Published in final edited form as:
Cancer Res. 2009 August 15; 69(16): 6482–6489. doi:10.1158/0008-5472.CAN-08-4372.

Atopic disease and risk of non-Hodgkin lymphoma: an InterLymph pooled analysis

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Abstract

We performed a pooled analysis of data on atopic disease and risk of non-Hodgkin lymphoma (NHL) from 13 case-control studies, including13,535 NHL cases and 16,388 controls. Self-reported atopic diseases diagnosed two or more years before NHL diagnosis (cases) or interview (controls) were analyzed. Pooled odds ratios (OR) and 95% confidence intervals were computed in two-stage random-effects or joint fixed-effects models, adjusted for age, sex, and study center. When modeled individually, lifetime history of asthma, hay fever, a specific allergy (excluding hay fever, asthma and eczema), and food allergy were associated with a significant reduction in NHL risk, and there was no association for eczema. When each atopic condition was included in the same model, reduced NHL risk was only associated with history of allergy (OR 0.80, 95% CI 0.68–0.94), and reduced B-cell NHL risk was associated with history of hay fever (OR 0.85, 95% CI 0.77–0.95) and allergy (OR 0.84, 95% CI 0.76–0.93). Significant reductions in B-cell NHL risk were also observed in individuals who were likely to be truly or highly atopic - those with hay fever, allergy or asthma and at least one other atopic condition over their lifetime. The inverse associations were consistent for the diffuse large B-cell and follicular subtypes. Eczema was positively associated with lymphomas of the skin; misdiagnosis of lymphoma as eczema is likely, but progression of eczema to cutaneous lymphoma cannot be excluded. This pooled study demonstrates evidence of a modest but consistent reduction in the risk of B-cell NHL associated with atopy.

Keywords

non-Hodgkin lymphoma; atopy; case-control; pooled analysis; risk

Introduction

A causal explanation for most cases of non-Hodgkin lymphoma (NHL) remains elusive. Given the established positive association between immune deficiency and NHL risk (1), and the origin of NHL from cells of the immune system, it is plausible that other forms of immune dysregulation, such as atopic disease, are also related to lymphoma. Case-control study results have been mixed (2–23), although recent studies predominantly have found a reduced risk of NHL in association with a history of atopy. In contrast, cohort studies, mostly of limited power and with few detailed questions on atopy, have found no consistent evidence of an association. (24–33)

Herein we report results from an international pooled analysis of case-control studies that examined history of self-reported atopic disease and risk of NHL.

Materials and methods

Study population

We performed a pooled analysis of data from 13 case-control studies identified through the InterLymph Consortium (www.epi.grants.cancer.gov/InterLymph). Participating studies (Table 1) met the following eligibility criteria: cases diagnosed with incident histologically confirmed NHL as adults (age 16–96 years); collection of personal history of 1 or more atopic conditions; and electronic data set available in March of 2007. Due to variations in study design between the six EpiLymph centers (Table 1), this study was treated statistically as six separate studies, to allow for assessment of center-specific effects and heterogeneity. Organ transplant recipients and individuals with HIV-infection, as well as hospital-based controls admitted for atopic conditions (n=39, 1.1%), were excluded.

Exposure assessment

All studies ascertained self-reported history of atopy. Reports of atopic disease onset less than 2 years prior to NHL diagnosis (cases) or interview (controls) were excluded. This was necessary because an effect of increased medical surveillance in the period prior to case diagnosis could not be ruled out, and it also partially reduced the possibility that subclinical disease influenced exposure.

Given the recognized potential for misclassification of self-reported history of atopic disease (34), we constructed variables to represent participants who were likely to be truly atopic (35–37). These exposures were: atopic disease of long duration and multiple atopic conditions during a lifetime (eczema was excluded *post-hoc*). These were defined *a priori* and we hypothesized they would be more strongly related to NHL risk.

Statistical analysis

Odds ratios (OR) and 95% confidence intervals (CI) were computed from unconditional logistic regression models, using a two-stage random-effects model to estimate relative risk (hereafter called ‘risk’) of NHL, and a joint fixed-effects model to estimate risk by NHL subtype.(38) All WHO classification (39) subtypes of NHL, except multiple myeloma, were included in the analysis, as recommended for epidemiological analyses (40). All models were adjusted for the matching variables age, sex, and region/study center. We first examined NHL risk in association with history of each individual atopic condition. We next examined NHL risk adjusted for history of each of the other atopic conditions, and thus included only the 12 study centers that collected data on all four major atopic conditions (asthma, hay fever, eczema and specific allergy). Third, we examined NHL risk in association with history of each

individual condition alone, or with one or more other atopic conditions, and included studies that collected data on more than one atopic condition over a lifetime.

Heterogeneity among study centers was assessed using Cochran´s *Q* statistic and the I^2 statistic. (41) In the presence of significant heterogeneity ($p<0.10$), forest plots were used to identify outlying studies, and sensitivity analyses were performed with and without the outlying studies; no individual study was consistently identified as outlying. Due to a predominance of study participants of Caucasian origin, stratification by race was not meaningful. Restriction to Caucasians gave similar results. All statistical tests were two-sided and assumed an α-error level of 0.05. Analyses were performed using the STATA software version 10.0 (Stata Corporation, College Station, TX).

The pooled analyses were approved by the University of New South Wales Human Research Ethics Committee.

Results

The sex distribution for the pooled cases (n=13,535) and controls (n=16,388) was similar (Table 2). However, compared to controls, cases were more likely to be older ($p<0.0001$), of lower socioeconomic status ($p<0.0001$), and of mixed race ($p=0.001$), and less likely to be black ($p=0.006$), although race was specified for fewer than 50% of participants (Table 2).

There was no statistically significant heterogeneity among studies for asthma ($p=0.70$, $I^2=0\%$) or hay fever ($p=0.15$, $I^2=28\%$), but there was for eczema ($p=0.03$, $I^2=46\%$; Figure 1). For allergies to specific substances, between-study heterogeneity was also evident for the summary measure ‘any specific allergy’ ($p<0.001$, $I^2=63\%$; Figure 1), allergy to one or more foods ($p<0.001$, $I^2=77\%$), animals ($p=0.06$, $I^2=53\%$), and plants ($p=0.01$, $I^2=72\%$). Stratification by study design features, including questionnaire and data collection format, doctor-diagnosed versus self-identified atopic disease, source of controls, response rates, and control exposure prevalence did not reveal any systematic or statistically significant differences between strata in the pooled estimates for any of the atopic conditions (data not shown). Hence, all studies were retained in the pooled analyses. Reassuringly, as described below, exclusion of outlying studies did not alter the significance of the pooled risk estimates.

Considering only studies that ascertained history of all 4 major atopic diseases, 767 (69%) controls with asthma also reported another atopic condition; 52% also had hay fever, 19% eczema and 43% a specific allergy. Of controls with hay fever, 1,556 (57%) also reported another atopic condition (21% asthma, 16% eczema and 45% specific allergy). Of controls with eczema, 333 (51%) also reported another atopic condition (23% asthma, 30% hay fever and 34% specific allergy), while 1,434 (57%) of controls with a specific allergy also reported another atopic condition (19% asthma, 47% hay fever and 15% eczema).

Asthma

A history of asthma was associated with a significant 10% reduction in risk of NHL (Figure 1). In the 12 studies that collected data on all 4 atopic conditions, the OR was not significant after adjustment for history of the other atopic conditions (Table 3). NHL risk was not attenuated in those who only experienced asthma (Table 4), and a significant reduction in NHL risk, and B-cell NHL risk, was observed in individuals with asthma and at least one other atopic condition during their lifetime (Table 4). After adjustment for history of other atopic conditions, the OR was 1.08 (95% CI 0.73–1.58) for those with asthma for up to 5 years, 0.80 (95% CI 0.51–1.27) for 6–10 years and 0.80 (95% CI 0.56–1.13) for more than 10 years.

Hay fever

Risk of NHL was reduced by 18% in participants with a history of hay fever (Figure 1), but the reduction in risk was not significant in a model that adjusted for history of the other atopic conditions (Table 3). History of hay fever was significantly inversely associated with risk of B-cell NHL, diffuse large B-cell (DLBCL), and follicular NHL after adjustment by history of the other atopic conditions (Table 3). NHL risk was reduced in those who only experienced hay fever and a significant reduction in risk of all NHL, B-cell NHL, DLBCL and follicular NHL was observed in those with hay fever and one or more other atopic conditions during their lifetime (Table 4). After adjustment by history of other atopic conditions, the OR was 1.31 (95% CI 0.86–2.00) for those with hay fever for up to 5 years, 1.48 (95% CI 0.96–2.28) for 6–10 years and 0.78 (95% CI 0.63–0.97) for more than 10 years.

Eczema

Risk of NHL was not associated with a history of eczema (Figure 1) and excluding the single potential outlying study responsible for the between-study heterogeneity did not materially alter the pooled risk (OR 1.03, 95% CI 0.89–1.19; p_{het}=0.10, I^2=35%). A history of eczema was also not associated with NHL risk after adjustment for history of the other atopic conditions (Table 3), or alone or with a history of one or more other atopic diseases (Table 4). A history of eczema and at least one other condition was inversely associated with risk of DLBCL (Table 4); no other B-cell subtypes were associated with eczema (Table 3 and Table 4). The ORs from the model adjusted for history of other atopic conditions were 1.11 (95% CI 0.82–1.50) for individuals with eczema for up to 5 years, 0.88 (95% CI 0.56–1.38) for 6–10 years and 0.88 (95% CI 0.68–1.13) for more than 10 years.

Eczema was associated with a significant 2-fold increased risk of T-cell NHL (Table 3 and Table 4), due to an excess risk of mycoses fungoides/Sézary syndrome (MF/SS, number (n) of exposed cases=26; OR 2.62, 95% CI 1.64–4.17) and the peripheral T-cell subtype angioimmunoblastic lymphoma (n=6; OR 2.60, 95% CI 1.02–6.62). Risk of primary cutaneous CD30-positive T-cell lymphoma was non-significantly elevated (n=4; OR 2.56, 95% CI 0.66–9.99). Although the estimates in association with duration of eczema were imprecise, the greatest excess risk of MF/SS was observed in those with a 6–10 year history of eczema (n=3; OR 5.51, 95% CI 1.55–19.56,); the OR for duration <5 years was 1.63 (95% CI 0.38–7.05; n=2) and for duration >10 years 3.15 (95% CI 1.26–7.85; n=6). Eczema also was associated with an increased risk of overall NHL that originated in the skin (OR 2.09, 95% CI 1.19–3.69), but not at the non-skin sites (OR 1.00, 95% CI 0.81–1.23).

Any specific allergy

A history of one or more specific allergies was associated with a significant 20% reduction in NHL risk (Figure 1). In a sensitivity analysis excluding the two outlying studies responsible for the between-study heterogeneity, the pooled OR was slightly weakened (OR 0.88, 95% CI 0.81–0.95; p_{het}=0.73, I^2=0%). In the 12 studies that collected data on all 4 atopic conditions, NHL risk was significantly reduced in individuals with a history of allergy when adjusted for lifetime history of other atopic conditions (Table 3). Significant inverse associations also were observed for B-cell NHL and DLBCL (Table 3). NHL risk was significantly reduced in those who experienced allergy alone, as well as those who experienced allergy and at least one other atopic condition (Table 4). This association was significant for B-cell NHL, DLBCL, and follicular NHL. The ORs obtained from the model adjusted for history of other atopic conditions were 1.38 (95% CI 0.68–2.79) for those with allergy for up to 5 years, 1.67 (95% CI 0.44–6.28) for 6–10 years and 0.76 (95% CI 0.45–1.29) for more than 10 years.

Food allergy was the only specific allergy significantly associated with overall NHL risk. Risk of NHL was reduced by 25% (Figure 1), and removing the three studies responsible for the

between-study heterogeneity had a negligible effect on the pooled estimate (OR 0.81, 95% CI 0.70–0.94). NHL risk remained significantly reduced (OR 0.60, 95% CI 0.40–0.91) after adjustment for lifetime history of other atopic conditions. An inverse association also was observed for B-cell NHL (OR 0.65, 95% CI 0.55–0.77), DLBCL (OR 0.67, 95% CI 0.52–0.86) and follicular lymphomas (OR 0.62, 95% CI 0.47–0.80).

The fully adjusted pooled ORs for all NHL were 1.05 (95% CI 0.81–1.38) for history of animal allergy, OR 1.33 (95% CI 0.57–3.10) for plant allergy, 0.91 (95% CI 0.67–1.23) for insect allergy, and 0.93 (95% CI 0.80–1.07) for 'other allergy' (data not shown in tables). Other than a reduced risk of marginal zone lymphoma associated with a history of 'other allergy' (OR 0.56, 95% CI 0.35–0.90), there were no significant subtype associations for these exposures.

Multiple atopic conditions

A history of any one atopic condition (asthma, hay fever or any specific allergy) was associated with a significant reduction in NHL risk (OR 0.87, 95% CI 0.82–0.93). Risk was further reduced for any two (OR 0.81, 95% CI 0.70–0.94) or all three of these conditions (OR 0.58, 95% CI 0.42–0.78) and the trend with increasing number of conditions was significant ($p_{trend}<0.0001$). When restricted to B-cell NHL, the results were very similar (data not shown). Amongst those with a history of all three conditions, risks for DLBCL, follicular and CLL/SLL/PLL/MCL lymphomas were reduced by 47–51% (data not shown). There were no cases of MCL with a history of 3 atopic conditions.

Discussion

In this large-scale, international pooled analysis, a personal history of atopy at any time of life was associated with a small reduction in NHL risk. History of a specific allergy, food allergy in particular, independently predicted risk of NHL, and history of a specific allergy or hay fever independently predicted risk of B-cell NHL. Asthma was inversely associated with overall and B-cell NHL risk in individuals who reported at least one other atopic condition. The observed inverse associations were consistent for the DLBCL and follicular subtypes. The specificity of the effect for B-cell lymphomas and the strengthening of the effect with exposure histories that were less likely to be misreported, such as individuals with multiple atopic diseases, support an effect of atopy on risk of NHL.

Case-control studies of NHL risk in relation to personal history of asthma, hay fever, and specific allergies that were not included in these pooled analyses have shown varied results, and none adjusted for history of other atopic diseases.(2–9,13,14,19) Of these 11 studies, three reported a significant increased risk of NHL (two with eczema (3,5) and one with hives (13)), while three reported a significant decreased risk of NHL (two with eczema (8,13) and one with asthma (19)). The eight cohort studies reported similarly mixed findings, although many were null.(24–31) Three reported a significant increased risk, one with hives (25), one with any specific allergy (26) and one with childhood eczema (30), while one reported a significant decreased risk of NHL with asthma (28). Across all studies, there was no pattern to the direction of the null findings.

The predominance of null findings in cohort studies is not unexpected given that most of these studies had limited power and assessed risk only in relation to atopic disease history at any time of life. Only two studies assessed risk in relation to history of multiple atopic diseases. (26,31) One reported an OR of 0.94 (95% CI 0.74–1.19) for a history of both asthma and hay fever (31); that study, though well powered, examined deaths from NHL, rather than incident NHL. The other study reported a non-significant excess risk in association with a history of multiple allergies, based on 46 incident haematopoietic tumors.(26,31)

Atopic diseases are characterized by immediate hypersensitivity reactions, initiated by the interaction of IgE antibodies (produced by B-cells) with foreign antigens (allergens), leading to a reaction that involves the release of many inflammatory molecules, cytokines and chemokines. (42) Our finding of a reduced risk of B-cell but not T-cell NHL in persons with a history of atopic disease is consistent with an inverse association between such Ig-mediated immune allergic responses and NHL risk. The heightened response to antigens that is manifested as atopy may also be associated with a heightened response to cancer-specific or cancer-associated antigens, and thus with a reduced risk of NHL. Several features of atopic responses have the potential to inhibit tumor cell growth. IgE can enhance antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis, antigen presentation, and mast cell responses.(43) The high affinity of the Fc receptors (including CD23) for IgE makes antibodies of the IgE subclass effective at mediating ADCC and allows enhanced antigen-presentation, potentially promoting the generation of anti-tumor cytotoxic T cells. (43,44) Additionally, eosinophils can mediate cellular cytotoxicity directly, and mast cells produce a wide range of mediators that can exert direct cytotoxic and growth-inhibitory effects on tumor cells. (43,45,46)

Whereas atopy is associated with the production of antibodies of the IgE subclass by B cells, some features of allergic responses, including induced immunoregulatory mechanisms, may result in the inhibition of B-cell activation. Such inhibition could decrease the occurrence of lymphomagenic molecular lesions (chromosomal translocation, oncogene mutation) that result from somatic DNA-modifying events that occur in germinal cell (GC) B-cells following activation, such as Ig class-switch recombination and somatic hypermutation.(47) In light of evidence that most B-cell NHLs are of GC or post-GC origin (48), a role for an allergy-associated decrease in such lymphomagenic molecular lesions is possible. However, we did not have sufficient biological data from a representative sample to test the hypothesis that only those NHLs that had undergone somatic hypermutation or class switching would be inversely associated with atopy.

The observed increased risk of cutaneous lymphoma (MF/SS) associated with a history of eczema may be an artifact of early misdiagnosis of some cutaneous lymphomas as eczema. Cutaneous lymphomas are difficult to diagnose, both clinically and histopathologically, but are thought to develop slowly over years to decades. The typical duration of eczema prior to T-cell NHL diagnosis in our pooled population was 6–10 years. MF/SS presents initially as patches, plaques, and/or tumors, and some early skin lesions may mimic eczema.(49) While there is no published evidence that persistent eczema is a precursor to MF/SS, we are unable to exclude this possibility.

A key strength of these pooled analyses is the large sample size, enabling the detection of weak to modest associations. Other strengths include the examination of risk by NHL subtype, of confounding, of influence by study design factors, and of risk in sub-groups of individuals who are likely to be truly atopic. However, as the analyses by B-cell subtype were exploratory, the possibility of chance associations due to multiple comparisons cannot be excluded. The consistency of the findings for the major B-cell types is nevertheless reassuring. In addition, this study modeled risk adjusted for history of other atopic conditions and this was shown to be necessary to avoid confounded associations due to the co-occurrence of atopic disease.

A limitation common to case-control studies is the retrospective collection of self-reported atopic histories with its inherent potential for selection bias, misclassification, and recall bias. Seven study centers had a large (>20%) differential in their case and control participation rates. However, the pooled estimates were unchanged when stratified by control participation rate or control source (population versus hospital), arguing against a strong contribution by selection bias. Furthermore, the magnitude and the rank order of the control prevalence of

different atopic conditions were largely consistent with published population-based prevalence surveys.(50,51) Misclassification that is not expected to be differential, may have contributed to the modest and null associations observed for some exposures. Self-reported hay fever, with its typical seasonal and well characterized symptoms, may be more reliable than self-reported asthma, but may still have been misclassified with plant allergies. Misclassification was addressed to some extent by analyzing risk in relation to duration and multiplicity of atopic disease. Recall bias due to a consistently greater under-reporting of atopic conditions by cases compared to controls cannot be excluded, particularly in light of the reported abatement of atopic symptoms with the development of haematopoietic neoplasms (2), especially for the less well defined conditions and for those with less severe symptoms. However, structured questionnaires, many of which asked about specific times over the life course and details of the type of allergy and use of medications, would be expected to minimize this potential bias. Furthermore, recall bias is less likely to explain the observed associations with multiple atopic conditions. However, the magnitude of the effect was weak to modest, and thus we cannot exclude the possibility that a moderately strong confounder present in most of the pooled studies could account for the association.

In summary, we found that atopic disease history is associated with a weak to moderate reduction in the risk of B-cell NHL. The inverse association was consistent for specific allergies, hay fever, and multiple atopic diseases, but was not observed for eczema or for asthma independent of other atopic diseases. Investigation of the genetic and environmental factors underlying atopy and its apparent inverse association with NHL risk will inform our understanding of the complex biological pathways that may be involved. Large-scale cohort study data assessing a range of measures of atopic phenotype throughout life, in addition to serial assessment of specific IgE at least 10 years prior to NHL diagnosis, are required to confirm these findings.

List of abbreviations

DLBCL, Diffuse large B-cell lymphoma
CLL, Chronic lymphocytic leukemia
CI, Confidence interval
MALT, Mucosa-associated lymphoid tissue
MCL, Mantle cell lymphoma
NHL, Non-Hodgkin lymphoma
OR, Odds ratio
PLL, Prolymphocytic lymphoma
SLL, Small lymphocytic lymphoma
Ig, immunoglobulin
GC, germinal center.

Acknowledgments

The pooled analysis was funded by the Leukaemia Foundation of Australia (LFA GIA 24). Individual studies were supported by the Italian Association for Cancer Research and the Italian League Against Cancer (Avi-N, Northern Italy); the Canadian Cancer Society through the National Cancer Institute of Canada, the Canadian Institutes for Health Research and the Chan Sisters Foundation (British Columbia); National Cancer Institute (CA62006) (Connecticut); European Commission (QLK4-CT-2000-00422) (EpiLymph); Association pour la Recherche contre le Cancer (5111) and Fondation de France (1999 008471) (EpiLymph-France); Compagnia di San Paolo di Torino, Programma Oncologia 2001 (EpiLymph-Italy); Health Research Board (EpiLymph-Ireland); Spanish Ministry of Health FISS (PI040091) and CIBERESP (06/06/0073) (EpiLymph-Spain); German Federal Office for Radiation Protection (StSch4261 and StSch4420) (EpiLymph-Germany); National Institutes of Health (CA51086), the European Community and the Italian League against Cancer (Italy); National Cancer Institute (CA92153) (Mayo); National Cancer Institute (PC65064, PC67008, PC67009, PC67010, PC71105) (NCI-SEER); American Institute for Cancer Research (99B083) (Nebraska); National Health and Medical Research Council of Australia (990920) (NSW); National Institutes of Health (CA69269-02) and the Swedish Cancer Society (04 0458) (SCALE); National Institutes

of Health (CA45614, CA89745, CA87014, CA104682) (UCSF); and the Leukaemia Research Fund of Great Britain (UK). The funders did not participate in the design, data collection or analyses of the individual studies, or in the interpretation and writing of manuscripts.

Dr Vajdic is supported by a National Health and Medical Research Council Career Development Award (ID 510346) and a Cancer Institute NSW Career Support and Development Fellowship (ID 07-CDF-1/38). Dr. Martínez-Maza received support from the National Institutes of Health (CA121195).

References

1. Beral V, Peterman T, Berkelman R, Jaffe H. AIDS-associated non-Hodgkin lymphoma. Lancet 1991;337:805–809. [PubMed: 1672911]
2. McCormick DP, Ammann AJ, Ishizaka K, Miller DG, Hong R. A study of allergy in patients with malignant lymphoma and chronic lymphocytic leukemia. Cancer 1971;27:93–99. [PubMed: 5539630]
3. Bernard SM, Cartwright RA, Bird CC, Richards ID, Lauder I, Roberts BE. Aetiologic factors in lymphoid malignancies: a case-control epidemiological study. Leuk Res 1984;8:681–689. [PubMed: 6471900]
4. Tielsch JM, Linet MS, Szklo M. Acquired disorders affecting the immune system and non-Hodgkin's lymphoma. Prev Med 1987;16:96–106. [PubMed: 3823013]
5. Cartwright RA, McKinney PA, O'Brien C, et al. Non-Hodgkin's? lymphoma: case control epidemiological study in Yorkshire. Leuk Res 1988;12:81–88. [PubMed: 3357350]
6. Franceschi S, Serraino D, Bidoli E, et al. The epidemiology of non-Hodgkin's lymphoma in the north-east of Italy: a hospital-based case-control study. Leuk Res 1989;13:465–472. [PubMed: 2770331]
7. La Vecchia C, Negri E, Franceschi S. Medical history and the risk of non-Hodgkin's lymphomas. Cancer Epidemiol Biomarkers Prev 1992;1:533–536. [PubMed: 1302565]
8. Bernstein L, Ross RK. Prior medication use and health history as risk factors for non-Hodgkin's lymphoma: preliminary results from a case-control study in Los Angeles County. Cancer Res 1992;52:5510s, 5515s. [PubMed: 1394165]
9. Doody MM, Linet MS, Glass AG, et al. Leukemia, lymphoma, and multiple myeloma following selected medical conditions. Cancer Causes Control 1992;3:449–456. [PubMed: 1525326]
10. Holly EA, Lele C, Bracci PM, McGrath MS. Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay Area, California. Am J Epidemiol 1999;150:375–389. [PubMed: 10453814]
11. Vineis P, Crosignani P, Sacerdote C, et al. Haematopoietic cancer and medical history: a multicentre case control study. J Epidemiol Community Health 2000;54:431–436. [PubMed: 10818118]
12. Tavani A, La Vecchia C, Franceschi S, Serraino D, Carbone A. Medical history and risk of Hodgkin's and non-Hodgkin's lymphomas. Eur J Cancer Prev 2000;9:59–64. [PubMed: 10777011]
13. Fabbro-Peray P, Daures JP, Rossi JF. Environmental risk factors for non-Hodgkin's lymphoma: a population-based case-control study in Languedoc-Roussillon, France. Cancer Causes Control 2001;12:201–212. [PubMed: 11405325]
14. Briggs NC, Levine RS, Brann EA. Allergies and risk of non-Hodgkin's lymphoma by subtype. Cancer Epidemiol Biomarkers Prev 2002;11:401–407. [PubMed: 11927501]
15. Holly EA, Bracci PM. Population-based study of non-Hodgkin lymphoma, histology, and medical history among human immunodeficiency virus-negative participants in San Francisco. Am J Epidemiol 2003;158:316–327. [PubMed: 12915497]
16. Zhang Y, Holford TR, Leaderer B, et al. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. Cancer Causes Control 2004;15:419–428. [PubMed: 15141141]
17. Becker N, Deeg E, Rudiger T, Nieters A. Medical history and risk for lymphoma: results of a population-based case-control study in Germany. Eur J Cancer 2005;41:133–142. [PubMed: 15617998]
18. Grulich AE, Vajdic CM, Kaldor JM, et al. Birth order, atopy, and risk of non-Hodgkin lymphoma. J Natl Cancer Inst 2005;97:587–594. [PubMed: 15840881]

19. Soderberg KC, Jonsson F, Winqvist O, Hagmar L, Feychting M. Autoimmune diseases, asthma and risk of haematological malignancies: a nationwide case-control study in Sweden. Eur J Cancer 2006;42:3028–3033. [PubMed: 16945522]
20. 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;15:1287–1294. [PubMed: 16835325]
21. Becker N, de Sanjose S, Nieters A, et al. Birth order, allergies and lymphoma risk: results of the European collaborative research project Epilymph. Leuk Res 2007;31:1365–1372. [PubMed: 17481729]
22. Cozen W, Cerhan JR, Martinez-Maza O, et al. The effect of atopy, childhood crowding, and other immune-related factors on non-Hodgkin lymphoma risk. Cancer Causes Control 2007;18:821–831. [PubMed: 17588155]
23. Melbye M, Smedby KE, Lehtinen T, et al. Atopy and risk of non-Hodgkin lymphoma. J Natl Cancer Inst 2007;99:158–166. [PubMed: 17227999]
24. Robinette CD, Fraumeni JF Jr. Asthma and subsequent mortality in World War II veterans. J Chronic Dis 1978;31:619–624. [PubMed: 744792]
25. McWhorter WP. Allergy and risk of cancer. A prospective study using NHANESI followup data. Cancer 1988;62:451–455. [PubMed: 3383143]
26. Mills PK, Beeson WL, Fraser GE, Phillips RL. Allergy and cancer: organ site-specific results from the Adventist Health Study. Am J Epidemiol 1992;136:287–295. [PubMed: 1415150]
27. Vesterinen E, Pukkala E, Timonen T, Aromaa A. Cancer incidence among 78,000 asthmatic patients. Int J Epidemiol 1993;22:976–982. [PubMed: 8144310]
28. Kallen B, Gunnarskog J, Conradson TB. Cancer risk in asthmatic subjects selected from hospital discharge registry. Eur Respir J 1993;6:694–697. [PubMed: 8519380]
29. Talbot-Smith A, Fritschi L, Divitini ML, Mallon DF, Knuiman MW. Allergy, atopy, and cancer: a prospective study of the 1981 Busselton cohort. Am J Epidemiol 2003;157:606–612. [PubMed: 12672680]
30. Soderberg KC, Hagmar L, Schwartzbaum J, Feychting M. Allergic conditions and risk of hematological malignancies in adults: a cohort study. BMC Public Health 2004;4:51. [PubMed: 15527506]
31. Turner MC, Chen Y, Krewski D, Ghadirian P, Thun MJ, Calle EE. Cancer mortality among US men and women with asthma and hay fever. Am J Epidemiol 2005;162:212–221. [PubMed: 15987724]
32. Lindelof B, Granath F, Tengvall-Linder M, Ekbom A. Allergy and cancer. Allergy 2005;60:1116–1120. [PubMed: 16076294]
33. Eriksson NE, Mikoczy Z, Hagmar L. Cancer incidence in 13811 patients skin tested for allergy. J Investig Allergol Clin Immunol 2005;15:161–166.
34. Turner MC, Chen Y, Krewski D, Ghadirian P. An overview of the association between allergy and cancer. Int J Cancer 2006;118:3124–3132. [PubMed: 16395696]
35. Kurukulaaratchy RJ, Matthews S, Arshad SH. Defining childhood atopic phenotypes to investigate the association of atopic sensitization with allergic disease. Allergy 2005;60:1280–1286. [PubMed: 16134995]
36. Burgess JA, Walters EH, Byrnes GB, et al. Who remembers whether they had asthma as children? J Asthma 2006;43:727–730. [PubMed: 17169822]
37. Annesi-Maesano I, Beyer A, Marmouz F, Mathelier-Fusade P, Vervloet D, Bauchau V. Concurrent allergic diseases: a cross-sectional study in a French population. Allergy 2006;61:390–391. [PubMed: 16436152]
38. Stukel TA, Demidenko E, Dykes J, Karagas MR. Two-stage methods for the analysis of pooled data. Stats Med 2001;20:2115–2130.
39. Jaffe, ES.; Stein, H.; Vardiman, JW., editors. Lyon, France: IARC Press; 2001. Pathology and Genetics of Tumours of Hamatopoietic and Lymphoid Tissues.
40. Morton LM, Turner JJ, Cerhan JR, et al. Proposed classificatin of lympoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph). Blood 2007;110:695–708. [PubMed: 17389762]

41. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stats Med 2002;21:1539–1558.

42. Wasserman, SI. Biochemical Mediators of Allergic Reactions. In: Grammer, LC.; Greenberger, PA., editors. Patterson's Allergic Diseases. Vol. 6th edition ed. Lippincott Williams & Wilkins; 2002.

43. Jensen-Jarolim E, Achatz G, Turner MC, et al. AllergoOncology:the role of IgE-mediated allergy in cancer. Allergy 2008;63:1255–1266. [PubMed: 18671772]

44. Gould HJ, Mackay GA, Karagiannis SN, et al. Comparison of IgE and IgG antibody-dependent cytotoxicity in vitro and in a SCID mouse xenograft model of ovarian carcinoma. Eur J Immunol 1999;29:3527–3537. [PubMed: 10556807]

45. Strik MC, de Koning PJ, Kleijmeer MJ, et al. Human mast cells produce and release the cytotoxic lymphocyte associated protease granzyme B upon activation. Mol Immunol 2007;44:3462–3472. [PubMed: 17485116]

46. Wang H, Diepgen TL. Is atopy a protective or a risk factor for cancer? A review of epidemiological studies. Allergy 2005;60:1098–1111. [PubMed: 16076292]

47. Pasqualucci L, Bhagat G, Jankovic M, et al. AID is required for germinal centre-derived lymphomagenesis. Nature Genetics 2008;40:108–112. [PubMed: 18066064]

48. Skibola CF, Curry JD, Nieters A. Genetic susceptibility to lymphoma. Haematologica 2007;92:960–969. [PubMed: 17606447]

49. Keehn CA, Belongie IP, Shistik G, Fenske NA, Glass LF. The diagnosis, staging, and treatment options for mycosis fungoides. Cancer Control 2007;14:102–111. [PubMed: 17387295]

50. Woods RK, Abramson M, Bailey M, Walters EH. Comparisons arising from the European Community Respiratory Health Survey (ECRHS) 1991–1994. Eur J Clin Nutr 2001;55:298–304. [PubMed: 11360135]

51. Pearce N, Sunyer J, Cheng S, et al. Comparison of asthma prevalence in the ISAAC and the ECRHS. ISAAC Steering Committee and the European Community Respiratory Health Survey. International Study of Asthma and Allergies in Childhood. Eur Respir J 2000;16:420–426. [PubMed: 11028654]

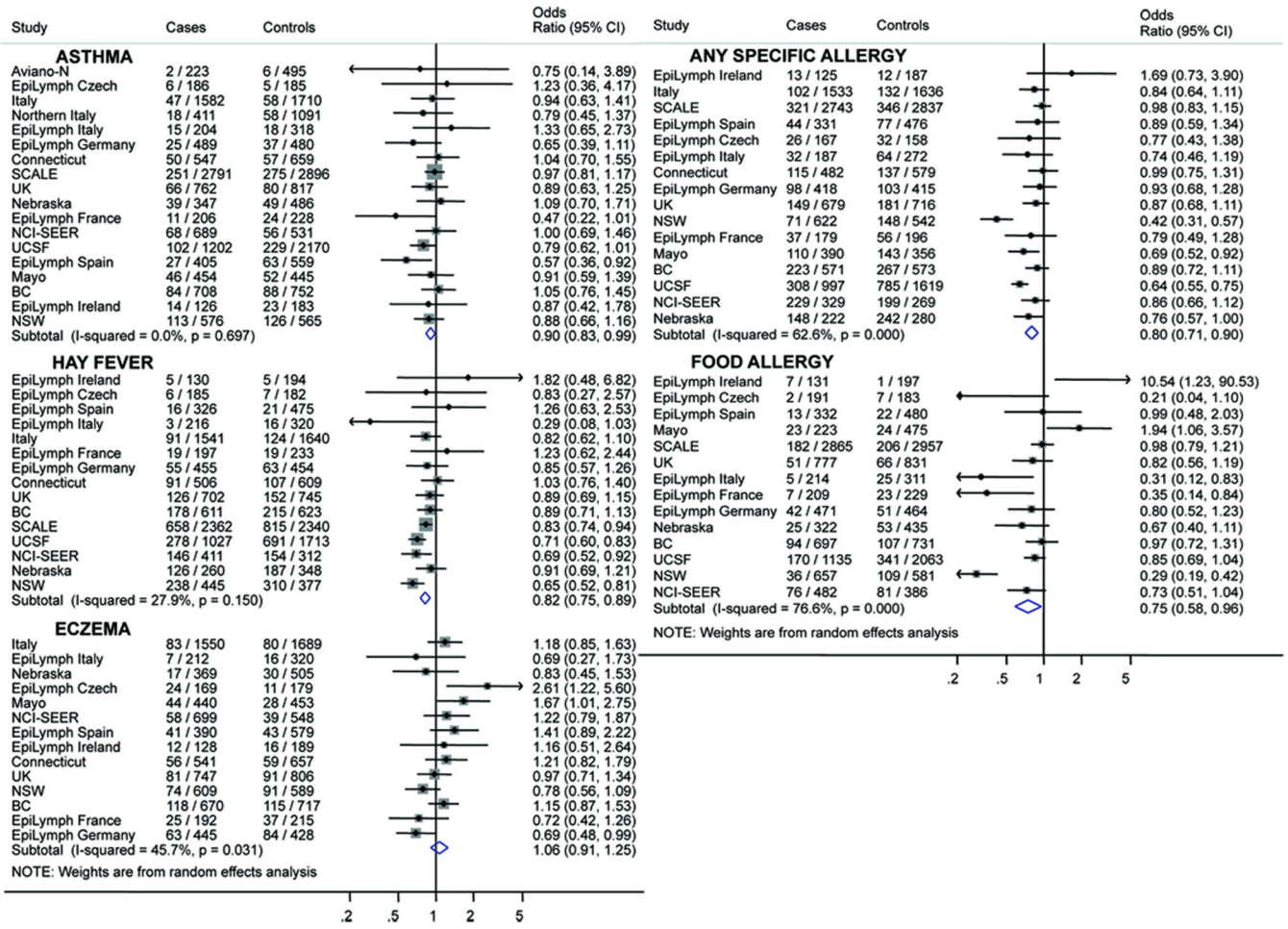

Figure 1.

Estimates of NHL risk restricted to individuals with a history of the atopic disease diagnosed at least 2 years prior to interview/NHL diagnosis, sorted by atopic disease prevalence in controls. Individual study odds ratios (OR, filled diamonds) and 95% confidence intervals (CI, horizontal bars), or pooled ('subtotal') ORs and CIs (large open diamonds) computed using a two-stage random-effects model adjusted for age (5 year categories), sex, and study centre, with no history of the atopic disease in question as reference category. The shaded boxes represent the weight given to a particular study when estimating the summary odds ratio. "Any specific allergy" was defined as one or more of: food allergy, animal allergy, plant allergy, insect allergy or other allergy; "other allergy" includes allergies to dust, mould, cosmetics, household products, or "other" allergens; drug allergies were excluded.

Study-specific and pooled estimates for lifetime personal history of individual atopic diseases and risk of NHL, in order of increasing atopic disease prevalence in controls

Table 1

Characteristics of case-control studies participating in the pooled analysis of history of atopic disease and risk of non-Hodgkin lymphoma (NHL)

Study acronym	Location	Year	Age (years)	Matching variables	Cases		Controls		Source of controls
					n	Rate† (%)	n	Rate† (%)	
Avi-N	Aviano; Napoli, Italy	1999–2002	18–84	None	225	97	501	91	Patients admitted to hospital for non-neoplastic, non-immunological conditions
BC	British Columbia, Canada	2000–2003	20–80	Age, sex, region	828	79	845	46	Random selection from client registry of Ministry of Health
Connecticut[16]	Connecticut, USA	1995–2001	21–84	Age	597	72	716	47–69	<65y: RDD‡; ≥65y: random selection from Centers for Medicare and Medicaid Services
EpiLymph(17, 21, 52)	Czech Republic	2001–2003	19–82	Age, sex, region	199	90	199	60	Patients admitted to hospital for infectious, parasitic, mental, nervous, circulatory, digestive, endocrine, metabolic and respiratory conditions
	France	2000–2003	18–82	Age, sex, region	217	91	252	74	
	Ireland	1998–2004	19–85	Age, sex, center	144	90	207	75	
	Spain	1998–2003	17–96	Age, sex, region	435	82	623	96	
	Germany	1999–2002	18–82	Age, sex, region	518	87	518	44	Random selection from population registries
	Italy (Sardinia)	1998–2004	25–81	Age, sex, region	219	93	336	66	
Italy(11)	Turin; Novara; Forli; Vercelli; Varese; Verona; Florence; Siena; Latina; Ragusa; Imperia	1990–1993	20–74	Age, sex, region	1,640	82	1,771	74	Random selection from demographic or National Health Service files
Mayo	Minnesota, Iowa, and Wisconsin, USA	2002–2005	20–87	Age, sex, region	500	65	499	69	Patients attending a pre-scheduled general medical exam

Study acronym	Location	Year	Age (years)	Matching variables	Cases		Controls		Source of controls
					n	Rate† (%)	n	Rate† (%)	
NCI-SEER(22)	Detroit; Iowa; Los Angeles; Seattle, USA	1998–2001	20–74	Age, sex, region, race	1,316	76	1,055	52	<65y: RDD‡; ≥65y: random selection from Centers for Medicare and Medicaid Services
Nebraska	Nebraska, USA	1999–2002	20–75	Age, sex	386	74	535	78	RDD‡
Northern Italy(12)	Aviano; Milan, Italy	1983–1992	17–85	None	429	>97	1,149	>97	Patients admitted for non-neoplastic, non-immunological conditions in hospitals where cases diagnosed
NSW(18, 53)	New South Wales, Australian Capital Territory, Australia	2000–2001	20–74	Age, sex, region	694	85	694	61	Random selection from electoral rolls
SCALE(23)	Denmark; Sweden	1999–2002	18–74	Age, sex, country	3,055	81	3,187	71	Random selection from population registries
UCSF(10, 15, 20)	San Francisco, CA, USA	1988–1993	21–74	Age, sex, region	1,305	72	2,404	78	<65y: RDD‡; ≥65y: random selection from Centers for Medicare and Medicaid Services
UK	Parts of north and southwest England	1998–2003	16–69	Age, sex, region	828	75	897	71	Random selection from general practice lists

The number of participants may differ from the published report because of the selection criteria for this analysis

† Participation rate

‡ RDD Random digit dialing

Table 2

Demographic and tumor characteristics of the pooled study participants

Demographics	NHL Cases (%)	Controls (%)	Tumor characteristics	NHL Cases (%)
Pooled total	13,535	16,388	**Pooled total**	13,535
Sex			**B-cell NHL**	11,208 (82.8)
Men	7,329 (54.1)	8,844 (54.0)	Follicular lymphoma	2,842 (21.0)
Women	6,206 (45.9)	7,544 (46.0)	Diffuse large B-cell lymphoma	3,820 (28.2)
Age (years)*			CLL / SLL / PLL / MCL	2,261 (16.7)
16–20	25 (0.2)	56 (0.4)	Marginal zone lymphoma	784 (5.8)
20 – 29	381 (2.8)	838 (5.1)	Burkitt's lymphoma	108 (0.8)
30 – 39	924 (6.8)	1596 (9.7)	Lymphoplasmacytic lymphoma	300 (2.2)
40 – 49	1,823 (13.5)	2,381 (14.5)	Hairy cell leukemia	118 (0.9)
50 – 59	3,472 (25.7)	3,719 (22.7)	Precursor B-cell	26 (0.2)
60 – 69	4,313 (31.9)	4,753 (29.0)	B-cell not otherwise specified	949 (7.0)
70 – 79	2,448 (18.1)	2,878 (17.6)	**T-cell NHL**	766 (5.7)
80–96	147 (1.1)	167 (1.0)	Mycosis fungoides / Sezary syndrome	254 (1.9)
Median (range)	60 (17 – 89)	58 (16 – 96)	Peripheral T-cell	399 (2.9)
Education / SES†			Adult T-cell leukemia / lymphoma	2 (0.0)
Low	5,216 (38.5)	5,770 (35.2)	NK/T-cell lymphoma nasal type/ aggressive NK-cell leukemia	20 (0.1)
Medium	4,643 (34.3)	5,867 (35.8)	T-cell large granular lymphocytic leukemia	7 (0.1)
High	3,566 (26.4)	4,651 (28.4)	T-cell prolymphocytic leukemia	7 (0.1)
Unknown / other	110 (0.8)	100 (0.6)	Precursor T-cell	29 (0.2)
Race‡			T-cell not otherwise specified	48 (0.4)
White	5,672 (42.0)	6,757 (41.2)	**NHL not otherwise specified**	1,561 (11.5)
Black	202 (1.5)	327 (2.0)	Precursor not otherwise specified	57 (0.4)
Other / mixed	539 (4.0)	558 (3.4)	Not otherwise specified	1,504 (11.1)
Missing	7,083 (52.5)	9,746 (53.4)		

*The inclusion of Hodgkin lymphoma cases and frequency matched controls in several studies led to an imbalance in the age distribution

†Education/socioeconomic status (SES) groups was based on the tertile distribution of years of education (10 studies) or SES levels obtained from census data (2 studies) in controls

‡Race was generally not recorded in the European studies

Table 3

The pooled relative risk of non-Hodgkin lymphoma (NHL) for a personal history of individual atopic conditions, adjusted by history of other atopic disease

	Atopic disease*, OR (95% CI)†			
	Asthma	**Hay fever**	**Eczema**	**Any specific allergy‡**
All NHL§	0.97 (0.84–1.11)	0.89 (0.77–1.02)	1.04 (0.87–1.25)	**0.80 (0.68–0.94)**
B-cell NHL**	0.97 (0.85–1.12)	**0.85 (0.77–0.95)**	0.96 (0.85–1.10)	**0.84 (0.76–0.93)**
Diffuse large B-cell**	0.92 (0.75–1.13)	**0.84 (0.71–0.98)**	0.86 (0.71–1.05)	**0.78 (0.67–0.90)**
Follicular**	0.97 (0.78–1.21)	**0.78 (0.66–0.92)**	1.02 (0.83–1.25)	0.93 (0.80–1.09)
CLL/SLL/PLL/MCL**	0.82 (0.60–1.11)	0.91 (0.71–1.16)	0.85 (0.65–1.13)	0.84 (0.68–1.05)
Marginal zone**	1.29 (0.94–1.75)	0.96 (0.74–1.26)	1.10 (0.81–1.50)	0.81 (0.63–1.04)
T-cell NHL**	0.99 (0.68–1.45)	1.08 (0.80–1.46)	**1.92 (1.43–2.58)**	0.78 (0.58–1.05)
NHL not otherwise specified**	0.93 (0.64–1.35)	0.96 (0.73–1.27)	**1.41 (1.06–1.87)**	**0.69 (0.53–0.91)**

*A history of the atopic disease diagnosed at least 2 years prior to interview/NHL diagnosis and restricted to the 12 study sites with data on all 4 atopic diseases

†Odds ratios (OR) and 95% confidence intervals (CI) computed in models adjusted for age (5 year categories), sex, study centre, each of the other atopic diseases, with no history of the atopic disease in question as reference category

‡One or more of: food allergy, animal allergy, plant allergy, insect allergy or other allergy where "other allergy" includes allergies to dust, mould, cosmetics, household products, or "other" allergens (excluding drug allergies)

§Computed using a two-stage random-effects model

**Computed using a joint-fixed effects model

Table 4

The pooled relative risk of non-Hodgkin lymphoma (NHL) for a personal history of individual atopic conditions, alone or in combination with at least one other specified atopic disease

	Atopic disease*, OR (95% CI)†							
	Asthma OR (95% CI)†		Hay fever OR (95% CI)†		Eczema OR (95% CI)†		Any specific allergy‡ OR (95% CI)†	
	Only atopy	With ≥1 other atopy	Only atopy	With ≥1 other atopy	Only atopy	With ≥1 other atopy	Only atopy	With ≥1 other atopy
All NHL§	0.99 (0.86–1.14)	**0.86 (0.76–0.96)**	0.88 (0.78–1.00)	**0.78 (0.68–0.90)**	1.11 (0.87–1.41)	0.98 (0.84–1.15)	**0.87 (0.79–0.96)**	**0.75 (0.63–0.89)**
B-cell NHL**	1.02 (0.88–1.18)	**0.82 (0.73–0.93)**	**0.83 (0.76–0.92)**	**0.75 (0.69–0.83)**	1.02 (0.87–1.20)	0.93 (0.78–1.09)	**0.90 (0.82–0.98)**	**0.74 (0.67–0.81)**
Diffuse large B-cell**	0.99 (0.80–1.23)	**0.83 (0.70–0.98)**	**0.81 (0.71–0.93)**	**0.69 (0.60–0.79)**	0.99 (0.78–1.25)	**0.71 (0.55–0.92)**	**0.84 (0.73–0.96)**	**0.64 (0.55–0.73)**
Follicular**	0.94 (0.73–1.21)	**0.77 (0.64–0.94)**	**0.86 (0.74–1.00)**	**0.77 (0.66–0.88)**	1.01 (0.78–1.31)	1.12 (0.88–1.42)	0.93 (0.80–1.08)	**0.76 (0.66–0.88)**
CLL/SLL/PLL/MCL**	0.92 (0.70–1.20)	**0.77 (0.60–0.98)**	**0.82 (0.68–0.98)**	0.86 (0.70–1.05)	0.88 (0.64–1.21)	0.95 (0.67–1.34)	0.89 (0.75–1.07)	0.87 (0.72–1.07)
Marginal zone**	1.34 (0.97–1.99)	0.79 (0.56–1.13)	0.94 (0.71–1.25)	0.81 (0.61–1.08)	1.00 (0.66–1.51)	1.12 (0.77–1.62)	1.00 (0.78–1.30)	0.89 (0.68–1.17)
T-cell NHL**	1.00 (0.65–1.53)	1.19 (0.88–1.62)	0.85 (0.64–1.13)	0.91 (0.70–1.19)	**2.34 (1.67–3.29)**	**1.81 (1.26–2.61)**	0.95 (0.73–1.25)	0.85 (0.64–1.12)
NHL not otherwise specified**	0.86 (0.62–1.21)	0.85 (0.62–1.18)	0.95 (0.73–1.25)	0.80 (0.63–1.02)	1.33 (0.96–1.85)	1.11 (0.73–1.69)	**0.72 (0.56–0.91)**	**0.65 (0.51–0.83)**

*A history of the atopic disease diagnosed at least 2 years prior to interview/NHL diagnosis

†OR and 95% CI computed in models adjusted for age (5 year categories), sex, study centre, each of the other atopic diseases, with no history of the atopic disease in question as reference category

‡One or more of: food allergy, animal allergy, plant allergy, insect allergy or other allergy where “other allergy” includes allergies to dust, mould, cosmetics, household products, or “other” allergens (excluding drug allergies).

§Computed using two-stage random-effects model

**Computed using joint-fixed effects model