.83-1.16)
2	271	(13)	1,315	(13)	0.92	(0.79-1.06)	0.97	(0.80-1.16)	0.91	(0.73-1.13)
3+	125	(6)	753	(8)	0.73	(0.60-0.89)	0.77	(0.62-0.98)	0.68	(0.51-0.91)
					P = 0.004		P = 0.06		P = 0.02	
<b>Sex</b>										
Male	1,260	(59)	5,263	(52)	1.00	—	1.00	—	1.00	—
Female	880	(41)	4,761	(48)	0.77	(0.70-0.85)	0.77	(0.70-0.85)	0.76	(0.68-0.85)
<b>Mother's age (years)</b>										
Under 20	106	(5)	508	(5)	0.91	(0.73-1.15)	0.90	(0.72-1.14)	0.92	(0.70-1.21)
20-24	577	(27)	2,535	(25)	1.00	—	1.00	—	1.00	—
25-29	692	(32)	3,165	(32)	0.97	(0.96-1.10)	0.99	(0.88-1.12)	1.05	(0.91-1.22)
30-39	694	(32)	3,393	(34)	0.91	(0.80-1.03)	0.96	(0.84-1.10)	1.05	(0.89-1.24)
40+	71	(3)	423	(4)	0.73	(0.56-0.95)	0.80	(0.60-1.05)	0.94	(0.60-1.46)
					P = 0.06		P = 0.50		P = 0.47	
<b>Father's occupation class</b>										
Lower social class	1,272	(82)	5,828	(82)	—	—	—	—	1.00	—
Higher social class	277	(18)	1,310	(18)	—	—	—	—	1.00	(0.86-1.15)

\*OR and 95% CI for risk of Hodgkin's lymphoma adjusted for age, sex, and urban residence.

†OR and 95% CI for risk of Hodgkin's lymphoma adjusted for age, sex, urban residence, only-child status (total siblings = 0 or 1+), number of older and younger siblings, and maternal age at birth.

‡OR and 95% CI for risk of Hodgkin's lymphoma adjusted for age, sex, urban residence, only-child status, number of older and younger siblings, maternal age at birth, and father's age and occupation at 1960 and 1970 Censuses. N = 1,549 cases and 7,138 controls.

§ORs and 95% CIs not additionally adjusted for number of older and younger siblings.

**Age Difference between Siblings.** The degree of physical interaction, as well as chances of exchanging infections, may vary by the age gap between siblings. Therefore, we examined whether there was a difference in the association of HL risk with having siblings who were relatively much older versus having older siblings who were relatively close in age. There was no apparent pattern in the association of HL risk with age difference between subjects and their older siblings. Decreased HL risk was not specifically associated with having one or more siblings up to 2 years older, 3 to 4

years older, 5 to 6 years older, or 7 to 15 years older, compared with having no siblings, even when the analysis was restricted to those without any younger siblings (data not shown).

In addition, there was no substantial difference in the HL risk reduction associated with having multiple siblings up to 5 years older, as opposed to having multiple siblings 6 or more years older (Table 2). For cases ages 15 to 39 years, the adjusted OR for having three or more siblings between 0 and 5 years older did not differ from the OR for having the same number of

siblings 6 to 15 years older, compared with having no siblings. Older adult cases were marginally more likely than controls to have one or more older siblings 3 to 4 years older.

## Discussion

We found that number of older siblings was associated with a decreased risk of HL in young adults. The lower risk of young-adult HL did not vary by difference in age of older siblings, although the inverse association grew stronger with a higher number of younger siblings. Because HL risk was only associated with having multiple older but not younger or total siblings, the apparent association between HL and number of siblings could not be attributed to overall sibship size, nor to mother's parity.

Although our study was large, most cases were diagnosed between 15 and 39 years of age; therefore, analyses of both pediatric and older-adult HL were relatively limited in statistical power. Nevertheless, we found that the risk of HL diagnosed after 40 years of

age did not decrease with increasing number of older siblings. In fact, having older siblings appeared to be, if anything, linked to higher risk of HL among older adults. Conversely, patients with childhood HL tended to be first-borns, although no risk estimates reached statistical significance.

Number of younger siblings, number of total siblings, and father's occupation were not associated with HL risk. The decreased risk of HL among fourth- or later-born young adults with three or more younger siblings can be attributed to their having multiple older siblings. The finding that males were at a higher risk of HL overall than females accords with previous studies (1, 2).

Our findings corroborate results from previous reports indicating that individuals with more siblings and later birth order—as proxies for earlier age at infection with common childhood pathogens—have a lower risk of HL in early adulthood (19, 27-30). In particular, our results substantiate the inverse association between later birth order—that is, having more older siblings—and HL risk. We detected an inverse association with large sibship size only in relation to older siblings, not younger or total siblings, whereas other studies have not differentiated

**Table 2. Association between risk of Hodgkin's lymphoma and having older siblings, stratified by patient age at diagnosis**

	Age at diagnosis <15 years N = 188 cases, 817 controls		Age at diagnosis = 15-39 years N = 1,708 cases, 8,150 controls		Age at diagnosis ≥40 years N = 244 cases, 1,057 controls		P value for test of heterogeneity by age group
	OR*	(95% CI)	OR*	(95% CI)	OR*	(95% CI)	
	<i>P</i> value for trend		<i>P</i> value for trend		<i>P</i> value for trend		
<b>No. of older siblings</b>							
0	1.00	—	1.00	—	1.00	—	0.23
1	1.13	(0.68-1.86)	0.96	(0.82-1.13)	1.07	(0.71-1.63)	
2	1.15	(0.60-2.21)	0.88	(0.72-1.09)	1.54	(0.92-2.58)	
3+	0.48	(0.17-1.35)	0.72	(0.55-0.93)	1.33	(0.75-2.34)	
	<i>P</i> = 0.43		<i>P</i> = 0.01		<i>P</i> = 0.14		0.09
<b>By total no. of siblings</b>							
0 older, 0 younger	1.00	—	1.00	—	1.00	—	0.33
0 older, 3+ younger	2.08	(0.81-5.34)	1.21	(0.89-1.63)	0.90	(0.40-2.03)	
1 older, 3+ younger	2.39	(0.55-10.4)	0.77	(0.46-1.29)	1.44	(0.60-3.49)	
2 older, 3+ younger	1.61	(0.14-18.6)	0.70	(0.29-1.67)	2.01	(0.66-6.12)	
3+ older, 3+ younger	undefined	—	0.35	(0.13-0.99)	0.98	(0.27-3.59)	
3+ older, 2 younger	undefined	—	0.70	(0.33-1.50)	0.74	(0.16-3.45)	
3+ older, 1 younger	1.04	(0.20-5.39)	0.65	(0.40-1.05)	1.75	(0.71-4.27)	
3+ older, 0 younger	0.39	(0.11-1.36)	0.76	(0.56-1.03)	1.32	(0.63-2.78)	
<b>No. of siblings 0-5 years older</b>							
0	1.00	—	1.00	—	1.00	—	0.29
1	0.95	(0.62-1.45)	0.99	(0.87-1.14)	1.37	(0.96-1.94)	
2	0.96	(0.46-2.00)	0.74	(0.58-0.94)	1.19	(0.70-2.04)	
3+	undefined	—	0.51	(0.26-1.03)	1.32	(0.47-3.69)	
	<i>P</i> = 0.53		<i>P</i> = 0.02		<i>P</i> = 0.22		0.12
<b>No. of siblings 6-15 years older</b>							
0	1.00	—	1.00	—	1.00	—	0.26
1	1.57	(0.89-2.77)	0.94	(0.78-1.13)	1.11	(0.70-1.76)	
2	1.19	(0.48-2.95)	0.92	(0.71-1.18)	1.16	(0.60-2.22)	
3+	undefined	—	0.75	(0.50-1.11)	0.92	(0.33-2.60)	
	<i>P</i> = 0.58		<i>P</i> = 0.15		<i>P</i> = 0.78		0.54

\*OR and 95% CI for risk of Hodgkin's lymphoma adjusted for age, sex, urban residence, only-child status (total siblings = 0 or 1+), number of younger and older siblings, and maternal age at birth.

between older and younger siblings. However, the inverse association between having multiple older siblings and HL risk in our study was strongest for those who also had multiple younger siblings, which is consistent with other reports of an inverse association with total sibship size.

Our results did not correspond with some previous findings of no association between birth order or sibship size and HL risk (31-33). One of these studies (33) was conducted in Brazil, where birth order and number of siblings may be less important determinants of childhood social milieu and HL risk than in Sweden. Other investigations have demonstrated that the epidemiology of HL differs between developed and developing countries (42, 43). However, the Brazilian study, along with a hospital-based case-control study in Italy (32), did find positive associations between HL risk and high socioeconomic status or educational level, which are both correlated with small sibship size (34, 44). The authors of the third investigation (31), a case-control study of young U.S. women from 1988 to 1994, suggested that due to demographic changes in recent years, family characteristics such as birth order and sibship size may no longer be appropriate measures of childhood exposures pertinent to HL risk. We stratified our analyses by year of diagnosis, but did not detect any difference in results between cases diagnosed in the 1960s and 1970s versus those in the 1980s and 1990s. However, the U.S. study did report an inverse association between HL risk and other measures of increased childhood social contact, such as shared bedrooms and larger households. Thus, their results are still consistent with our conclusion that early interaction with other children is inversely associated with HL risk, although determinants of the level of this interaction may have changed in smaller contemporary families.

Being born later and having multiple siblings, particularly older siblings, favor early exposure to common childhood pathogens, which are often transmitted to young children by their older siblings who have encountered bacteria and viruses via classmates at school. This process may be particularly enhanced among those with a large total sibship size—that is, multiple younger siblings in addition to multiple older siblings—thereby explaining the strongest inverse association with HL risk for those with three or more older as well as three or more younger siblings in our study.

Earlier exposure to EBV in particular protects against development of adolescent mononucleosis, which is an established HL risk factor. Also, earlier exposure to common bacteria and viruses in general may decrease HL risk by priming the maturation of type 1 helper T-cell (Th1) immunity, which defends against intracellular bacterial and viral infections (45, 46). Infants are born with relatively weak Th1 phagocytic, cell-mediated immunity, counterbalanced by relatively strong type 2 helper T-cell (Th2), or B-cell antibody-mediated, immunity (47). Children exposed to bacteria and viruses are prompted to develop a Th1 response to these antigens (48, 49). In contrast, children who are raised in environments that shelter them from Th1-stimulatory antigens may continue to be biased toward Th2 immunity (50-52). Skewing toward Th2 immunity can leave children more vulnerable to Th1-type pathogens, including but not

limited to EBV, that could be involved in HL pathogenesis. This model may also partly explain the increased risk of HL among males compared with females, because males are generally more susceptible to common infections than females (53).

The delayed-infection model has been proposed not only with respect to HL, but also other hematopoietic malignancies, including leukemia and non-Hodgkin's lymphoma (54-56), although these diseases seem to be otherwise etiologically distinct from HL. Age at infection is not the only means through which older siblings could influence HL risk. Alternatively, number of older siblings could affect the route, intensity, or frequency of exposure to infectious agents, or could have an impact on other exposures such as maternal breastfeeding patterns or childhood nutrition (57, 58). However, the delayed-infection model remains the most biologically plausible and compelling explanation for our data and others'.

The finding that having older siblings was only marginally, if at all, associated with higher HL risk among adults over age 40 years suggests that early infection may be associated with a slightly elevated risk of HL among older adults, or may not have any association. Our results are consistent with previous studies that found a weak positive association between older-adult HL risk and correlates of early childhood infection (34, 35). These findings suggest that HL among older adults has a different etiology from that among younger adults, and may be associated with very early childhood EBV infection.

On the basis of data obtained from population registries, our investigation was limited by the inability to gather additional personal data from subjects, particularly information about childhood social environment and socioeconomic status. For a subset of our participants, however, data were available on father's occupation, which is one determinant of socioeconomic status. In this group, father's occupation was not significantly associated with HL risk, making it unlikely to be an important confounder of the results in the overall study population. However, the possibility of residual confounding by unmeasured factors, including other childhood socioeconomic variables, cannot be ruled out.

Information on number of siblings was obtained from the Multi-Generation Register, which was started in 1932. To improve the quality of our information on family structure, especially older siblings, we included only subjects who were born after 1941. Although some underestimation of the number of older siblings may still have occurred for older individuals in our study, this misclassification was most likely non-differential between cases and controls, and would have biased some OR estimates toward unity. The incompleteness of registry information for individuals who died before 1991 should not have introduced substantial differential bias between cases and controls, since survival for HL patients has been high (above 80% for young adults), following the introduction of effective treatment in the late 1960s (59). However, survival is lower for HL patients more than age 50. In addition, cases diagnosed before the 1980s, especially among older adults, may have been misclassified as non-Hodgkin's lymphoma. To address these potential sources of bias, we re-analyzed

the data, including only cases diagnosed and controls matched after 1991, and although the results were unstable, they were consistent with the findings from the full population.

Information on HL diagnosis was obtained from the Swedish Cancer Registry, which was initiated in 1958. Although HL is a rare disease, it is possible that some individuals diagnosed with HL between 1941 and 1957 were included in our study as controls, a form of misclassification that would have biased our estimated associations toward the null. To address this problem, we redid the analysis on only those individuals born after 1958. Because we found no appreciable differences in the results, we concluded that there was little bias introduced by including controls with an unknown history of cancer before 1958.

Overall, our results reinforce the notion that age at infection, as an indicator of both severity of infection and childhood immune system development, is an important factor in HL pathogenesis. In addition, our findings support previous studies proposing that HL can be divided into three disease entities based on age at diagnosis. Whether childhood infection contributes to the etiology of pediatric HL remains unclear, but our data indicate that the role of childhood environment in both childhood and older-adult HL is different from that in young-adult HL.

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