DOI:10.1093/jnci/djs225
Advance Access publication on May 22, 2012.

ARTICLE

Perinatal and Family Risk Factors for Non-Hodgkin Lymphoma in Early Life: A Swedish National Cohort Study

Casey Crump, Kristina Sundquist, Weiva Sieh, Marilyn A. Winkleby, Jan Sundquist

Manuscript received September 20, 2011; revised March 28, 2012; accepted March 29, 2012.

Correspondence to: Casey Crump, MD, PhD, Department of Medicine, Stanford University, 900 Blake Wilbur Dr, Stanford, CA 94304-2205 (e-mail: kccrump@stanford.edu).

Background The incidence of non-Hodgkin lymphoma (NHL) in early life has increased in recent decades, but the relevant risk factors remain largely unknown. We examined perinatal and family risk factors for NHL in childhood through young adulthood.

Methods We conducted a national cohort study of 3 571 574 individuals born in Sweden in 1973–2008 who were followed for incidence of NHL through 2009 (ages 0–37 years). Detailed information on perinatal and family characteristics and NHL diagnoses were obtained from national birth and cancer registries. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between perinatal and family variables and NHL; *P* values are from two-sided tests.

Results There were 936 NHL case patients identified in 66.3 million person-years of follow-up. Independent risk factors for NHL included family history of NHL in either a sibling (adjusted HR = 9.84; 95% CI = 2.46 to 39.41; *P* = .001) or parent (adjusted HR = 2.36; 95% CI = 1.27 to 4.38; *P* = .007); high fetal growth (for ≥2 SDs relative to 0 to <1 SD from the mean: adjusted HR = 1.64; 95% CI = 1.19 to 2.25; *P* = .002); older maternal age (adjusted HR for each 5-year increment = 1.11; 95% CI = 1.04 to 1.19; P_{trend} = .004); low birth order (adjusted HR for each increment of one birth = 0.91; 95% CI = 0.84 to 0.99; P_{trend} = .02); and male sex (adjusted HR = 1.58; 95% CI = 1.38 to 1.80; *P* < .001). Male sex was associated with onset of NHL before 15 years of age but not with later-onset NHL, whereas the other risk factors did not vary by age at diagnosis. No association was found between gestational age at birth, twinning, paternal age, or parental education and NHL.

Conclusion In this large national cohort study, family history of NHL, high fetal growth, older maternal age, low birth order, and male sex were independent risk factors for NHL in early life.

J Natl Cancer Inst 2012;104:923–930

The worldwide incidence of non-Hodgkin lymphoma (NHL) has increased dramatically in the past 50 years (1,2). Although the overall incidence began to stabilize in the 1990s, it has continued to increase among children, adolescents, and young adults (3,4). This increase remains unexplained and does not appear to be entirely attributable to diagnostic methods (1,2,5,6). NHL has heterogeneous etiologies that may involve genetic factors (7–9), immunodeficiency disorders (10), Epstein–Barr virus and other infections (11), other environmental exposures (12,13), and perinatal factors (14,15). The increasing incidence in early life has led to a growing interest in identifying etiologic factors that may act during the perinatal period. Elucidation of perinatal risk factors may facilitate the identification of high-risk infants and potentially enable earlier detection and treatment of NHL.

Perinatal factors such as high birth weight, older maternal age, and low birth order have been hypothesized to increase the risk of NHL via growth factor pathways (16), age-related changes in DNA repair pathways (17) or gene expression (18), and the immunologic effects of delayed infectious exposures (19). Previous studies of these factors have reported discrepant results but have been limited by small sample sizes, wide variability in adjustment for confounding, and potential selection bias due to socioeconomic and other differences between case and control subjects. In addition, most studies of birth weight have not examined its specific components, gestational age at birth and fetal growth; hence, the specific contributions of these factors are still unknown.

We conducted a national cohort study of 3.5 million people born in Sweden in 1973–2008, who were followed for NHL incidence through 2009, to examine risk factors for NHL in childhood through young adulthood. Detailed information on perinatal and family characteristics and NHL diagnoses were obtained by linkage of national birth and cancer registries that are nearly 100% complete.

CONTEXT AND CAVEATS

Prior knowledge

The incidence of non-Hodgkin lymphoma (NHL) has been increasing among children and adolescents. It was unclear whether perinatal and family characteristics contribute to the incidence of pediatric NHL.

Study design

More than 3.5 million individuals who were born from 1973 to 2008 and had complete birth records in the Swedish birth registry were followed until the end of 2009 (age 0–37 years) for incidence of NHL. Cox proportional hazard models were used to estimate the association of perinatal and family characteristics (from registry records) with risk of NHL.

Contribution

Among the 936 persons who developed NHL, independent risk factors included having a history of NHL in a sibling or parent, a high fetal growth rate, an older mother, and low birth order. Male sex was associated with incidence of NHL among subjects younger than 15 years. Time of gestation, twinning, paternal age, and parental education were not associated with risk of NHL.

Implication

Genetic factors and conditions in utero may contribute to the incidence of pediatric NHL.

Limitations

Information concerning a history of infection or immune disorders, smoking, and/or environmental exposures was unavailable. Statistical power was limited for determining associations with histological subtypes.

From the Editors

Methods

Study Population

We identified 3 595 055 individuals in the Swedish Birth Registry who were born from 1973 through 2008. We excluded 8113 individuals (0.2%) who had missing information for gestational age at birth and 10 029 others (0.3%) who had missing information for birth weight. To remove possible coding errors, we also excluded 5339 persons (0.1%) who had a reported birth weight more than 4 SDs above or below the mean birth weight for gestational age and sex based on a Swedish reference growth curve (20). A total of 3 571 574 individuals (99.3% of the original cohort) remained for inclusion in the study. This study was approved by the Ethics Committee of Lund University in Malmö, Sweden.

NHL Ascertainment

The study cohort was followed for NHL incidence from birth through December 31, 2009 (maximum attained ages ranged from 1 to 37 years). All primary NHL diagnoses (codes 200 and 202 in *International Classification of Diseases, Seventh Revision* [*ICD-7*]) were identified from the Swedish Cancer Registry. This registry includes all primary incident cancers in Sweden since 1958, with compulsory reporting nationwide. Histological subtypes were classified according to Systemized Nomenclature of Medicine (SNOMED) codes since 1993 and synonymous definitions provided by the World Health Organization before this period (21), and were categorized as diffuse B-cell subtypes, other or unspecified B-cell subtypes, and T-cell subtypes.

Perinatal and Family Variables

Perinatal and family characteristics that may be associated with NHL were identified from the Swedish Birth Registry and national census data, which were linked using an anonymous personal identification number (22). The following were included as predictors of interest and adjustment variables: sex (23); birth year (1973–1979, 1980–1984, 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2008) (1,2); fetal growth (measured as the number of standard deviations from the mean birth weight for gestational age and sex based on a Swedish reference growth curve (20), and categorized into six groups [<-2; -2 to <-1; -1 to <0; 0 to <1; 1 to <2; ≥ 2 SD] to allow for a nonlinear effect) (13,24–28); gestational age at birth (based mainly on maternal report of last menstrual period in the 1970s, at which time ultrasound estimation was gradually introduced until it was used exclusively starting in the 1990s; categorized into five groups [22–27, 28–33, 34–36, 37–42, $\geq$43 weeks] to allow for a nonlinear effect); multiple birth status (singleton or twin) (29); birth order (1, 2, 3, 4, or ≥ 5) (19,30–37); maternal age at delivery (<20, 20–24, 25–29, 30–34, 35–39, $\geq$40 years; paternal age was also examined but not retained in the final model because of its collinearity with maternal age) (38); maternal and paternal education level (compulsory high school or less [$\leq$9 years], practical or some theoretical high school [10–11 years], theoretical high school and/or some college [12–14 years], college and/or post-graduate study [$\geq$15 years], or unknown; entered into the model separately for mothers and fathers) (39); and family history of NHL in a sibling or parent (yes or no; identified from the Swedish Cancer Registry from 1958 through 2009, not self-reported, thus enabling complete and unbiased ascertainment during this period, and entered into the model separately for siblings and parents) (40).

Statistical Analysis

Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between perinatal and family variables and NHL. Individuals were censored at death (n = 32 566; 0.9%) or at emigration as determined by the absence of a Swedish residential address in census data (n = 102 217; 2.9%). Analyses were at first conducted without adjustment and then adjusted for covariates in a single model in which each variable was adjusted for all the others. Robust standard errors were used to account for clustering within families (41). First-order interactions among the covariates were explored using a likelihood ratio test. The proportional hazards assumption was evaluated using the method described by Grambsch and Therneau (42). In addition, multinomial logistic regression was used to test for heterogeneity in the association between each risk factor and NHL by age at diagnosis, comparing patients diagnosed at less than 15 years of age vs those diagnosed at 15 or more years of age. All statistical tests were two-sided and used an α level of .05. All analyses were conducted using Stata statistical software, version 11.0 (43).

Results

Among the 3 571 574 individuals in this cohort, 936 (0.03%) NHL case patients were identified in 66.3 million person-years of

Table 1. Incidence rates for non-Hodgkin lymphoma by age and sex (1973–2009)

	Both sexes			Boys or Men			Girls or Women		
Age, y	Case patients	Person-years*	Rate†	Case patients	Person-years*	Rate†	Case patients	Person-years*	Rate†
0–4	230	16.8	1.4	145	8.6	1.7	85	8.2	1.0
5–9	186	14.3	1.3	142	7.4	1.9	44	6.9	0.6
10–14	138	12.1	1.1	94	6.2	1.5	44	5.9	0.8
15–19	120	9.6	1.3	81	4.9	1.7	39	4.7	0.8
20–24	92	6.7	1.4	54	3.5	1.6	38	3.2	1.2
25–29	92	4.4	2.1	38	2.2	1.7	54	2.2	2.5
30–37	78	2.3	3.3	32	1.2	2.7	46	1.1	4.1
Total									
0–14	554	43.3	1.3	381	22.2	1.7	173	21.1	0.8
15–37	382	23.0	1.7	205	11.8	1.7	177	11.2	1.6
Overall	936	66.3	1.4	586	34.0	1.7	350	32.3	1.1

* Person-years in millions.

† Incidence rate per 100 000 person-years.

follow-up. NHL incidence rates, stratified by age and sex, are presented in Table 1; the overall incidence rate was 1.4 per 100 000 person-years (1.7 for males and 1.1 for females). The mean duration of follow-up was 18.6 ± 10.4 years (median, 18.6 years), and the mean age at NHL diagnosis was 13.8 ± 10.0 years (median, 11.8 years). Compared with individuals who were never diagnosed with NHL, those with NHL were more likely to have been born early in the study period, to be male, to have parents with the lowest educational attainment, or to have a family history of NHL in a sibling or parent (Table 2).

All NHLs

The strongest risk factor for NHL was family history of NHL in either a sibling (adjusted HR = 9.84; 95% CI = 2.46 to 39.41; $P = .001$) or a parent (adjusted HR = 2.36; 95% CI = 1.27 to 4.38; $P = .007$) (Table 3). These risk estimates were based on a small number of case patients with an affected sibling (n = 4, consisting of two sibling pairs, all male) or parent (n = 10, consisting of six case patients with an affected same-sex parent and four with an affected opposite-sex parent). There was no evidence that the association with family history depended on whether the affected family member was male or female (P for heterogeneity = .31). However, having a same-sex sibling or a same-sex parent with NHL (adjusted HR = 2.63; 95% CI = 1.18 to 5.88; based on 10 case patients) was a stronger risk factor than having an opposite-sex sibling or an opposite-sex parent with NHL (adjusted HR = 2.01; 95% CI = 0.75 to 5.38; based on four case patients) (P for heterogeneity = .02).

Other statistically significant risk factors for NHL included male sex, high fetal growth, older maternal age, and low birth order. Male sex was associated with a 1.5-fold risk of NHL relative to female sex (adjusted HR = 1.58; 95% CI = 1.38 to 1.80; $P < .001$). High fetal growth (≥2 SD above the reference birth weight for gestational age and sex, relative to 0 to <1 SD) was also associated with an increased risk of NHL (adjusted HR = 1.64; 95% CI = 1.19 to 2.25; $P = .002$), although there was no linear trend across the full range of fetal growth levels ($P_{trend} = .12$). In addition, older maternal age was associated with an increased risk of NHL (adjusted HR for each 5-year increment = 1.11; 95% CI = 1.04 to 1.19 [not shown in table]; $P_{trend} = .004$), and birth order was inversely associated with NHL (ie, higher birth order was associated with reduced risk) (adjusted HR for each increment of one birth = 0.91; 95% CI = 0.84 to 0.99 [not shown in table]; $P_{trend} = .02$). An ancillary analysis showed that there was no association between number of siblings (1, 2, 3, 4, ≥5) and NHL ($P_{trend} = .76$; not included in the final model due to collinearity with birth order). Each of the statistically significant trends reported in Table 3 had no evidence of departure from linearity (likelihood ratio test, $P > .05$).

Maternal age was an important confounder of the association between low birth order and NHL: the inverse relationship between birth order and NHL was evident only after adjusting for maternal age ($P_{trend} = .02$) and not in the unadjusted model ($P_{trend} = .52$). All other risk estimates were only modestly affected, if at all, by adjustment for covariates. Ancillary analyses showed that the association between older maternal age and NHL remained statistically significant after further adjusting for paternal age ($P_{trend} = .005$), whereas paternal age was not associated with NHL, with ($P_{trend} = .31$) or without ($P_{trend} = .30$) adjustment for maternal age and the other covariates.

Neither low nor high gestational age at birth was associated with NHL (Table 3). Maternal and paternal education levels also were not associated with NHL, regardless of whether only one or both of these variables were included in the model. Excluding either had no effect on other risk estimates.

We explored the effect of age at NHL diagnosis on these results. Male sex was a strong risk factor for NHL among the 554 case patients diagnosed before age 15 years (adjusted odds ratio [OR] = 2.09; 95% CI = 1.74 to 2.50) but was not a risk factor among the 382 case patients diagnosed at age 15 years or older (adjusted OR = 1.09; 95% CI = 0.89 to 1.33; P for heterogeneity < .001). There was no evidence of heterogeneity by age at diagnosis for the association between any other variable and NHL (P for heterogeneity > .05 for each). Specifically, the association between maternal age and NHL was similar comparing individuals diagnosed before age 15 years (adjusted OR for each 5-year increment of maternal age = 1.07; 95% CI = 0.97 to 1.17) with those diagnosed at age 15 years or older (adjusted OR = 1.16; 95% CI = 1.04 to 1.30; P for heterogeneity = .27). The association between birth order and NHL was also similar comparing these two groups (adjusted ORs for each increment of one birth = 0.94 [95% CI = 0.85 to 1.04] and 0.87 [95% CI = 0.77 to 0.99], respectively; P for heterogeneity = .39).

Table 2. Individual characteristics by non-Hodgkin lymphoma (NHL) status (1973–2009)*

Characteristic	Any NHL (N = 936) No. (%)	No NHL (N = 3 570 638) No. (%)
Age at diagnosis, y		
0–9	416 (44.4)	
10–19	258 (27.6)	
20–29	184 (19.7)	
≥30	78 (8.3)	
Mean ± SD	13.8 ± 10.0	
Sex		
Female	350 (37.4)	1 735 636 (48.6)
Male	586 (62.6)	1 835 002 (51.4)
Birth year		
1973–1979	350 (37.4)	692 504 (19.4)
1980–1984	188 (20.1)	455 074 (12.7)
1985–1989	140 (15.0)	521 042 (14.6)
1990–1994	113 (12.1)	581 630 (16.3)
1995–1999	78 (8.3)	447 850 (12.6)
2000–2004	55 (5.9)	460 926 (12.9)
2005–2008	12 (1.3)	411 612 (11.5)
Birth weight, g		
<2500	44 (4.7)	149 315 (4.2)
2500–3999	701 (74.9)	2 778 980 (77.8)
≥4000	191 (20.4)	642 343 (18.0)
Mean ± SD	3527 ± 582	3505 ± 574
Fetal growth, SD		
<−2	32 (3.4)	112 408 (3.2)
−2 to <−1	139 (14.8)	535 678 (15.0)
−1 to <0	336 (35.9)	1 266 464 (35.5)
0 to <1	288 (30.8)	1 118 509 (31.3)
1 to <2	97 (10.4)	428 660 (12.0)
≥2	44 (4.7)	108 919 (3.0)
Gestational age at birth, wk		
22–28	1 (0.1)	10 966 (0.3)
29–33	14 (1.5)	42 567 (1.2)
34–36	39 (4.2)	153 257 (4.3)
37–42	871 (93.1)	3 322 947 (93.1)
≥43	11 (1.2)	40 901 (1.1)
Mean ± SD	39.9 ± 1.8	39.8 ± 1.9
Multiple birth status		
Singleton	916 (97.9)	3 486 184 (97.6)
Twin	20 (2.1)	84 454 (2.4)
Birth order		
1	401 (42.9)	1 499 472 (42.0)
2	337 (36.0)	1 300 623 (36.4)
3	146 (15.5)	541 844 (15.2)
4	43 (4.6)	157 170 (4.4)
≥5	9 (1.0)	71 529 (2.0)
Maternal age at delivery, y		
<20	28 (3.0)	84 077 (2.4)
20–24	192 (20.5)	678 800 (19.0)
25–29	336 (35.9)	1 252 891 (35.1)
30–34	252 (26.9)	1 035 399 (29.0)
35–40	114 (12.2)	432 810 (12.1)
≥40	14 (1.5)	86 661 (2.4)
Maternal education, y		
≤9	217 (23.2)	674 982 (18.9)
10–11	326 (34.8)	1 150 055 (32.2)
12–14	247 (26.4)	1 045 242 (29.3)
≥15	108 (11.5)	554 787 (15.5)
Unknown	38 (4.1)	145 572 (4.1)
Paternal education, y		
≤9	258 (27.6)	767 475 (21.5)
10–11	304 (32.5)	1 128 965 (31.6)
12–14	217 (23.2)	960 102 (26.9)
≥15	122 (13.0)	538 015 (15.1)
Unknown	35 (3.7)	176 081 (4.9)
NHL in a sibling	4 (0.4)	1270 (<0.1)
NHL in a parent	10 (1.1)	10 946 (0.3)

* SD = standard deviation.

We found no statistically significant first-order interactions among the covariates, including between fetal growth and birth cohort (P = .49), with respect to NHL risk.

NHL Subtypes

NHL subtypes were categorized as diffuse B-cell (n = 320), other or unspecified B-cell (n = 170), or T-cell (n = 114), whereas subtype data were missing for 332 case patients. Individuals with missing subtype data had a similar sex and family history distribution, and similar fetal growth, maternal age, and birth order, compared with individuals with reported subtype data (P > .05 for each, using binomial test for proportions for sex and family history, t test for fetal growth and maternal age, and Kruskal–Wallis nonparametric test for birth order).

Male sex was associated with each of these subtype categories (Table 3). Family history of NHL in a sibling was associated with diffuse B-cell subtypes (adjusted HR = 13.62; 95% CI = 1.92 to 96.77; P = .009) but was not estimable for other subtypes because there were no affected siblings. Older maternal age was associated with an increased risk of diffuse B-cell subtypes (P_{trend} = .02) and a borderline increased risk of T-cell subtypes (P_{trend} = .05).

We also found birth cohort effects, with a decreasing risk of diffuse B-cell subtype and an increasing risk of other B-cell and T-cell subtypes in more recent birth years (P_{trend} < .001 for each). We assessed the possibility that the apparent subtype-specific birth cohort effects were due to more complete reporting by performing two sensitivity analyses. In the first analysis, case patients with missing subtype in each birth cohort were randomly assigned a subtype according to previously reported approximate frequencies (50% diffuse B-cell, 40% other B-cell, 10% T-cell) (44,45). In the second analysis, case patients with missing subtype were randomly assigned a subtype according to the distribution of known subtypes that were observed in these data for the same birth cohort, age, and sex. In both of these sensitivity analyses, the birth cohort effect for each subtype persisted and remained highly statistically significant (P_{trend} < .01 for each), suggesting that this was unlikely to be due to temporal changes in reporting.

Discussion

In this large national cohort study, we identified several perinatal and family risk factors for NHL in early life. The strongest risk

Table 3. Hazard ratios for associations between perinatal or family characteristics and non-Hodgkin lymphoma (NHL) in 1973–2009*

	Any NHL (N = 936)			Diffuse B-cell (N = 320)		B-cell, other or not specified (N = 170)		T-cell (N = 114)	
	Unadjusted	Adjusted*		Adjusted*		Adjusted*		Adjusted*	
Characteristic	HR (95% CI)	HR (95% CI)	*P*†	HR (95% CI)	*P*†	HR (95% CI)	*P*†	HR (95% CI)	*P*†
Sex									
Female	1.00 (referent)	1.00 (referent)	< .001	1.00 (referent)	< .001	1.00 (referent)	< .001	1.00 (referent)	.04
Male	1.58 (1.39 to 1.81)	1.58 (1.38 to 1.80)		1.61 (1.28 to 2.02)		2.03 (1.47 to 2.81)		1.50 (1.03, 2.19)	
Birth year									
1973–1979	1.00 (referent)	1.00 (referent)	.97	1.00 (referent)	< .001	1.00 (referent)	< .001	1.00 (referent)	< .001
1980–1984	1.20 (0.99 to 1.45)	1.17 (0.97 to 1.41)		1.14 (0.86 to 1.53)		1.47 (0.94 to 2.28)		1.41 (0.76 to 2.62)	
1985–1989	1.01 (0.82 to 1.25)	0.98 (0.79 to 1.21)		0.70 (0.48 to 1.01)		1.06 (0.61 to 1.85)		2.42 (1.29 to 4.52)	
1990–1994	0.96 (0.76 to 1.21)	0.91 (0.72 to 1.15)		0.29 (0.17 to 0.49)		1.94 (1.15 to 3.26)		4.44 (2.32 to 8.48)	
1995–1999	1.14 (0.88 to 1.50)	1.07 (0.82 to 1.41)		0.31 (0.17 to 0.60)		3.07 (1.61 to 5.87)		5.33 (2.32 to 11.75)	
2000–2004	1.28 (0.94 to 1.74)	1.18 (0.86 to 1.62)		0.44 (0.22 to 0.90)		7.58 (3.84 to 14.97		5.44 (1.86 to 15.91)	
2005–2008	0.77 (0.43 to 1.40)	0.85 (0.43 to 1.68)		0.28 (0.04 to 2.06)		NE		7.43 (0.88 to 62.80)	
Fetal growth, SD									
<−2	0.90 (0.62 to 1.29)	0.92 (0.64 to 1.33)	.12	0.69 (0.36 to 1.35)	.03	1.00 (0.42 to 2.34)	.66	0.56 (0.14 to 2.17)	.66
−2 to <−1	0.90 (0.74 to 1.10)	0.92 (0.75 to 1.12)		0.79 (0.55 to 1.13)		1.05 (0.66 to 1.66)		0.94 (0.52 to 1.71)	
−1 to <0	0.99 (0.85 to 1.16)	1.00 (0.85 to 1.17)		0.95 (0.72 to 1.24)		0.92 (0.64 to 1.34)		1.06 (0.67 to 1.67)	
0 to <1	1.00 (referent)	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
1 to <2	0.90 (0.72 to 1.14)	0.90 (0.71 to 1.13)		1.10 (0.76 to 1.60)		0.62 (0.34 to 1.14)		1.12 (0.61 to 2.06)	
≥2	1.65 (1.20 to 2.26)	1.64 (1.19 to 2.25)		1.46 (0.82 to 2.61)		1.73 (0.85 to 3.51)		1.19 (0.42 to 3.36)	
Gestational age at birth, wk									
22–28	0.72 (0.10 to 5.11)	0.69 (0.10 to 4.94)	.30	NE	.37	NE	.61	NE	.30
29–33	1.46 (0.86 to 2.48)	1.41 (0.81 to 2.43)		1.43 (0.52 to 3.90)		0.55 (0.08 to 3.62)		1.72 (0.39 to 7.53)	
34–36	1.01 (0.73 to 1.39)	0.98 (0.71 to 1.36)		0.81 (0.43 to 1.53)		1.11 (0.54 to 2.27)		1.07 (0.42 to 2.75)	
37–42	1.00 (referent)	1.00 (referent)		1.00 (referent)		1.00 (referent)		1.00 (referent)	
≥43	0.69 (0.38 to 1.24)	0.72 (0.39 to 1.31)		1.71 (0.90 to 3.28)		NE		NE	
Multiple birth									
Singleton	1.00 (referent)	1.00 (referent)	.71	1.00 (referent)	.21	1.00 (referent)	.81	1.00 (referent)	.82
Twin	1.06 (0.67 to 1.69)	1.10 (0.67 to 1.80)		0.40 (0.10 to 1.66)		0.87 (0.28 to 2.69)		0.84 (0.19 to 3.71)	
Birth order									
1	1.00 (referent)	1.00 (referent)	.02	1.00 (referent)	.07	1.00 (referent)	.38	1.00 (referent)	.66
2	0.96 (0.83 to 1.11)	0.90 (0.77 to 1.05)		0.75 (0.58 to 0.98)		0.97 (0.67 to 1.40)		1.13 (0.72 to 1.77)	
3	1.01 (0.84 to 1.22)	0.87 (0.71 to 1.08)		0.76 (0.53 to 1.09)		1.06 (0.63 to 1.76)		0.85 (0.44 to 1.63)	
4	1.07 (0.78 to 1.46)	0.88 (0.62 to 1.23)		0.92 (0.52 to 1.61)		0.93 (0.41 to 2.09)		1.16 (0.49 to 2.78)	
≥5	0.52 (0.27 to 1.00)	0.41 (0.21 to 0.81)		0.27 (0.07 to 1.11)		0.61 (0.14 to 2.67)		NE	
Maternal age at delivery, y									
<20	1.00 (referent)	1.00 (referent)	.004	1.00 (referent)	.02	1.00 (referent)	.32	1.00 (referent)	.05
20–24	0.94 (0.63 to 1.40)	0.97 (0.65 to 1.44)		1.03 (0.53 to 2.01)		0.81 (0.35 to 1.92)		1.24 (0.28 to 5.40)	
25–29	1.01 (0.68 to 1.48)	1.07 (0.72 to 1.59)		1.40 (0.72 to 2.71)		0.78 (0.33 to 1.85)		1.49 (0.34 to 6.46)	
30–34	1.09 (0.74 to 1.61)	1.20 (0.80 to 1.81)		1.39 (0.70 to 2.76)		0.89 (0.36 to 2.17)		2.21 (0.49 to 9.88)	
35–40	1.32 (0.87 to 2.00)	1.50 (0.97 to 2.33)		1.76 (0.83 to 3.75)		1.00 (0.38 to 2.65)		2.62 (0.56 to 12.26)	
≥40	0.86 (0.45 to 1.64)	1.04 (0.53 to 2.02)		1.27 (0.39 to 4.17)		0.89 (0.21 to 3.72)		0.94 (0.08 to 10.80)	
Maternal education, y									
≤9	1.00 (referent)	1.00 (referent)	.91	1.00 (referent)	.73	1.00 (referent)	.33	1.00 (referent)	.67
10–11	0.97 (0.82 to 1.16)	0.96 (0.81 to 1.14)		1.01 (0.75 to 1.36)		1.23 (0.82 to 1.84)		1.05 (0.60 to 1.84)	
12–14	1.10 (0.91 to 1.32)	1.07 (0.88 to 1.31)		1.17 (0.83 to 1.64)		1.28 (0.80 to 2.06)		1.22 (0.67 to 2.25)	
≥15	0.96 (0.76 to 1.21)	0.93 (0.71 to 1.21)		0.90 (0.56 to 1.46)		1.34 (0.72 to 2.47)		1.04 (0.47 to 2.31)	

(Table continues)

Table 3 (Continued).

Characteristic	Any NHL (N = 936)			Diffuse B-cell (N = 320)			B-cell, other or not specified (N = 170)			T-cell (N = 114)		
	Unadjusted	Adjusted*		Adjusted*			Adjusted*			Adjusted*		
	HR (95% CI)	HR (95% CI)	*P*†	HR (95% CI)	*P*†		HR (95% CI)	*P*†		HR (95% CI)	*P*†	
Unknown	1.01 (0.71 to 1.42)	1.06 (0.75 to 1.50)		1.11 (0.63 to 1.96)			0.83 (0.32 to 2.17)			1.71 (0.71 to 4.08)		
Paternal education, y												
≤9	1.00 (referent)	1.00 (referent)	.09	1.00 (referent)	.07		1.00 (referent)	0.20		1.00 (referent)	.51	
10–11	1.00 (0.85 to 1.18)	1.00 (0.84 to 1.18)		0.96 (0.72 to 1.27)			1.00 (0.67 to 1.48)			1.13 (0.69 to 1.87)		
12–14	0.94 (0.78 to 1.12)	0.89 (0.73 to 1.08)		0.77 (0.56 to 1.06)			0.91 (0.59 to 1.40)			0.79 (0.44 to 1.40)		
≥15	0.92 (0.74 to 1.14)	0.85 (0.67 to 1.09)		0.74 (0.48 to 1.14)			0.69 (0.38 to 1.24)			0.95 (0.47 to 1.91)		
Unknown	0.74 (0.52 to 1.05)	0.73 (0.51 to 1.03)		0.37 (0.17 to 0.77)			1.00 (0.46 to 2.16)			0.94 (0.37 to 2.35)		
NHL in a sibling												
No	1.00 (referent)	1.00 (referent)	.001	1.00 (referent)	.009		1.00 (referent)	NE		1.00 (referent)	NE	
Yes	10.03 (2.50 to 40.28)	9.84 (2.46 to 39.41)		13.62 (1.92 to 96.77)			NE			NE		
NHL in a parent												
No	1.00 (referent)	1.00 (referent)	.007	1.00 (referent)	.34		1.00 (referent)	0.18		1.00 (referent)	.48	
Yes	2.40 (1.29 to 4.49)	2.36 (1.27 to 4.38)		1.74 (0.56 to 5.42)			2.64 (0.65 to 10.81)			2.03 (0.29 to 14.31)		

* CI = confidence interval; HR = hazard ratio; NE = not estimable; SD = standard deviation. The adjusted model included sex, birth year, fetal growth, gestational age at birth, multiple birth, birth order, maternal age at delivery, maternal and paternal education level, and family history of NHL in a sibling or parent.

† *P* for trend for ordered polytomous variables and Wald *P* for dichotomous variables, in the adjusted model. In each case where the *P* value for linear trend was less than .05, a separate likelihood ratio test for departure from linearity was not statistically significant ($P > .05$). All *P* values were from two-sided tests.

factor was family history of NHL, particularly in a sibling. High fetal growth was also associated with NHL, independent of gestational age and other perinatal factors, and this was consistent with a possible threshold rather than linear effect. In addition, older maternal (but not paternal) age, low birth order, and male sex were independent risk factors for NHL. Male sex was associated with NHL onset before 15 years of age but not later-onset, whereas the other risk factors did not vary by age at diagnosis.

These findings suggest several heterogeneous mechanisms. First, the associations between family history and risk of NHL were based on a small number of case patients with affected family members and therefore should be interpreted with caution. However, they are generally consistent with earlier findings and may reflect both genetic and shared environmental factors. There is increasing evidence for a role of genetic polymorphisms in NHL carcinogenesis (7–9), although the heritability of NHL in the Swedish population has been estimated to be only 10% (46). The ninefold risk we observed among individuals with a family history of NHL in a sibling was stronger than the approximately twofold risk reported in previous studies (40). The strength of this association relative to that for a parental history of NHL, as well as the stronger association we found with a same-sex compared with opposite-sex family history, are suggestive of important shared environmental factors that have yet to be identified. Increased sex concordance of sibling pairs has been reported for other diseases associated with immunologic dysfunction, including multiple sclerosis, sarcoidosis, Behcet disease, Hodgkin lymphoma, and chronic lymphocytic leukemia (47,48). Pooled studies with larger samples of NHL-affected sibling pairs would be useful to further elucidate potential gene–environment interactions.

The association we found between high fetal growth and NHL is in contrast to most findings for birth weight based mainly on case–control studies. A recent meta-analysis of five case–control studies (2660 case and 69 274 control subjects, aged <18 years) and two cohort studies (278 751 children, aged <9 years) reported no overall association between high or low birth weight and NHL (49). However, unlike this study, those studies were limited to children and/or adolescents, and most did not account for gestational age at birth. Another smaller cohort study in Australia reported that a high proportion of optimal birth length was associated with an increased risk of NHL in girls but not boys younger than 15 years of age (15). The mechanism by which high fetal growth may affect the risk of NHL is not well established, but one hypothesis involves growth factor pathways, specifically insulinlike growth factor 1 (IGF-1), which is associated with fetal growth and has been shown to inhibit apoptosis and enhance tumor growth (16).

The association we found between older maternal age and increased risk of NHL is consistent with a statistically nonsignificant trend reported in a US pooled case–control study (38), but in contrast to smaller Swedish (50) and Californian (51) cohort studies. We found that older maternal age was associated with NHL even after adjusting for paternal age, whereas paternal age was not associated with NHL with or without adjustment for maternal age and other covariates. These relationships warrant further confirmation in other large cohort studies. Possible mechanisms may involve impaired DNA repair pathways in oocytes of older mothers (17), age-related decreases in oocyte gene expression

(18), or transgenerational inheritance of epimutations in oocyte genes (38). Age-related germline mutations are also possible but are more likely to be a paternal rather than maternal effect (because of more cell divisions in sperm during gametogenesis) (52), and therefore are not strongly supported by these findings.

We also found that the risk of NHL was inversely related to birth order, after adjusting for maternal age. This was consistent with earlier findings from a UK case–control study (37) and with a statistically nonsignificant inverse trend in a US pooled case–control study (53), but in contrast to other smaller studies that found an opposite trend (30,34) or no association (19,35,36). One study indicated that some of the opposite (positive) trends previously reported between birth order and NHL may be spurious because of selection bias and confounding by socioeconomic status (54). This study also suggests that maternal age is an important confounder that should be accounted for in future analyses. The inverse association we found between birth order and NHL is consistent with the "delayed exposure hypothesis," which postulates that delayed exposure to Epstein–Barr virus and other infectious agents (which may result from the absence of older siblings) impairs the normal maturation of the immune system from a T helper cell type 2 (Th2) to a T helper cell type 1 (Th1) preponderance. This in turn leads to an altered immune response, which may predispose to the development of NHL (19).

NHL incidence rates (per 100 000 person-years) during childhood (age <15 years) in this cohort (1.7 for males and 0.8 for females) were higher than those reported in the United States during 1998–2002 (1.2 for white males and 0.6 for white females) (2) or England during 1954–1998 (0.6 for males and 0.3 for females) (55) and were similar to various others previously reported in Asia, Africa, and South America (56,57). To our knowledge, the decreasing risk of diffuse B-cell subtypes that we found during this study period (1973–2009) has not been previously reported, whereas the increasing risk of other B-cell and T-cell subtypes is generally consistent with trends reported for Europe during 1985–1992 (44) and the United States during 1975–1995 (45). These trends are still not well explained and warrant further investigation for important unmeasured environmental exposures.

The most important strengths of this study were its national cohort design and large sample size, enabling more robust and generalizable inferences. Linkage of birth and cancer registries provided detailed information on perinatal factors and NHL incidence that was nearly 100% complete. A cohort design prevented selection bias that may potentially occur in case–control studies, and the use of registry-based data prevented bias that may result from self-reporting. We were able to examine the specific contributions of fetal growth and gestational age at birth. In addition, family history of NHL was based on registry data with virtually complete ascertainment rather than self-report, thus improving the reliability of those risk estimates.

Study limitations included the unavailability of information on infection history, immune-related disorders, smoking, and other environmental exposures; hence, we were unable to examine the potentially important effects of these factors. Although statistical power was greater than in most previous studies, it was still limited for detecting associations with specific histological subtypes. Subtype data were also missing for some individuals, although there was no evidence that this occurred differentially with respect to perinatal factors or family history.

In summary, in this large national cohort study, family history of NHL, high fetal growth, older maternal age, low birth order, and male sex were identified as independent risk factors for NHL in early life. These findings suggest several heterogeneous mechanisms including possible growth factor pathways in utero, immunologic effects of delayed infectious exposures, as well as other unmeasured environmental and genetic factors. Further elucidation of these risk factors may facilitate the identification of high-risk individuals at young ages and potentially enable earlier detection and treatment.

References

1. Ekstrom-Smedby K. Epidemiology and etiology of non-Hodgkin lymphoma—a review. *Acta Oncol.* 2006;45(3):258–271.
2. Alexander DD, Mink PJ, Adami HO, et al. The non-Hodgkin lymphomas: a review of the epidemiologic literature. *Int J Cancer.* 2007;120(suppl 12): 1–39.
3. Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCIS project): an epidemiological study. *Lancet.* 2004;364(9451):2097–2105.
4. Ries LAG, Eisner MP, Kosary CL, et al. *SEER Cancer Statistics Review, 1975-2000.* Bethesda, MD: National Cancer Institute; 2003.
5. Banks PM. Changes in diagnosis of non-Hodgkin's lymphomas over time. *Cancer Res.* 1992;52(19 suppl):5453s–5455s.
6. Hartge P, Devesa SS. Quantification of the impact of known risk factors on time trends in non-Hodgkin's lymphoma incidence. *Cancer Res.* 1992; 52(19 suppl):5566s–5569s.
7. Shen M, Menashe I, Morton LM, et al. Polymorphisms in DNA repair genes and risk of non-Hodgkin lymphoma in a pooled analysis of three studies. *Br J Haematol.* 2010;151(3):239–244.
8. Hosgood HD III, Purdue MP, Wang SS, et al. A pooled analysis of three studies evaluating genetic variation in innate immunity genes and non-Hodgkin lymphoma risk. *Br J Haematol.* 2011;152(6):721–726.
9. Lan Q, Wang SS, Menashe I, et al. Genetic variation in Th1/Th2 pathway genes and risk of non-Hodgkin lymphoma: a pooled analysis of three population-based case-control studies. *Br J Haematol.* 2011;153(3):341–350.
10. Kersey JH, Shapiro RS, Filipovich AH. Relationship of immunodeficiency to lymphoid malignancy. *Pediatr Infect Dis J.* 1988;7(5 suppl):S10–S12.
11. Niedobitek G, Young LS, Herbst H. Epstein-Barr virus infection and the pathogenesis of malignant lymphomas. *Cancer Surv.* 1997;30:143–162.
12. John EM, Savitz DA, Sandler DP. Prenatal exposure to parents' smoking and childhood cancer. *Am J Epidemiol.* 1991;133(2):123–132.
13. Petridou ET, Dikalioti SK, Skalkidou A, et al. Sun exposure, birth weight, and childhood lymphomas: a case control study in Greece. *Cancer Causes Control.* 2007;18(9):1031–1037.
14. Adami J, Glimelius B, Cnattingius S, et al. Maternal and perinatal factors associated with non-Hodgkin's lymphoma among children. *Int J Cancer.* 1996;65(6):774–777.
15. Milne E, Laurvick CL, Blair E, et al. Fetal growth and the risk of childhood CNS tumors and lymphomas in Western Australia. *Int J Cancer.* 2008;123(2):436–443.
16. Pollak MN, Schernhammer ES, Hankinson SE. Insulin-like growth factors and neoplasia. *Nat Rev Cancer.* 2004;4(7):505–518.
17. Steuerwald NM, Bermudez MG, Wells D, et al. Maternal age-related differential global expression profiles observed in human oocytes. *Reprod Biomed Online.* 2007;14(6):700–708.
18. Esteller M. Epigenetics in cancer. *N Engl J Med.* 2008;358(11):1148–1159.
19. Vineis P, Miligi L, Crosignani P, et al. Delayed infection, family size and malignant lymphomas. *J Epidemiol Community Health.* 2000;54(12):907–911.
20. Marsal K, Persson PH, Larsen T, et al. Intrauterine growth curves based on ultrasonically estimated foetal weights. *Acta Paediatr.* 1996;85(7): 843–848.
21. Jaffe ESHN, Stein H, Vardiman JW. *Pathology and Genetics of Tumours of Hematopoietic and Lymphoid Tissues.* Lyon, France: IARC Press; 2001.

22. Crump C, Sundquist K, Sundquist J, et al. Gestational age at birth and mortality in young adulthood. *JAMA.* 2011;306(11):1233–1240.
23. Parkin DM, Whelan SL, Ferlay J, et al. *Cancer in Five Continents, vol. VIII.* Lyon, France: IARC; 2002.
24. Rangel M, Cypriano M, de Martino Lee ML, et al. Leukemia, non-Hodgkin's lymphoma, and Wilms tumor in childhood: the role of birth weight. *Eur J Pediatr.* 2010;169(7):875–881.
25. Yeazel MW, Ross JA, Buckley JD, et al. High birth weight and risk of specific childhood cancers: a report from the Children's Cancer Group. *J Pediatr.* 1997;131(5):671–677.
26. Spector LG, Puumala SE, Carozza SE, et al. Cancer risk among children with very low birth weights. *Pediatrics.* 2009;124(1):96–104.
27. Smith A, Lightfoot T, Simpson J, et al. Birth weight, sex and childhood cancer: a report from the United Kingdom Childhood Cancer Study. *Cancer Epidemiol.* 2009;33(5):363–367.
28. Schuz J, Kaatsch P, Kaletsch U, et al. Association of childhood cancer with factors related to pregnancy and birth. *Int J Epidemiol.* 1999;28(4):631–639.
29. Hemminki K, Li X. Cancer risks in twins: results from the Swedish family-cancer database. *Int J Cancer.* 2002;99(6):873–878.
30. Smedby KE, Hjalgrim H, Chang ET, et al. Childhood social environment and risk of non-Hodgkin lymphoma in adults. *Cancer Res.* 2007;67(22):11074–11082.
31. Holly EA, Lele C, Bracci PM, et al. 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(4):375–389.
32. Grulich AE, Vajdic CM, Kaldor JM, et al. Birth order, atopy, and risk of non-Hodgkin lymphoma. *J Natl Cancer Inst.* 2005;97(8):587–594.
33. Bracci PM, Dalvi TB, Holly EA. Residential history, family characteristics and non-Hodgkin lymphoma, a population-based case-control study in the San Francisco Bay Area. *Cancer Epidemiol Biomarkers Prev.* 2006;15(7):1287–1294.
34. 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(3):211–222.
35. Becker N, Deeg E, Nieters A. Population-based study of lymphoma in Germany: rationale, study design and first results. *Leuk Res.* 2004;28(7):713–724.
36. Chatenoud L, Gallus S, Altieri A, et al. Number of siblings and risk of hodgkin's and other lymphoid neoplasms. *Cancer Epidemiol Biomarkers Prev.* 2005;14(2):552.
37. Cartwright RA, McKinney PA, O'Brien C, et al. Non-Hodgkin's lymphoma: case control epidemiological study in Yorkshire. *Leuk Res.* 1988;12(1):81–88.
38. Johnson KJ, Carozza SE, Chow EJ, et al. Parental age and risk of childhood cancer: a pooled analysis. *Epidemiology.* 2009;20(4):475–483.
39. Cantor KP, Fraumeni JF Jr. Distribution of non-Hodgkin's lymphoma in the United States between 1950 and 1975. *Cancer Res.* 1980;40(8, pt 1):2645–2652.
40. Wang SS, Slager SL, Brennan P, et al. Family history of hematopoietic malignancies and risk of non-Hodgkin lymphoma (NHL): a pooled analysis of 10 211 cases and 11 905 controls from the International Lymphoma Epidemiology Consortium (InterLymph). *Blood.* 2007;109(8):3479–3488.
41. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. *J Am Stat Assoc.* 1989;84(408):1074–1078.
42. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika.* 1994;81(3):515–526.
43. StataCorp. *Stata Statistical Software: Release 11.0.* College Station, TX: StataCorp; 2010.
44. Cartwright R, Brincker H, Carli PM, et al. The rise in incidence of lymphomas in Europe 1985-1992. *Eur J Cancer.* 1999;35(4):627–633.
45. Groves FD, Linet MS, Travis LB, et al. Cancer surveillance series: non-Hodgkin's lymphoma incidence by histologic subtype in the United States from 1978 through 1995. *J Natl Cancer Inst.* 2000;92(15):1240–1251.
46. Czene K, Lichtenstein P, Hemminki K. Environmental and heritable causes of cancer among 9.6 million individuals in the Swedish Family-Cancer Database. *Int J Cancer.* 2002;99(2):260–266.
47. Grufferman S, Barton JW III, Eby NL. Increased sex concordance of sibling pairs with Behcet's disease, Hodgkin's disease, multiple sclerosis, and sarcoidosis. *Am J Epidemiol.* 1987;126(3):365–369.
48. Sellick GS, Allinson R, Matutes E, et al. Increased sex concordance of sibling pairs with chronic lymphocytic leukemia. *Leukemia.* 2004;18(6):1162–1163.
49. Papadopoulou C, Antonopoulos CN, Sergentanis TN, et al. Is birth weight associated with childhood lymphoma? A meta-analysis. *Int J Cancer.* 2011;130(1):179–189.
50. Yip BH, Pawitan Y, Czene K. Parental age and risk of childhood cancers: a population-based cohort study from Sweden. *Int J Epidemiol.* 2006;35(6):1495–1503.
51. Lu Y, Ma H, Sullivan-Halley J, et al. Parents' ages at birth and risk of adult-onset hematologic malignancies among female teachers in California. *Am J Epidemiol.* 2010;171(12):1262–1269.
52. Crow JF. The origins, patterns and implications of human spontaneous mutation. *Nat Rev Genet.* 2000;1(1):40–47.
53. Von Behren J, Spector LG, Mueller BA, et al. Birth order and risk of childhood cancer: a pooled analysis from five US States. *Int J Cancer.* 2010;128(11):2709–2716.
54. Grulich AE, Vajdic CM, Falster MO, et al. Birth order and risk of non-Hodgkin lymphoma—true association or bias? *Am J Epidemiol.* 2010;172(6):621–630.
55. McNally RJ, Cairns DP, Eden OB, et al. Examination of temporal trends in the incidence of childhood leukaemias and lymphomas provides aetiological clues. *Leukemia.* 2001;15(10):1612–1618.
56. Bao PP, Zheng Y, Gu K, et al. Trends in childhood cancer incidence and mortality in urban Shanghai, 1973-2005. *Pediatr Blood Cancer.* 2010;54(7):1009–1013.
57. Stiller CA, Parkin DM. International variations in the incidence of childhood lymphomas. *Paediatr Perinat Epidemiol.* 1990;4(3):303–324.

Funding

This study was supported by grants from the National Institute of Child Health and Human Development (1R01HD052848-01), the Swedish Research Council (2008-3110 and 2008-2638), the Swedish Council for Working Life and Social Research (2006-0386, 2007-1754, and 2007-1962), and ALF project grant (Lund, Sweden).

Notes

The funding agencies had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the article. There were no conflicts of interest for any authors.

Affiliations of authors: Department of Medicine (CC) and Department of Health Research and Policy (WS), Stanford University, Stanford, CA; Center for Primary Health Care Research, Lund University, Malmö, Sweden (KS, JS); Stanford Prevention Research Center, Department of Medicine, Stanford University, Stanford, CA (MAW, JS).