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Infectious, autoimmune, and allergic diseases and risk of Hodgkin lymphoma in children and adolescents: A Children's Oncology Group (COG) study

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Abstract

An infectious origin for pediatric Hodgkin lymphoma (HL) has long been suspected and Epstein-Barr virus (EBV) has been implicated in a subset of cases. Increased HL incidence in children with congenital and acquired immunodeficiencies, consistent associations between autoimmune diseases and adult HL, and genome-wide association and other genetic studies together suggest immune dysregulation is involved in lymphomagenesis. Here, healthy control children identified by random digit dialing were matched on sex, race/ethnicity, and age to HL cases diagnosed in 1989-2003 at 0-14 years at Children's Oncology Group institutions. Parents of 517 cases and 784 controls completed telephone interviews, including items regarding medical histories. Tumor EBV status was determined for 355 cases. Using conditional logistic regression, we calculated odds ratios (ORs) and 95% confidence intervals (CIs) for risk of HL. Cases were more likely to have had an infection >1 year prior to HL diagnosis (OR=1.69, 95% CI:0.98-2.91); case siblings were also more likely to have had a prior infection (OR=2.04, 95% CI:1.01-4.14). Parental history of autoimmunity associated with increased EBV+ HL risk (OR=2.97, 95% CI:1.34-6.58), while having a parent (OR=1.47, 95% CI:1.01-2.14) or sibling (OR=1.62, 95% CI:1.11-2.36) with an allergy was associated with EBV- HL. These results may indicate true increased risk for infections and increased risk with family history of autoimmune and allergic conditions that varies by tumor EBV status, or they may be attributable to inaccurate recall. In addition to employing biomarkers to confirm the role of immune-modulating conditions in pediatric HL, future studies should focus on family-based designs.

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Keywords

Hodgkin lymphoma; children; infections; autoimmune disease; allergies

Little research has been devoted to understanding the causes of pediatric and adolescent Hodgkin lymphoma (HL), the 8th most common malignancy among those <15 years of age in the U.S.¹ Established risk factors include immunodeficiency,^{2,3} infection with Epstein-Barr virus (EBV),^{4,5} and family history of HL.⁶ In the US and other economically developed countries, HL diagnosed among children <15 years has distinct demographic and clinical characteristics from HL in older adolescents and young adults (AYA; 15-39 years) and older adults (>50 years), including a modestly higher incidence rate in males versus females (incidence rate ratios: 1.13 vs. 0.71 and 1.56, respectively),¹ intermediate distribution of the nodular sclerosis (NS, 68% vs. 74% and 39%) and mixed cellularity (MC, 13% vs. 9% and 23%) subtypes,¹ and a higher proportion of cases with EBV-infected tumor cells than AYA cases (47% vs. 29% and 50%).⁴ In addition, opposite trends have been reported for the effects of increasing socio-economic status (SES), birth order, and sibship size on HL risk in children and young adolescents versus AYA.⁷⁻⁹ These differences imply a unique HL etiology among children.⁵

While an infectious cause for HL had long been suspected, detection of higher serum anti-EBV antibody titers preceding HL diagnosis¹⁰ and EBV DNA in Hodgkin/Reed-Sternberg (HRS) cells,¹¹ and demonstration that EBV can transform lymphoblastoid cells *in vitro*¹² cemented the infectious origins for at least a portion of HLs. Evidence of latent EBV infection, i.e., EBV-encoded small RNAs (EBER) or latent membrane protein-1, has been found in ~50% of pediatric tumors overall, most notably in MC HL (~80%).⁴ That 50-60% of individuals are seropositive for EBV by 4-6 years of age in economically developed countries,¹³ yet only a small fraction of the population develops HL, suggests important individual differences in timing and response to infection.

At the level of the microenvironment, HL tumors display a skewed immune cell profile, with a reduced pool of Type 1 helper T (Th1) cells, cytotoxic T lymphocytes, and natural killer cells, and elevated Th2 cells, regulatory T cells, and eosinophils.¹⁴ Results of several lines of inquiry also support a role for global immune dysregulation in the pathogenesis of HL. Children with congenital and acquired immunodeficiencies, including ataxia telangiectasia, common variable immunodeficiency, and HIV, are at substantially increased risk for HL compared to the general population.^{2,3} Rheumatoid arthritis has been consistently associated with HL in adults, conferring an estimated 3.3-fold greater risk,¹⁵ while associations between other autoimmune diseases and HL have been observed in adults as well.^{16,17} In addition, genome-wide association¹⁸ and other genetic studies¹⁹ have identified variants in HLA genes linked to increased HL susceptibility.

Etiologic research in adult HL has demonstrated that there are risk factors shared by HL patients irrespective of EBV tumor status, and risk factors that are specific to EBV+ versus EBV- HL.^{4,18,19} To our knowledge, no prior studies have examined risk by tumor EBV status in pediatric and adolescent HL, although the available data indicate such stratification is warranted.

Given the compelling evidence implicating immune dysregulation in HL etiology, we evaluated associations between a personal or family history of infections and other immune-mediated conditions and HL in children and adolescents, overall and by tumor EBV status, using data from the largest case-control study conducted to date.

Materials and Methods

The current analysis employed data and specimens collected through Children's Cancer Group (CCG; now Children's Oncology Group, COG) Protocol E13: "Case-control study of Hodgkin's Disease in Children."

Cases

Eligible cases were identified via the CCG/COG patient registry; eligibility criteria included a pathologically confirmed diagnosis of HL between the ages of 0-14 years at a participating CCG/COG institution in the United States, Puerto Rico, or Canada between January 31, 1989 and July 28, 2003, physician approval for contact, telephone in residence, and at least one biological parent that spoke English or Spanish and consented to participate. Deceased cases meeting these criteria were eligible. Once the treating physician had provided permission to contact the family, an initial phone contact was made to determine potential interest and hard copies of study materials (study description, interview guide, consent form) were sent by conventional mail.

Controls

Healthy control children were identified via random digit dialing (RDD) as described previously,²⁰ and were individually matched to cases on sex, race/ethnicity, birth date (± 1 year for cases <5 years, ± 3 years for cases 5-14 years), and geographic location. Children were eligible if they had no prior cancer diagnosis, had a telephone in the residence, and had a biological parent that spoke English or Spanish and consented to an interview. To increase statistical power, up to three controls were selected for cases 0-9 years at diagnosis due to the rarity of HL in this age group, while one control was selected for cases aged 10-14 years. To enhance the matching success rate, the criteria were relaxed near the end of the study using a sequential algorithm which allowed for an increased age matching increment, a different race/ethnicity, or a neighboring area code, in turn. Control parents were provided with the same study materials as case parents by mail prior to interview and gave verbal consent before the interview.

Interviews

Parental report of medical histories, gathered through separate structured telephone interviews with mothers and fathers, was used in this analysis. Interviews were conducted a mean 1.11 (SD=0.97) years after diagnosis for cases and 2.79 (1.97) years after the assigned reference date for controls. A parent of each case (n=517) and control (n=784) was asked if the index child had been diagnosed by a physician with a list of infectious, autoimmune, or allergic conditions shown in Table 2 before the reference date (case's HL diagnosis date). Parents who stated a positive history were then asked to supply the age (in months or years) at first episode. To allow for a latency period for HL development, we restricted our analysis

to conditions diagnosed 1 year or more before the case's HL diagnosis. For index children with 1 full or half siblings, parents were asked if the siblings had experienced any condition listed in Table 3 prior to the case's HL diagnosis date ($n_{\text{cases}}=453$, $n_{\text{controls}}=650$). Mothers and fathers were each asked to indicate whether they had been diagnosed with the autoimmune or allergic conditions shown in Table 4 before the case's HL diagnosis date. All medical conditions reported by parents were subsequently coded with the corresponding ICD-9 codes. In some instances, a grandparent or other relative completed a surrogate interview in the absence of a biological parent.

Tumor Epstein-Barr virus detection

Case parents were asked to provide consent for the release of their child's formalin-fixed paraffin-embedded tumor specimen for EBV typing; these were requested from the treating CCG/COG institutions. Tumors were available for 355 cases. There were no differences in tumor availability by age at diagnosis, sex, race/ethnicity, or other factors related to SES (maternal age, maternal education, household income); however, there were proportionally more NS and fewer "other" cases with tumors available.

Tumor EBV status was determined by detection of EBER-1 and EBER-2 via a standard digoxigenin-based *in situ* hybridization technique.²¹ HL specimens known to be EBV+ and B95-8 cells served as positive controls, while EBER sense probes served as negative controls. U6 probes were used to verify that RNA had been preserved in all tumor specimens.

Statistical Analysis

Conditional logistic regression (PROC PHREG, SAS Enterprise Guide version 5.1, SAS Institute Inc., Cary, NC, USA) was used to quantify associations between infectious, autoimmune and allergic diseases and HL overall, and by tumor EBV status (EBV+, EBV-), HL subtype (NS, MC, lymphocyte predominant, LP), and age group (0-9 years, 10-14 years) analyzed separately; odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Analyses restricted to NS and MC HL (i.e., classical HL) yielded nearly identical results to those for HL overall; thus all HL cases were retained in the final multivariate models. The individual infectious, autoimmune, and atopic conditions were primarily coded as dichotomous variables (i.e., present vs. absent). In addition, the total number of infections and allergic diseases in the index children, the total number of siblings with 1 infections and allergic diseases, and the number of allergic diseases in parents were each summed to evaluate dose response, where sums were represented as ordinal variables in regression models and *P*-values for linear trend were obtained. We selected *a priori* variables that are known to correlate with immune system development and exposure to infections, including birth order, number of siblings, breastfed (ever vs. never), household income, and maternal educational attainment, smoking, and age at the index child's birth, to evaluate as potential confounders. Variables that altered the $\ln(\text{OR})$ by 10% were retained in final multivariate models. The Wald chi-square test was used to test the null hypothesis that subgroup-specific ORs were equivalent, producing *P*-values for interaction.

Sensitivity analyses in specific patient subgroups were also conducted in the manner described above, including an analysis of infections in the first year of life in cases diagnosed with HL at >2 years of age and infections in cases with 1 older siblings. We also examined the robustness of the results with respect to the person interviewed (i.e., biological mother, biological father, surrogate).

Considering the more common conditions queried, minimal detectable ORs were estimated using Quanto version 1.2.4,²² given the sample sizes of 517 case-control pairs overall (and 84 EBV+ and 271 EBV- pairs), a type I error rate of 0.05, 80% power, and assuming observed control exposure prevalences between 5-90% are representative of the underlying target population.

Protection of Human Subjects

The study was approved by Institutional Review Boards at the University of Minnesota, the University of Pittsburgh and the University of New Mexico (the original coordinating centers), and participating CCG/COG institutions.

Results

Response rates and subject characteristics

A total of 646 potentially eligible HL cases were identified at 117 CCG/COG institutions throughout North America. Interviews were completed for 517 cases (80%), including 324 cases with NS HL, 86 cases with MC HL, and 60 cases with LP HL. An additional 68 cases (11%) were excluded from analysis because there was no matched control enrolled and 1 case was found to be age-ineligible (0.2%). The remaining subjects did not complete interviews due to parental refusal (4%), inability to locate families (3%), and physician refusal (2%). Biological mothers completed maternal interviews for 451 cases, while biological fathers (9) or other willing first degree relatives (57) completed surrogate interviews for the remainder. Similarly, biological fathers completed paternal interviews for the majority of cases (329), and mothers (95) or other relatives (93) responded when the father was unavailable.

At last tally, 207,438 telephone calls to 88,429 telephone numbers were made to select controls. Of the 88,429 numbers, 50,258 were non-residential, 2,822 refused to provide a household census or hung up, and 360 were ineligible. Of the 34,991 providing a census (RDD screening response rate=91.7%), 25,100 had no resident children, 8,682 had children who did not match, and 1,209 had a matching child (136 were matched via the relaxed criteria). Of the 1,209 matches, 784 (64.8%) were interviewed and included in the study, while 323 (26.7%) actively refused participation, 101 (8.4%) were passive refusals, and 1 (0.1%) was ineligible.

As shown in Table 1, cases and controls had comparable distributions of the matching variables sex and race/ethnicity, while there was a greater proportion of younger controls as prescribed by the matching scheme. Cases and controls were similar with respect to birth order, however, the distributions of sibship, breastfeeding, maternal age, maternal educational attainment, and household income were lower in cases than in controls. With

respect to the tumor analysis, 16.3% were found to have EBV RNAs present, with 22.7% EBV+ in the 0-4 year age group, 29.5% in the 5-9 group and 11.5% in the 10-14 group, while 52.4% had no evidence of EBV involvement, and 31.3% were not examined. The distribution of cases by diagnosis age, HL subtype, and tumor EBV status is shown in Supplementary Table 1. Importantly, the cases with determined tumor EBV status included a higher percentage of NS HL and a lower percentage of cases with “other” histologic subtypes compared with cases with undetermined EBV status; however, no differences were observed across categories of age at diagnosis, sex, race/ethnicity, maternal age, maternal education, or household income.

Infections

Overall, case parents were more likely than control parents to report a physician diagnosis of one or more infections in the index child >1 year prior to the reference date (OR=1.69, 95% CI: 0.98-2.91), however, there was no evidence for increasing risk with increasing number of infectious episodes and no significant associations were observed for the individual infections queried (Table 2). Stronger positive associations were observed for EBV+ (OR=2.01, 95% CI: 0.61-6.57) and EBV- HL (OR=3.41, 95% CI: 1.36-8.57) examined separately. Although none of the ORs reached statistical significance, previous exposure to any infectious diseases was positively associated with the NS and MC HL subtypes, while an inverse OR was observed for LP HL (Supplementary Table 2). Additional stratification by EBV status indicated a strong positive association for EBV- NS HL (OR=3.43, 95% CI: 1.22-9.62; Supplementary Table 3). The increased risk of HL associated with infections (OR=2.41, 95% CI: 1.05-5.52) was more pronounced in the 0-9 year age group, although the OR was not statistically significantly different from that in 10-14-year-olds ($P_{interaction}=0.31$; Supplementary Table 4).

The most frequently reported infections of childhood followed the expected pattern and included: ear infections (69% cases, 68% controls); strep or sore throat, scarlet fever, or tonsillitis (66% cases, 61% controls); and chicken pox (50% cases, 45% controls). A variety of “other infections” were also specified (11% cases, 8% controls), however, associations were nearly identical after removal of this category from the overall “any infection” summary variable in index children and siblings (data not shown) indicating the overall association was not attributed to the report of other infections.

Few parents recalled a physician diagnosis of infectious mononucleosis (IM) in the index children (9 cases, 10 controls), yielding a nonsignificant overall OR for HL of 1.35 (95% CI: 0.52-3.50). A non-statistically significant 9.1-fold increased odds of HL was observed for IM in EBV+ cases only (95% CI: 0.81-102.31; Table 2), although based on only 3 exposed cases and 1 exposed control. A positive association was also observed between strep or sore throat, scarlet fever, or tonsillitis and HL for EBV+ cases (OR=2.19, 95% CI: 1.06-4.53) that was not observed for EBV- cases (OR=1.09, 95% CI: 0.76-1.56, $P_{interaction}=0.09$). Significant associations with the combined sore throat variable and chicken pox were similarly observed in the younger children 0-9 years (Supplementary Table 4).

In sensitivity analyses, the overall association with one or more infections did not persist upon examination of only those infections occurring within the first year of life among cases

diagnosed at 2 years compared with their matched controls (OR=1.18, 95% CI: 0.92-1.50) or upon restriction to the 139 cases and 179 controls with 1 or more older siblings (OR = 2.29, 95% CI: 0.34-15.46; data not shown).

After adjusting for household income at birth, mother's educational attainment, and number of (full and half) siblings, case siblings were also more likely to have had an infection preceding HL diagnosis (OR=2.04, 95% CI: 1.01-4.14; Table 3) with an increasing risk for HL observed with increasing number of affected siblings ($P_{\text{trend}}=0.0006$). There was no pattern with regard to EBV status and HL subtype, however (Table 3 and Supplementary Table 3). In examining specific infections, case siblings had experienced ear infections (overall, EBV+, EBV-), ringworm or athlete's foot (overall and EBV+), and thrush (EBV+) in greater proportions than had control siblings (Table 3).

Autoimmune diseases

Parents reported few autoimmune conditions in index children (5 cases, 13 controls) or their siblings (8 cases, 16 controls) (Tables 2-3, Supplementary Tables 2-4). With respect to affected parents, there was no association observed for HL overall, however, parental history of any autoimmune condition (OR=2.97, 95% CI: 1.34-6.58) or arthritis (OR=7.79, 95% CI: 2.37-25.63) appeared to increase risk of EBV+ HL in offspring, while no association was observed in EBV- cases ($P_{\text{interaction}}=0.008$ and $P_{\text{interaction}}=0.0007$, respectively). Risk was particularly increased for EBV+ NS HL (OR=10.14, 95% CI: 2.18-47.22; Supplementary Table 3).

Allergic diseases

In the index children, allergic diseases diagnosed by a physician >1 year prior to HL were not associated with HL overall (OR=1.22, 95% CI: 0.93-1.59) or by EBV status (Table 2). One or more allergic conditions was associated with HL in children 0-9 years (OR=1.63, 95% CI: 1.00-2.66; Supplementary Table 4), but not in older children (OR_{10-14 years}=1.06, 95% CI: 0.71-1.57); these ORs were not statistically significantly different, however ($P_{\text{interaction}}=0.18$). Similarly, there were no associations for allergic diseases in siblings or parents for HL overall. However, having a sibling (OR=1.62, 95% CI: 1.11-2.36) or parent (OR=1.47, 95% CI: 1.01-2.14) with one or more allergic conditions was positively associated with EBV- HL (Tables 3 and 4). With respect to histologic subtypes, associations were observed in EBV- NS HL cases for sibling allergic history (OR=1.75, 95% CI: 1.11-2.76; Supplementary Table 3) and for EBV- MC HL in parental allergic history (OR=21.91, 95% CI: 1.15-416.55). For specific allergic conditions, positive associations were observed between a sibling history of hay fever and other allergies, respectively, and EBV- HL (Table 3).

Discussion

In the largest case-control study of risk factors for childhood and adolescent HL conducted to date, a history of infections in the index children was positively associated with HL overall, EBV+ and EBV- HL, NS and MC HL, and HL diagnosed at ages 0-9 years, although not all of the associations achieved statistical significance. Infections in siblings

also associated positively with HL. While these findings offer some support for an infectious etiology for HL in childhood and early adolescence, the overall associations were not attributed to any particular pathogen(s). Additionally, a family history of conditions signifying immune dysregulation was found to vary by tumor EBV status. Specifically, we report for the first time that a parental history of autoimmune diseases was strongly associated with increased EBV+ HL risk, while having a parent or sibling with an allergic disease was associated with EBV– HL.

The summary variables of “any infections” and “number of infections” are non-specific markers that may reveal an underlying susceptibility to infections, a particularly infectious childhood environment, or a combination of these. In addition, the summary variables may represent more severe infections, since these may have been recalled by parents with greater frequency, while milder infections may have been forgotten. In our study, most case (95.2%) and control (91.6%) parents reported one or more infectious diagnoses at least 1 year before the case’s HL diagnosis. Validation studies have shown that the accuracy of parental recall of prior infectious episodes is generally modest in comparison to medical records,²³⁻²⁵ with more recent infections remembered marginally better than lifetime history and with mothers remembering somewhat better than fathers.²⁴ Overall, the positive predictive value for maternal recall of any infection was found high among both cases (88.9%) and controls (86.5%), although case mothers showed slightly better recall.²³ We compared the ORs for all respondents to those generated from responses by biological mothers only ($N_{\text{cases}}=451$, $N_{\text{controls}}=721$) and found very similar or identical results for infections, autoimmune diseases, and allergies among index children and their siblings. Notably, recall has been shown to be more accurate for some infections (e.g., $\kappa=0.8$ for recall of meningitis compared to medical records) than for others (e.g., $\kappa=0.1$ for gastro-intestinal and respiratory tract infections, respectively),²⁵ but does not vary substantially by demographics.²⁴ Here, few associations were observed for the specific infectious pathogens we queried, either overall or among subgroups. It is unclear, therefore, if the overall associations are due to a general susceptibility to infection, if specific infectious agents are involved in HL development in EBV– cases, or if the observed associations are an artifact due to differential recall.

It is further possible that the associations may be attributable to reverse causation, where the process of lymphoma development has enhanced the host susceptibility to infection. We included a 1-year latency period in our analysis to minimize this concern, however, the pathogenesis of HL in children may have a longer latency period. Newton *et al.* found that compared with healthy controls, older adolescents and adults had significantly more visits to their general practitioners for infections beginning 10 years prior to HL diagnosis and the number of visits increased monotonically as the HL diagnosis neared; no specific infectious agents were implicated, however.²⁶

In our study, 41% of cases <10 years with known tumor EBV status were EBV+, which is concordant with the ~50% expected, while the percentage of EBV+ tumors among the children 10-14 years (17%) was lower than expected. As mentioned above, there were proportionately more NS HL cases represented in the available tumor set than in the total case set; since NS tumors are less often EBV+,⁴ this may have contributed to the lower than

expected percentage of EBV+ tumors observed. Given that specimens were unavailable for 1/3 of participants, it is possible that a majority of the tumors with unknown EBV status were positive, or participants in the current study may have been less often EBV+ by chance. For the ~50% of pediatric HL that are EBV–, earlier efforts to identify responsible pathogenic causes were generally uninformative, despite investigations of several putative infectious agents (reviewed in ²⁷). Notably, human herpesvirus 6 (HHV-6) infection was not consistently identified in tumor tissue from childhood cases,^{28,29} however, HHV-6 may merit another look given that Siddon *et al.* recently published strong data supporting HHV-6 infection in HRS cells in adult NS HL specimens.³⁰

Few studies have examined history of infections as a risk factor for pediatric HL.³¹⁻³³ Our results are consistent with those by Goldin *et al.*, who found a nonsignificant 1.61-fold increased risk for HL at ages 2-14 years in children hospitalized for infections in the first year of life (95% CI: 0.79-3.31).³¹ In contrast, Rudant *et al.* examined parental report of several immune-mediating factors in a population-based case-control study in France, and found an inverse association for repeated early common infections overall (OR=0.5, 95% CI: 0.3-0.9) and across each of the HL subtypes, although small numbers precluded statistical significance in the latter.³² Finally, Michos *et al.* did not find evidence for an association for seroprevalence for 9 common infectious pathogens at the time of HL diagnosis in 52 childhood cases and their matched controls,³³ however, their cross-sectional study design did not allow for proper temporality and a latency period between infection and lymphomagenesis.

An increased risk of childhood/adolescent HL associated with greater exposure to childhood infections is consistent with the observed elevated risk with increasing sibship size, a surrogate measure of exposure to infections in childhood, both in our study ($P_{trend}=0.04$, Table 1) and in a population-based study in Denmark (OR_{per sibling}=1.28, 95% CI: 1.00-1.63),⁷ although this association has not been replicated in all studies.³⁴ Together, these results may suggest an immune-mediated pathogenic effect of infection or may be an indicator of underlying immune dysregulation. Conversely, studies of AYA HL have generally shown an opposing pattern: both exposure to childhood infections³⁵ and increased sibship size⁷ have been associated with reduced HL risk. This pattern in AYA HL is hypothesized to be due to delayed exposure followed by an aberrant response to an infectious pathogen.⁸ Of note, infection with EBV accounts for a smaller proportion of AYA than childhood cases,⁴ suggesting involvement of other infectious agents.

Given the known link between a personal history of rheumatoid arthritis and HL in adult patients,¹⁵ as well as observed associations with systemic lupus erythematosus, sarcoidosis, Sjogren's syndrome, Hashimoto thyroiditis, and localized scleroderma,^{16,17} we expected a similar association for autoimmune diseases and childhood/adolescent HL. This hypothesis is further supported by reports describing increased rates of HL in offspring of rheumatoid arthritis patients.³⁶ With respect to personal history of autoimmunity, a registry-based study in Denmark did not detect increased childhood HL risk (i.e., there were no cancer diagnoses among the 188 children with autoimmune diseases).³⁷ Although a nonsignificant inverse association was reported in the current study, the rarity of autoimmune conditions hampered interpretation.

With respect to family history, neither the same registry-based study in Denmark³⁷ nor one from Sweden³⁸ found evidence for an association between parental autoimmune disease and offspring HL (standardized incidence ratios were 1.3 (95% CI:0.6-2.5) and 0.90 (95% CI: 0.61-1.28), respectively), however, the number of affected children in each study was modest ($n_{\text{Denmark}}=8$ HL cases, $n_{\text{Sweden}}=31$ HL cases). In the current study, there were substantially more autoimmune diseases in parents (122 cases and 153 controls), with no evidence for associations for HL overall. Interestingly, however, positive associations for any autoimmune conditions and arthritis were observed for EBV+ HL only. Parents indicating a history of arthritis were asked to further specify arthritis type. Parental rheumatoid arthritis (9 cases, 14 controls) was not significantly associated with offspring HL overall, but was positively associated with EBV+ HL (affecting parents of 3 cases and 0 controls; OR could not be calculated) and inversely associated with EBV- HL (OR=0.19, 95% CI: 0.04-0.93; $P_{\text{interaction}}$ could not be calculated; data not shown). Due to the serious nature of autoimmune diseases, parents would be expected to recall a diagnosis in themselves or their children with high accuracy,²⁴ thus minimizing concerns about recall bias. It is not known whether the increased risks can be ascribed to shared genetic or epigenetic factors, or if both sets of conditions could arise as rare responses to infections.³⁷ A comprehensive family-based study design that includes medical record review and biomarker analysis could help address these questions.

Although inverse associations have been observed for other pediatric B-cell lineage hematologic malignancies, including any allergic disease, asthma, eczema, and hay fever and childhood ALL,³⁹ and allergic diseases or asthma and childhood and adolescent NHL,^{32,40} our results are consistent with those from two smaller studies that did not find associations for pediatric HL with allergic diseases, asthma, or eczema examined separately.^{32,40} Results from case-control studies in adults have been less consistent, with no association found for HL in three studies,⁴¹⁻⁴³ reduced HL risk reported for prevalent hay fever (OR=0.5, 95% CI:0.3-0.8)⁴⁴ and previous hospitalization for asthma (OR=0.6, 95% CI: 0.4-0.9),⁴⁵ and increased HL risk observed for those reporting a history of eczema (OR=4.2, 95% CI: 1.2-14.8).⁴⁶ The association of allergic history in siblings and parents with EBV- HL in our study is a new finding that would also benefit from further family- or registry-based studies, particularly since the association with parental allergic history was attenuated upon exclusion of surrogate interviews.

Parents were asked to recall physician-diagnosed allergies, which may result in misclassification due to failure to recognize allergy symptoms, changes in allergic symptoms over time (possibly in relation to HL development), or other reasons.³⁹ Indeed, a comparison of control prevalences for asthma (11.1%) and hay fever (13.4%) in our study to national rates for children 0-17 years (11.4% and 17.5%, respectively) during the period 1997-1999⁴⁷ suggested high parental reporting rates for asthma, but potential underreporting of hay fever. These results align with validation studies, in which parental report of allergy history was compared to medical records, indicating higher parental recollection of asthma and lower recall of eczema;^{24,48} similar recall was noted for the individual allergic conditions across cases and controls, however.⁴⁸ The failure to detect consistent associations in this and other studies of childhood and adult HL despite observations of elevated IgE

levels in serum and detectable IgE in HRS cells⁴⁹ implies either that there is no association and the excess IgE is produced as a result of the lymphoma, or that the association is modest or relevant only for a subgroup of cases.

Three other limitations are worthy of mention. First, we did not adjust for multiple comparisons, however we acknowledge that ORs with *P*-values near the 0.05 significance level may be spurious. Second, selection bias may be a limitation, since control families had higher distributions of maternal educational attainment and annual household income in the year of the child's birth. Because factors related to SES have been associated with pediatric/adolescent HL,⁸ we have adjusted for measured SES-related factors (maternal educational attainment and annual household income) herein, although residual confounding by SES may remain. Third, North American children are routinely vaccinated for infectious diseases. In the interviews, parents reported high immunization rates for whooping cough, mumps, or rubella for cases (range: 91-96%) and controls (86-93%), although parents of controls had somewhat lower recall (7-9% did not know if their child had received immunizations vs. 4-6% of case parents). The fact that most children were immunized means that they were less likely to have contracted these diseases, thereby lowering statistical power to detect an association. This should not have introduced bias into the study, however, since vaccinations were provided nondifferentially to cases and controls (all *P* 0.07).

Strengths include study size, with enrollment of a considerable proportion of North American HL cases diagnosed during the period 1989-2003 through CCG/COG institutions. Our current analysis is also the first to consider epidemiologic data for childhood HL by tumor EBV status, which was advantageous given the new insights revealed upon stratification by EBV status. Because there was 80% statistical power to detect ORs of 1.5-1.7 for conditions with prevalences of 10-80% and 2 for conditions with prevalences of 5 and 90% for the entire study population, and corresponding ORs of 1.7-2.1 and 2.5-2.7, respectively, for EBV- cases, we can likely rule out large associations. Nonetheless, our method required parents to recall health histories over several years.

Considering the limitations in using history data collected from parental report or medical records, future studies should examine biomarkers to better characterize the role of infections and immune dysregulation preceding a diagnosis of pediatric HL, such as the application of next generation sequencing to the identification of known and novel viruses in pre-diagnostic serum or tumor specimens.⁵⁰ Further, in view of the documented familial aggregation of HL⁶ and the observed associations with family history of autoimmune and allergic conditions that are specific to EBV+ and EBV- tumors, respectively, family-based studies may provide a powerful tool for identifying genetic risk factors and exposures shared among affected family members.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AYA	Adolescent and young adult
CCG	Children's Cancer Group
CI	Confidence interval
COG	Children's Oncology Group
EBER	Epstein-Barr virus-encoded small RNA
EBV	Epstein-Barr virus
HHV-6	Human herpesvirus 6
HL	Hodgkin lymphoma
HRS	Hodgkin/Reed-Sternberg
IgE	Immunoglobulin E
IM	Infectious mononucleosis
LMP1	Latent membrane protein 1
LP	Lymphocyte predominant
MC	Mixed cellularity
NS	Nodular sclerosis
OR	Odds ratio
RDD	Random digit dialing
SES	Socio-economic status
Th1	Type 1 helper T cells
Th2	Type 2 helper T cells

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Novelty and impact of the research:

We present data from the largest etiologic study devoted to understanding the causes of pediatric/adolescent HL. Our results support the hypothesis of an infectious etiology for HL, both in the presence and absence of tumor EBV, although no specific infectious agents were implicated. Moreover, distinct patterns between family history of autoimmunity and allergy and HL risk by EBV status emphasize the need for comprehensive family-based studies.

Table 1

Selected descriptive characteristics of 517 childhood and adolescent Hodgkin lymphoma cases and 784 matched controls.*

	Controls N (%)	Cases N (%)	Unadjusted OR	95% CI	<i>P</i> _{trend}
Gender [†]					
Male	518 (66.1)	320 (61.9)			
Female	266 (33.9)	197 (38.1)			
Age at diagnosis (years) [†]					
0-4	97 (12.4)	22 (4.3)			
5-9	302 (38.5)	122 (23.6)			
10-14	326 (41.6)	373 (72.2)			
15+	59 (7.5)				
Race/ethnicity [†]					
White	631 (80.5)	386 (74.7)			
African-American	67 (8.6)	54 (10.4)			
Hispanic	78 (10.0)	62 (12.0)			
Other	8 (1.0)	15 (2.9)			
Birth order [‡]					
First	307 (39.7)	206 (40.2)	Ref		0.25
Second	274 (35.5)	161 (31.5)	0.90	0.69, 1.18	
Third or higher	192 (24.8)	145 (28.3)	1.22	0.91, 1.63	
Sibship [‡]					
0	67 (8.6)	28 (5.4)	Ref		0.04
1-2	533 (68.0)	339 (65.6)	1.32	0.82, 2.12	
3+	184 (23.5)	150 (29.0)	1.62	0.97, 2.71	
Breastfed					
Yes	496 (63.3)	263 (50.1)	0.62	0.48, 0.79	
No	288 (36.7)	254 (49.1)	Ref		
Maternal age at child's birth (years)					
<25	318 (40.6)	248 (48.1)	Ref		0.04
25-29	271 (34.6)	165 (32.0)	0.82	0.63, 1.07	
30	194 (24.8)	103 (20.0)	0.74	0.54, 1.01	
Maternal educational attainment					
Some high school	65 (8.3)	73 (14.2)	Ref		0.0001
High school graduate	248 (31.8)	175 (34.0)	0.55	0.36, 0.83	
Beyond high school	468 (60.0)	267 (51.9)	0.44	0.29, 0.66	
Household income at child's birth					
0 - \$19,999	268 (35.6)	243 (48.4)	Ref		<0.0001
\$20,000 - \$39,999	333 (44.2)	206 (41.0)	0.70	0.53, 0.92	
\$40,000+	152 (20.2)	53 (10.6)	0.42	0.28, 0.63	

OR = odds ratio; 95% CI = 95% confidence interval

* Numbers in tables may not sum to total number of cases/controls due to missing values.

† Cases and controls were matched on gender, race/ethnicity, and age; ORs were not calculated for matching variables.

‡ Birth order and sibship are based on full and half full siblings. Birth order could not be determined for those with missing sibling birthdates (5 cases, 11 controls).

Table 2

Association between a personal history of infectious, autoimmune, and allergic disease (diagnosed by a health professional >1 year prior to Hodgkin lymphoma diagnosis, ascertained via maternal report) and childhood and adolescent Hodgkin lymphoma overall and by EBV status^{*,†}

	Combined cases				EBV+				EBV−			
	N _{controls}	N _{cases}	OR [‡]	95% CI	N _{controls}	N _{cases}	OR [‡]	95% CI	N _{controls}	N _{cases}	OR [‡]	95% CI
<i>Infectious diseases</i>												
Any infectious disease [§]	679	474	1.69	0.98, 2.91	138	77	2.01	0.61, 6.57	327	254	3.41	1.36, 8.57
None	62	24	Ref		19	5	Ref		31	7	Ref	
Number of infectious diseases [§]												
0	62	24	Ref		19	5	Ref		31	7	Ref	
1-2	249	167	1.73	0.98, 3.07	50	25	1.86	0.51, 6.74	121	83	3.25	1.26, 8.37
3-4	284	201	1.64	0.93, 2.89	57	35	2.03	0.60, 6.88	134	110	3.60	1.40, 9.28
5+	146	106	1.70	0.93, 3.11	31	17	2.17	0.56, 8.38	72	61	3.40	1.27, 9.07
			0.29				0.34				0.31	
<i>P</i> _{trend}												
Infectious mononucleosis	10	9	1.35	0.52, 3.50	1	3	9.10	0.81, 102.31	7	4	0.88	0.24, 3.26
None	731	489	Ref		156	79	Ref		351	257	Ref	
Strep or sore throat/Scarlet fever/Tonsillitis	450	328	1.09	0.83, 1.42	81	54	2.19	1.06, 4.53	225	180	1.09	0.76, 1.56
None	291	170	Ref		76	28	Ref		133	81	Ref	
Chicken pox	336	249	1.14	0.88, 1.48	66	36	1.10	0.57, 2.12	169	128	0.97	0.67, 1.39
None	405	249	Ref		91	46	Ref		189	133	Ref	
Cold sores	35	30	0.93	0.53, 1.61	4	7	1.77	0.41, 7.57	19	11	0.67	0.30, 1.53
None	706	468	Ref		153	75	Ref		339	250	Ref	
Red measles	13	12	1.02	0.42, 2.45	2	1	0.98	0.05, 19.69	6	6	0.87	0.25, 3.01
None	728	486	Ref		155	81	Ref		352	255	Ref	
German measles	23	24	1.18	0.62, 2.27	5	4	1.41	0.30, 6.69	11	15	1.58	0.62, 4.03
None	718	474	Ref		152	78	Ref		347	246	Ref	
Roseola	78	41	0.77	0.51, 1.17	19	6	0.67	0.24, 1.83	39	24	0.85	0.49, 1.49
None	663	457	Ref		138	76	Ref		319	237	Ref	
Mumps	14	8	0.65	0.26, 1.60	1	2	2.96	0.20, 43.90	7	2	0.22	0.04, 1.14
None	727	490	Ref		156	80	Ref		351	259	Ref	

	Combined cases				EBV+				EBV−			
	N _{controls}	N _{cases}	OR [‡]	95% CI	N _{controls}	N _{cases}	OR [‡]	95% CI	N _{controls}	N _{cases}	OR [‡]	95% CI
Ringworm/Athlete's foot	49	39	1.09	0.67, 1.77	12	8	1.29	0.40, 4.20	21	20	1.17	0.58, 2.36
None	692	459	Ref		145	74	Ref		337	241	Ref	
Thrush	58	48	1.45	0.93, 2.23	13	9	1.48	0.55, 3.97	27	28	1.54	0.84, 2.80
None	683	450	Ref		144	73	Ref		331	233	Ref	
Macroparasites	46	45	1.32	0.83, 2.10	13	9	0.81	0.29, 2.26	20	21	1.45	0.70, 2.99
None	695	453	Ref		144	73	Ref		338	240	Ref	
Ear infections	502	345	1.17	0.89, 1.53	107	55	1.11	0.55, 2.25	231	192	1.50	1.02, 2.18
None	239	153	Ref		50	27	Ref		127	69	Ref	
Croup	104	55	0.88	0.59, 1.30	31	7	0.48	0.18, 1.26	44	39	1.35	0.81, 2.26
None	637	443	Ref		126	75	Ref		314	222	Ref	
Bronchiolitis/Bronchitis	183	109	0.89	0.66, 1.19	37	18	1.22	0.57, 2.63	90	63	0.93	0.63, 1.39
None	558	389	Ref		120	64	Ref		268	198	Ref	
Pneumonia	80	67	1.15	0.78, 1.70	16	10	0.88	0.30, 2.60	42	35	1.03	0.60, 1.78
None	661	431	Ref		141	72	Ref		316	226	Ref	
UTI	43	22	0.68	0.38, 1.21	9	3	0.23	0.04, 1.26	24	10	0.54	0.25, 1.21
None	698	476	Ref		148	79	Ref		334	251	Ref	
Impetigo	66	61	1.20	0.80, 1.80	15	12	1.51	0.62, 3.65	34	31	1.03	0.58, 1.84
None	675	437	Ref		142	70	Ref		324	230	Ref	
Other skin infections	29	26	1.35	0.75, 2.43	6	2	0.84	0.13, 5.35	15	19	1.76	0.83, 3.73
None	712	472	Ref		151	80	Ref		343	242	Ref	
Other infectious diseases	61	53	1.48	0.98, 2.25	16	13	1.76	0.71, 4.37	26	24	1.42	0.76, 2.65
None	680	445	Ref		141	69	Ref		332	237	Ref	
Autoimmune diseases												
Any autoimmune disease	13	5	0.46	0.16, 1.38	3	2	1.85	0.19, 17.84	6	3	0.58	0.14, 2.41
None	728	493	Ref		154	80	Ref		352	258	Ref	
Allergic diseases												
Any allergy [¶]	238	175	1.22	0.93, 1.59	51	22	0.95	0.48, 1.86	113	97	1.32	0.90, 1.94
None	503	323	Ref		106	60	Ref		245	164	Ref	
Number of allergies [¶]												

	Combined cases				EBV+				EBV−			
	N _{controls}	N _{cases}	OR [‡]	95% CI	N _{controls}	N _{cases}	OR [‡]	95% CI	N _{controls}	N _{cases}	OR [‡]	95% CI
0	503	323	Ref		106	60	Ref		245	164	Ref	
1	142	104	1.23	0.89, 1.70	25	13	1.12	0.49, 2.57	69	62	1.50	0.96, 2.34
2	63	43	1.09	0.69, 1.72	16	7	0.83	0.26, 2.65	30	22	1.01	0.53, 1.93
3+	33	28	1.38	0.79, 2.42	10	2	0.62	0.12, 3.24	14	13	1.21	0.53, 2.78
<i>P</i> _{trend}												
Asthma	82	58	1.20	0.81, 1.77	22	9	0.86	0.35, 2.14	42	29	0.98	0.57, 1.69
None	659	440	Ref		135	73	Ref		316	232	Ref	
Eczema	42	31	1.52	0.89, 2.62	9	2	0.88	0.15, 5.09	23	18	1.55	0.72, 3.34
None	699	467	Ref		148	80	Ref		335	243	Ref	
Hay fever	99	64	0.88	0.60, 1.30	20	8	0.57	0.19, 1.69	44	33	0.92	0.54, 1.59
None	642	434	Ref		137	74	Ref		314	228	Ref	
Hives	56	50	1.37	0.88, 2.14	13	7	2.23	0.72, 6.96	22	23	1.37	0.71, 2.68
None	685	448	Ref		144	75	Ref		336	238	Ref	
Contact dermatitis	26	21	1.05	0.54, 2.06	6	1	0.08	0.01, 1.55	11	13	1.23	0.49, 3.11
None	715	477	Ref		151	81	Ref		347	248	Ref	
Other allergy	73	55	1.12	0.75, 1.68	19	6	0.68	0.23, 2.04	35	32	1.11	0.63, 1.93
None	668	443	Ref		138	76	Ref		323	229	Ref	

CI = confidence interval ; EBV = Epstein-Barr virus; OR = odds ratio; UTI = urinary tract infection

* Numbers in tables may not sum to total number of cases/controls due to missing values.

[‡] EBV status was not determined for 162 cases.

[‡] ORs adjusted for household income at birth, mother's education, and birth order (considering full and half siblings).

[§] Any infectious disease and number of infectious diseases include: tuberculosis, whooping cough, strep or sore throat/scarlet fever/tonsillitis, spinal meningitis, chicken pox, cold sores, red measles, German measles, roseola, hepatitis, mumps, infectious mononucleosis, cytomegalovirus, ringworm/athlete's foot, thrush, macroparasites, ear infections, rheumatic fever, croup, bronchiolitis/bronchitis, pneumonia, urinary tract infection (UTI), impetigo, other skin infections, other infectious diseases. Less than five cases reported the following individual infectious diseases asked about in the interview: tuberculosis (0 cases, 6 controls), whooping cough (3 cases, 7 controls), spinal meningitis (2 cases, 4 controls), hepatitis (3 cases, 0 controls), cytomegalovirus (0 cases, 0 controls), rheumatic fever (2 cases, 1 control).

^{||} Any autoimmune disease variable includes: arthritis or any other autoimmune condition indicated by parent. Less than five cases reported arthritis (2 cases, 6 controls), diabetes (1 case, 1 control), psoriasis (1 case, 5 controls), other autoimmune diseases (1 case, 1 control).

[¶] Any allergy and number of allergies variables include: asthma, eczema, hay fever, hives, contact dermatitis, other allergy.

Table 3

Association between infectious, autoimmune, and allergic diseases in (full and half) siblings and childhood and adolescent Hodgkin lymphoma overall and by EBV status^{*,†}

	Combined cases				EBV+				EBV-			
	N _{controls}	N _{cases}	OR [‡]	95% CI	N _{controls}	N _{cases}	OR [‡]	95% CI	N _{controls}	N _{cases}	OR [‡]	95% CI
<i>Infectious diseases in siblings</i>												
Any infectious disease [‡]	615	441	2.04	1.01, 4.14	126	74	1.79	0.47, 6.83	307	234	1.70	0.60, 4.79
None	35	12	<i>Ref</i>		10	4	<i>Ref</i>		14	6	<i>Ref</i>	
Number of siblings with infectious disease [‡]												
0	35	12	<i>Ref</i>		10	4	<i>Ref</i>		14	6	<i>Ref</i>	
1 - 2	517	337	1.89	0.93, 3.85	105	56	1.69	0.43, 6.68	256	177	1.61	0.57, 4.57
3 - 4	81	84	3.45	1.52, 7.84	21	15	4.55	0.78, 26.55	38	45	2.75	0.83, 9.08
5+	17	20	4.49	1.42, 14.21	0	3	-	-	13	12	2.59	0.62, 13.00
<i>P_{trend}</i>			0.0006				0.02				0.11	
Infectious mononucleosis	28	20	0.97	0.50, 1.88	10	5	0.91	0.24, 3.49	12	10	0.87	0.34, 2.25
None	622	433	<i>Ref</i>		126	73	<i>Ref</i>		309	230	<i>Ref</i>	
Whooping cough	12	11	1.51	0.61, 3.73	2	2	0.84	0.11, 6.38	6	5	1.33	0.35, 5.01
None	638	442	<i>Ref</i>		134	76	<i>Ref</i>		315	235	<i>Ref</i>	
Strep or sore throat/Scarlet fever/Tonsillitis	502	346	0.94	0.69, 1.29	100	55	0.77	0.37, 1.60	256	188	0.92	0.59, 1.43
None	148	107	<i>Ref</i>		36	23	<i>Ref</i>		65	52	<i>Ref</i>	
Spinal meningitis	9	9	1.51	0.56, 4.09	2	1	0.55	0.04, 8.01	6	0	-	-
None	641	444	<i>Ref</i>		134	77	<i>Ref</i>		315	240	<i>Ref</i>	
Chicken pox	504	366	1.20	0.87, 1.66	99	59	1.08	0.54, 2.19	251	202	1.45	0.90, 2.34
None	146	87	<i>Ref</i>		37	19	<i>Ref</i>		70	38	<i>Ref</i>	
Cold sores	86	71	1.15	0.80, 1.66	23	13	1.08	0.48, 2.46	33	38	1.57	0.93, 2.65
None	564	382	<i>Ref</i>		113	65	<i>Ref</i>		288	202	<i>Ref</i>	
Red measles	22	28	1.47	0.81, 2.67	2	6	3.22	0.57, 18.36	15	13	0.94	0.42, 2.07
None	628	425	<i>Ref</i>		134	72	<i>Ref</i>		306	227	<i>Ref</i>	
German measles	39	44	1.58	0.98, 2.54	10	9	2.69	0.86, 8.43	19	21	1.44	0.71, 2.92

	Combined cases				EBV+			EBV-		
	N _{controls}	N _{cases}	OR [‡]	95% CI	N _{controls}	N _{cases}	OR [‡]	N _{controls}	N _{cases}	95% CI
None	611	409	Ref		126	69	Ref	302	219	Ref
Roseola	73	60	1.28	0.86, 1.91	17	5	0.52	40	41	0.85, 2.37
None	577	393	Ref		119	73	Ref	281	199	Ref
Mumps	28	36	1.32	0.77, 2.26	2	6	5.72	15	20	0.69, 2.81
None	622	417	Ref		134	72	Ref	306	220	Ref
Ringworm/Athlete's foot	76	86	1.50	1.04, 2.15	9	17	3.44	41	45	0.78, 2.13
None	574	367	Ref		127	61	Ref	280	195	Ref
Thrush	73	57	1.23	0.83, 1.84	17	13	2.88	32	32	0.78, 2.43
None	577	396	Ref		119	65	Ref	289	208	Ref
Macroparasites	52	39	1.03	0.64, 1.65	11	7	1.49	28	17	0.35, 1.39
None	598	414	Ref		125	71	Ref	293	223	Ref
Ear infections	431	324	1.39	1.04, 1.86	85	51	2.21	213	182	1.02, 2.27
None	219	129	Ref		51	27	Ref	108	58	Ref
Croup	90	64	1.02	0.69, 1.49	22	9	0.52	45	35	0.53, 1.53
None	560	389	Ref		114	69	Ref	276	205	Ref
Bronchiolitis/Bronchitis	175	139	1.22	0.91, 1.65	33	22	1.19	89	82	0.89, 2.00
None	475	314	Ref		103	56	Ref	232	158	Ref
Pneumonia	96	89	1.25	0.88, 1.78	20	15	0.86	54	52	0.70, 1.88
None	554	364	Ref		116	63	Ref	267	188	Ref
UTI	73	55	1.09	0.72, 1.64	16	8	1.26	37	29	0.56, 1.83
None	577	398	Ref		120	70	Ref	284	211	Ref
Impetigo	74	71	1.23	0.85, 1.78	17	11	1.12	38	43	0.77, 2.15
None	576	382	Ref		119	67	Ref	283	197	Ref
Other skin infections	16	12	1.07	0.46, 2.49	4	4	2.89	8	5	0.30, 3.28
None	634	441	Ref		132	74	Ref	313	235	Ref
Other infectious diseases	59	47	1.24	0.82, 1.88	14	7	0.95	28	22	0.62, 2.06
None	591	406	Ref		122	71	Ref	293	218	Ref
Autoimmune diseases in siblings										
Any autoimmune disease [§]	16	8	0.59	0.24, 1.46	0	1	-	7	5	0.74
										0.21, 2.63

	Combined cases				EBV+				EBV−			
	N _{controls}	N _{cases}	OR [‡]	95% CI	N _{controls}	N _{cases}	OR [‡]	95% CI	N _{controls}	N _{cases}	OR [‡]	95% CI
None	634	445	Ref		136	77	Ref		314	235	Ref	
Arthritis	7	5	1.00	0.29, 3.44	0	1	-	-	4	2	0.64	0.11, 3.91
None	643	448	Ref		136	77	Ref		317	238	Ref	
Allergic diseases in siblings												
Any allergy ^{//}	246	197	1.21	0.93, 1.59	56	30	0.61	0.30, 1.24	116	116	1.62	1.11, 2.36
None	404	256	Ref		80	48	Ref		205	124	Ref	
Number of siblings with allergies ^{//}												
0	404	256	Ref		80	48	Ref		205	124	Ref	
1	181	146	1.18	0.87, 1.58	45	22	0.43	0.19, 0.98	86	90	1.72	1.14, 2.59
2	53	39	1.24	0.75, 2.05	11	6	1.38	0.40, 4.72	24	18	1.10	0.52, 2.36
3+	12	12	1.86	0.76, 4.54	0	2	-	-	6	8	2.22	0.69, 7.11
P _{trend}												
			0.20				0.86				0.03	
Asthma	87	72	1.27	0.89, 1.83	21	13	0.95	0.38, 2.41	43	41	1.39	0.86, 2.26
None	563	381	Ref		115	65	Ref		278	199	Ref	
Eczema	51	50	1.34	0.86, 2.09	11	7	1.15	0.39, 3.36	26	29	1.39	0.75, 2.58
None	599	403	Ref		125	71	Ref		295	211	Ref	
Hay fever	127	109	1.30	0.94, 1.78	26	18	1.14	0.51, 2.53	57	67	1.92	1.22, 3.03
None	523	344	Ref		110	60	Ref		264	173	Ref	
Hives	78	60	1.04	0.70, 1.53	13	8	1.55	0.55, 4.37	35	34	1.06	0.62, 1.81
None	572	393	Ref		123	70	Ref		286	206	Ref	
Contact dermatitis	26	14	0.80	0.39, 1.65	7	2	0.48	0.07, 3.08	10	8	1.31	0.44, 3.92
None	624	439	Ref		129	76	Ref		311	232	Ref	
Other allergy	54	40	1.24	0.77, 1.98	12	5	0.63	0.18, 2.20	23	32	2.39	1.25, 4.55
None	596	413	Ref		124	73	Ref		298	208	Ref	

CI = confidence interval ; OR = odds ratio; UTI = urinary tract infection

* Numbers in tables may not sum to total number of cases/controls due to missing values.

[†] ORs adjusted for household income at birth, mother's education, and number of (full and half) siblings

‡ Any infectious disease and number of siblings with infectious disease include: tuberculosis, whooping cough, strep or sore throat/scarlet fever/tonsillitis, spinal meningitis, chicken pox, cold sores, red measles, German measles, roseola, hepatitis, mumps, infectious mononucleosis, cytomegalovirus, ringworm/atlete's foot, thrush, macroparasites, ear infections, rheumatic fever, croup, bronchiolitis/bronchitis, pneumonia, urinary tract infection (UTI), impetigo, other skin infections, other infectious diseases. Less than five cases had one or more siblings with the individual infectious diseases: tuberculosis (1 case, 4 controls), hepatitis (2 cases, 3 controls), cytomegalovirus (1 case, 0 controls), rheumatic fever (1 case, 2 controls).

§ Any autoimmune disease variable includes: arthritis, diabetes, or any other autoimmune condition indicated by parent. Less than five cases had one or more siblings with diabetes (2 cases, 3 controls), psoriasis (0 cases, 4 controls), other autoimmune diseases (1 case, 3 controls).

// Any allergy and number of allergies variables include: asthma, eczema, hay fever, hives, contact dermatitis, other allergy.

Table 4

Association between a parental history of autoimmune and allergic disease and childhood and adolescent Hodgkin lymphoma overall and by EBV status^{*, †}

	Combined cases				EBV+				EBV-			
	N _{controls}	N _{cases}	OR [‡]	95% CI	N _{controls}	N _{cases}	OR [‡]	95% CI	N _{controls}	N _{cases}	OR [‡]	95% CI
<i>Autoimmune diseases in parents</i>												
Any autoimmune disease [‡]	153	122	1.17	0.87, 1.58	23	23	2.97	1.34, 6.58	83	61	0.88	0.58, 1.35
None	587	376	<i>Ref</i>		133	59	<i>Ref</i>		275	200	<i>Ref</i>	
Arthritis	88	67	1.05	0.72, 1.54	9	14	7.79	2.37, 25.63	45	33	0.82	0.48, 1.41
None	652	431	<i>Ref</i>		147	68	<i>Ref</i>		313	228	<i>Ref</i>	
Diabetes [§]	27	24	1.35	0.73, 2.50	3	5	5.40	0.82, 35.44	18	12	0.86	0.38, 1.96
None	713	474	<i>Ref</i>		153	77	<i>Ref</i>		340	249	<i>Ref</i>	
Psoriasis	40	29	1.15	0.65, 2.02	9	6	1.29	0.35, 4.76	23	12	0.71	0.31, 1.65
None	700	469	<i>Ref</i>		147	76	<i>Ref</i>		335	249	<i>Ref</i>	
Other autoimmune	4	10	2.75	0.73, 10.41	1	0	-	-	2	9	5.64	1.09, 29.17
None	736	488	<i>Ref</i>		155	82	<i>Ref</i>		356	252	<i>Ref</i>	
<i>Allergic diseases in parents</i>												
Any allergy	426	287	1.14	0.88, 1.48	84	44	1.00	0.51, 1.96	201	163	1.47	1.01, 2.14
None	314	211	<i>Ref</i>		72	38	<i>Ref</i>		157	98	<i>Ref</i>	
Number of allergies												
0	314	211	<i>Ref</i>		72	38	<i>Ref</i>		157	98	<i>Ref</i>	
1	210	133	1.00	0.73, 1.36	38	18	0.86	0.38, 1.96	102	71	1.19	0.77, 1.85
2	124	96	1.44	1.01, 2.06	28	14	0.99	0.37, 2.68	55	56	1.94	1.18, 3.18
3+	92	58	1.08	0.71, 1.65	18	12	1.50	0.50, 4.54	44	36	1.60	0.88, 2.91
<i>P</i> _{trend}			0.22				0.77				0.02	
Asthma	103	72	1.21	0.85, 1.73	20	16	2.26	0.90, 5.66	46	40	1.38	0.84, 2.29
None	637	426	<i>Ref</i>		136	66	<i>Ref</i>		312	221	<i>Ref</i>	
Eczema	74	55	1.14	0.75, 1.74	18	7	0.65	0.21, 1.99	30	35	1.75	0.94, 3.26
None	666	443	<i>Ref</i>		138	75	<i>Ref</i>		328	226	<i>Ref</i>	

	Combined cases				EBV+				EBV-			
	N _{controls}	N _{cases}	OR [†]	95% CI	N _{controls}	N _{cases}	OR [†]	95% CI	N _{controls}	N _{cases}	OR [†]	95% CI
Hay fever	265	179	1.18	0.91, 1.54	50	30	1.47	0.74, 2.90	126	95	1.19	0.83, 1.72
None	475	319	Ref		106	52	Ref		232	166	Ref	
Hives	170	124	1.18	0.88, 1.58	32	23	1.32	0.62, 2.80	85	74	1.39	0.92, 2.10
None	570	374	Ref		124	59	Ref		273	187	Ref	
Contact dermatitis	50	30	0.81	0.48, 1.37	12	3	0.33	0.07, 1.49	23	19	0.98	0.50, 1.94
None	690	468	Ref		144	79	Ref		335	242	Ref	
Other allergy	94	61	1.04	0.70, 1.54	20	9	0.88	0.26, 2.92	46	41	1.41	0.84, 2.38
None	646	437	Ref		136	73	Ref		312	220	Ref	

OR = odds ratio; 95% CI = 95% confidence interval

* Numbers in tables may not sum to total number of cases/controls due to missing values.

[†] ORs adjusted for household income at birth, maternal age at the child's birth, mother's education, and birth order of index child (considering full and half siblings)

[‡] Any autoimmune disease variable includes: arthritis, Crohn's disease, diabetes, lupus erythematosus, multiple sclerosis, *Myasthenia Gravis*, psoriasis, scleroderma, other autoimmune disease. Less than five cases had one or more parents with the autoimmune conditions: Crohn's disease (2 cases, 6 controls), lupus erythematosus (2 cases, 3 controls), multiple sclerosis (0 cases, 1 control), *Myasthenia Gravis* (1 case, 1 control), pernicious anemia (2 cases, 1 control), scleroderma (0 cases, 0 controls),.

[§] Includes both type I and type II diabetes; information regarding type was not requested in the questionnaire.

// Any allergy and number of allergies variables include: asthma, eczema, hay fever, hives, contact dermatitis, other allergy.