

Allergic conditions are not associated with the risk of non-Hodgkin's lymphoma or Hodgkin's lymphoma: a systematic review and meta-analysis

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Abstract: We aimed to systematically evaluate the association between allergic conditions and the risk of Hodgkin's lymphoma (HL) and non-HL (NHL). Systematic literature searches in PubMed and Embase were conducted up to October 2015 to identify eligible studies. Either a fixed-effects model or a random-effects model was adopted to estimate overall odds ratios (ORs) according to heterogeneity across studies. Subgroup and publication bias analyses were applied. A total of 24 case-control studies and 13 cohort studies (conducted from 1987 to 2015) were included in the analysis of the risk of NHL. History of any allergic condition was inversely associated with the risk of NHL in case-control studies (OR = 0.83, 95% CI 0.76–0.91), while the reduction in the risk of NHL was not observed in cohort studies (OR = 1.18, 95% CI 0.98–1.42). Significant association with the risk of NHL was found for asthma, hay fever, food allergy, allergic rhinitis, and hives. In the pooled analysis of the risk of HL, 12 studies (two were cohort studies) were included. The pooled OR was 0.96 (95% CI 0.84–1.09) for case-control studies and 1.46 (95% CI 0.63–3.38) for cohort studies. For specific allergic condition, we observed a reduced risk of HL in individuals with hay fever and food allergy. In conclusion, history of any allergic condition was not significantly associated with the risk of NHL or HL. Several specific allergic conditions, including asthma, hay fever, food allergy, and allergic rhinitis, might be associated with a reduced risk of NHL, while individuals with hay fever or food allergy may have a reduced risk of HL.

Keywords: allergic condition, non-Hodgkin's lymphoma, Hodgkin's lymphoma, risk

Introduction

Lymphomas represent a group of heterogeneous malignancies, which are the sixth most common cancer in men and fifth most common cancer among women.¹ Previous epidemiological studies have suggested significant association between lymphoma and severe immune deficiencies (such as primary and acquired immunodeficiency diseases and organ transplantation).^{2,3} For organ transplantation, an increased risk of non-Hodgkin's lymphoma (NHL) and abnormal proliferation of lymphocytes were observed, possibly because of the antigenic stimulation by the transplanted organ and the immunosuppressive therapy. Moreover, the origin of NHL was from cells of the immune system.⁴ Allergic conditions, such as asthma, hay fever, and allergic dermatitis, are characterized by immediate hypersensitivity reactions to environmental allergens and may indicate a heightened immune system, which may contribute to recognition and removal of malignant cells and thus reduce the risk of cancer. Thus, it is plausible that allergic conditions are also associated with the risk of lymphomas. In contrast, antigenic stimulation may lead to a chronic inflammation and stimulate cell growth, which may increase the risk of malignancies.⁵

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There has long been interest in the association between allergic conditions and the risk of lymphoma. Several case-control studies have indicated that people with a history of allergic conditions might have a lower risk of NHL.^{6–8} In a meta-analysis of 13 case-control studies, allergic conditions, such as hay fever and asthma, were observed to be modestly associated with the risk of NHL.⁹ However, results from cohort studies are inconsistent,^{10–12} as evidence from cohort studies is generally considered to be stronger than that from retrospective studies; a meta-analysis including both case-control studies and cohort studies might be warranted. Moreover, no meta-analysis has been conducted to assess the association between allergic conditions and the risk of Hodgkin's lymphoma (HL) in general population.

Thus, we performed this systematic review and meta-analysis to further clarify the association between allergic conditions and the risk of NHL/HL.

Methods

Literature search and study selection

This systematic review and meta-analysis was planned, conducted, and reported according to the PRISMA statement.¹³ A systematic literature search was conducted in the PubMed and Embase databases without restrictions (up to October 2015). The following terms were used in the search procedure: (“allergies” OR “allergy” OR “allergic” OR “atopy” OR “atopic” OR “asthma” OR “allergic rhinitis” OR “hay fever” OR “atopic dermatitis” OR “hive” OR “eczema”) AND lymphoma. We also scanned the reference lists of relevant articles and reviews to avoid missing studies. The retrieved articles were carefully examined to exclude duplicated studies. Titles and abstracts of the articles retrieved from the literature search were first scanned, and then, full articles were reviewed for those potentially eligible studies.

Two investigators independently evaluated the eligibility of studies for inclusion. Studies were eligible for inclusion if all the following criteria were fulfilled: 1) the study should be cohort or case-control, 2) the study should assess the association between allergic conditions and the risk of lymphoma, 3) the study should report the risk estimate as an odds ratio (OR), relative risk (RR), hazard ratio (HR), or standardized incidence ratio (SIR) with 95% confidence interval (CI). If data were reported in two or more studies, the most detailed one should be included.

Data extraction

Two authors independently performed data extraction with standardized forms, and any discrepancy was resolved

by discussion or by a third investigator. The following information was extracted from each study: first author and publication year, study design, country of origin, age and gender of the participants, numbers of participants and lymphoma cases, variables adjusted for in the analysis, and OR (RR or HR) estimates with 95% CIs for the risk of NHL/HL. For studies that reported both adjusted ratios and crude ratios, ratios reflecting the greatest degree of control for potential confounders were adopted in the meta-analysis.

Statistical analysis

The extent of heterogeneity across the included studies was evaluated by the chi-square test and I^2 test; $P \leq 0.05$ and $I^2 > 50\%$ were defined as significant heterogeneity.¹⁴ Study-specific effect estimates were pooled using a random-effects model if there was significant heterogeneity, otherwise a fixed-effects model was applied. We first assessed the association between history of any allergic condition and the risk of NHL and HL. Subgroup analyses for the risk of NHL and HL were then performed, stratifying by study design, type of allergic conditions, type of lymphoma, and country of origin. When heterogeneity across studies was significant, subgroup analyses were used to explore the source. Begg's funnel plots and Egger's linear regression method were used to evaluate the risk of publication bias. Two-sided P -values were calculated, and $P < 0.05$ was defined as significant for all the tests. All analyses were performed using the Stata software (Version 11.0; StataCorp, College Station, TX, USA).

Results

Description of the included studies

The systematic literature search of PubMed and Embase databases resulted in the identification of 2,875 articles, of which 81 were potentially eligible. Among these articles, 40 were excluded for the following reasons: did not report the association between allergic conditions and the risk of lymphoma ($n=24$), not original articles ($n=5$), insufficient data ($n=6$), and duplicate reports from the same study population ($n=5$). A total of 41 articles were finally included in the present meta-analysis,^{2,4,6–8,10–12,15–47} as shown in Figure 1.

The characteristics of the included studies are presented in [Table S1](#). Among the included studies, 37 studies reported the association between allergic conditions and the risk of NHL,^{2,4,6–8,10–12,16–18,20–23,25,27–47} while 12 studies investigated the risk of HL (several studies reported both NHL and HL).^{2,7,10,15,19,24,26,27,29,32,33,39}

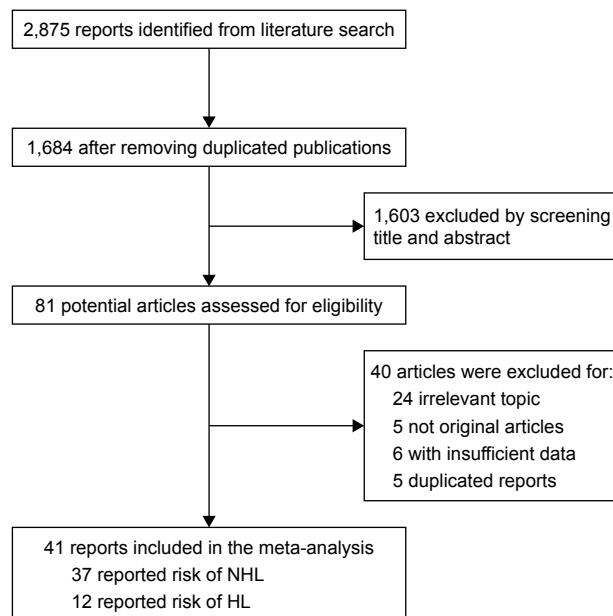


Figure 1 Flow diagram of the selection process.

Note: Several studies assessed the risk of both NHL and HL.

Abbreviations: NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma.

Association between allergic conditions and the risk of NHL

A total of 37 articles evaluated the association between allergic conditions and the risk of NHL. Among these studies, 24 were case-control studies including 35725 NHL patients (15 population based and 9 hospital based), while 13 were cohort studies (nine prospective and four retrospective) that comprised 4452 NHL patients. Two studies enrolled only female participants, and three studies included only males, while the other studies assessed the risk of NHL in both males and females. Most of the included studies were conducted in North America (USA and Canada) and European countries, while one study was performed in China and another in Australia.

We observed a significant difference between case-control studies and cohort studies. The pooled analysis of the 24 case-control studies resulted in an OR of 0.83 (95% CI 0.76–0.91) with significant heterogeneity ($I^2=66.7\%$, $P<0.001$), indicating an inverse association between history of any allergic condition and the risk of NHL (Figure 2A and Table 1). The reduction in the risk of NHL was found in population-based case-control studies (pooled OR =0.80, 95% CI 0.73–0.88) but not in hospital-based case-control studies (pooled OR =0.90, 95% CI 0.71–1.13) (Figure 2A and Table 1). There was no significant association between allergic conditions and the risk of NHL in cohort studies (pooled OR =1.18, 95% CI 0.98–1.42) ($I^2=88.7\%$, $P<0.001$)

(Figure 2B and Table 1). Null associations were found both in prospective cohorts (pooled OR=1.05, 95% CI 0.86–1.28) and in retrospective cohorts (pooled OR=1.54, 95% CI 0.91–2.58) (Figure 2B and Table 1). The pooled analysis of all the 37 included studies represented an OR of 0.93 (95% CI 0.84–1.04) ($I^2=87.8\%$, $P<0.001$) (Table 1).

Subgroup analyses were also conducted for specific allergic condition and the risk of NHL. The pooled results suggested that several allergic conditions, including asthma, hay fever, food allergy, and allergic rhinitis, were inversely associated with the risk of NHL (for asthma, pooled OR=0.94, 95% CI 0.88–0.99; for hay fever, pooled OR=0.72, 95% CI 0.64–0.82; for food allergy, pooled OR=0.71, 95% CI 0.51–0.98; for allergic rhinitis, pooled OR=0.80, 95% CI 0.73–0.88) (Figure 3 and Table 2). The pooled OR for the association between hives and the risk of NHL was 1.67 (95% CI 1.37–2.04), indicating that population with hives were at a higher risk of NHL (Table 2). We also assessed the association between allergic conditions and subtypes of NHL, as listed in Table 3. As the pooled results suggested, allergic conditions were inversely associated with both B-cell NHL (pooled OR=0.74, 95% CI 0.59–0.92) and T-cell NHL (pooled OR=0.70, 95% CI 0.52–0.94). Allergic conditions were indicated to be inversely associated with the risk of diffuse large B-cell lymphoma (DLBCL) (pooled OR=0.85, 95% CI 0.75–0.97), while there was no evidence that allergic conditions were associated with follicular lymphoma or marginal zone lymphoma. The results of subgroup analyses for geographic region are listed in Table 3. Subgroup analyses suggested that heterogeneity could be partially explained by the type of allergic conditions.

Association between allergic conditions and the risk of HL

Finally, 12 studies comprising 2750 HL cases were included in the analysis of the risk of HL in individuals with allergic conditions. Two of the included studies were designed as cohort study, and the others were case-control studies (seven were population based and three were hospital based). One study enrolled only males, while the other studies assessed the association between allergic conditions and the risk of HL in both males and females. All the included studies were conducted in North America and European countries.

There was no significant association in case-control studies (pooled OR=0.96, 95% CI 0.84–1.09) ($I^2=19.4\%$, $P=0.265$) (Figure 4 and Table 1). The results were consistent in population-based case-control studies (pooled OR=1.00, 95% CI 0.86–1.15) and hospital-based case-control studies

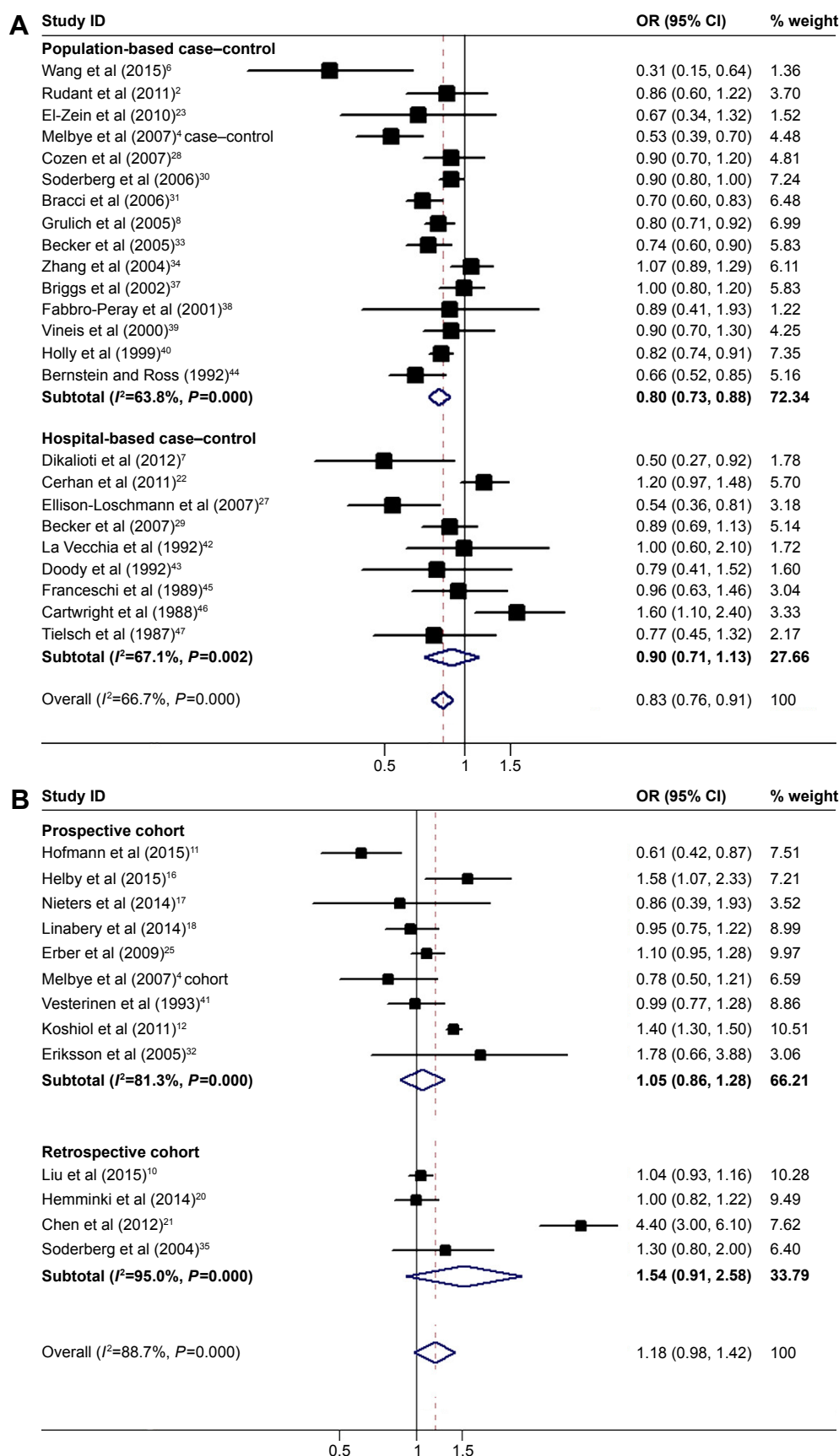


Figure 2 Association between history of allergic conditions and the risk of NHL.

Notes: (A) Pooled analysis of case-control studies. (B) Pooled analysis of cohort studies. Weights are from random-effects analysis.

Abbreviations: CI, confidence interval; NHL, non-Hodgkin's lymphoma; OR, odds ratio.

Table 1 Association between history of allergic conditions and the risk of NHL/HL according to study design

Factor	Number of studies	Pooled OR/RR (95% CI)	Heterogeneity	
			<i>I</i> ² (%)	<i>P</i> -value
NHL				
All case-control study	24	0.83 (0.76–0.91)	66.7	<0.001
Population based	15	0.80 (0.73–0.88)	63.8	<0.001
Hospital based	9	0.90 (0.71–1.13)	67.1	0.002
All cohort study	13	1.18 (0.98–1.42)	88.7	<0.001
Prospective	9	1.05 (0.86–1.28)	81.3	<0.001
Retrospective	4	1.54 (0.91–2.58)	95.0	<0.001
All case-control and cohort studies	37	0.93 (0.84–1.04)	87.8	<0.001
HL				
All case-control study	10	0.96 (0.84–1.09)	19.4	0.265
Population based	7	1.00 (0.86–1.15)	34.6	0.164
Hospital based	3	0.79 (0.58–1.08)	0	0.893
All cohort study	2	1.46 (0.63–3.38)	58.3	0.121
All case-control and cohort studies	12	0.99 (0.88–1.11)	26.5	0.184

Note: The OR/RR of individual study was pooled with a random-effects model if there was significant heterogeneity, otherwise a fixed-effects model was used.

Abbreviations: CI, confidence interval; HL, Hodgkin's lymphoma; NHL, non-HL; OR, odds ratio; RR, relative risk.

(pooled OR =0.79, 95% CI 0.58–1.08) (Figure 4 and Table 1). The pooled OR of cohort studies was 1.46 (95% CI 0.63–3.38) ($I^2=58.3\%$, $P=0.121$). The pooled analysis of all the 12 case-control and cohort studies represented an OR of 0.99 (95% CI 0.88–1.11) ($I^2=26.5\%$, $P=0.184$), indicating that history of allergic conditions was not significantly associated with the risk of HL.

Stratifying by the type of allergic conditions, an inverse association with the risk of HL was indicated for hay fever (pooled OR =0.71, 95% CI 0.54–0.93) and food allergy (pooled OR =0.54, 95% CI 0.33–0.88) (Table 4). We found no significant association for asthma and eczema, as listed in Table 4. Results of subgroup analyses according to geographic region are listed in Table 4.

Publication bias

Begg's funnel plot and Egger's tests suggested no publication bias in the current study.

Discussion

Epidemiological studies have suggested possible relationships between allergic conditions and kinds of malignant diseases, while results of those studies were inconsistent. Previous meta-analyses of case-control studies have confirmed a reduction in the risk of NHL in people with several specific allergic conditions, including hay fever and asthma.^{9,48} However, these reports did not include cohort studies, which mostly report a null association. This

large-scale meta-analysis included 37 articles on the risk of NHL and a total of 12 studies evaluating the risk of HL. As the pooled studies suggested, history of any allergic condition was significantly associated with the risk of NHL in case-control studies (pooled OR =0.83, 95% CI 0.76–0.91) but not in cohort studies (pooled OR =1.18, 95% CI 0.98–1.42). Stratifying by different allergic conditions, we observed an inverse association between hay fever, food allergy, and allergic rhinitis and the risk of NHL, while hives were positively associated with the risk of NHL. No significant association between allergic conditions and the risk of HL was suggested in case-control studies (pooled OR =0.96, 95% CI 0.84–1.09) or cohort studies (pooled OR =1.46, 95% CI 0.63–3.38). However, a reduction in the risk of HL was suggested in individuals with hay fever and food allergy.

In the analysis of the relationship between allergic conditions and the risk of NHL, a significant difference was observed between cohort studies and case-control studies. Though the number of NHL cases in some of the cohort studies was limited, a total of 13 cohort studies enrolling 4452 NHL cases were included in the current analysis, which increased the power to assess the association. Some of the included cohort studies were retrospective and based on registers using national data as external comparison, while studies adopting internal controls might estimate the risk more accurately.⁴⁹ However, null association was suggested in both prospective cohort studies (pooled OR =1.05, 95% CI 0.86–1.28) and retrospective register-based cohort studies (pooled OR =1.54, 95% CI 0.91–2.58). The inconsistency between cohort studies and case-control studies might be partially due to the reliance on self-report of allergic conditions, which is prone to recall bias and less objective.¹² Moreover, patients with NHL might be associated with a reduced immunoglobulin reactivity; thus, these NHL cases might have a reduced immune response and allergic responses.^{4,50} The negative association between allergic conditions and the risk of NHL might be explained by reverse causality. A pooled analysis of 13 case-control studies assessed the association between atopic diseases and the risk of NHL, suggesting a modest reduction in the risk of NHL in atopic disease.⁹ Another pooled analysis of 20 case-control studies from the International Lymphoma Epidemiology Consortium (InterLymph) indicated that some allergic conditions, such as asthma and hay fever, were negatively associated with the risk of NHL.⁴⁸ However, no pooled analysis of cohort studies has been conducted. Cohort studies are more adept at evaluating causal relationships, and evidence from cohort studies is usually considered stronger than case-control studies. Thus, more

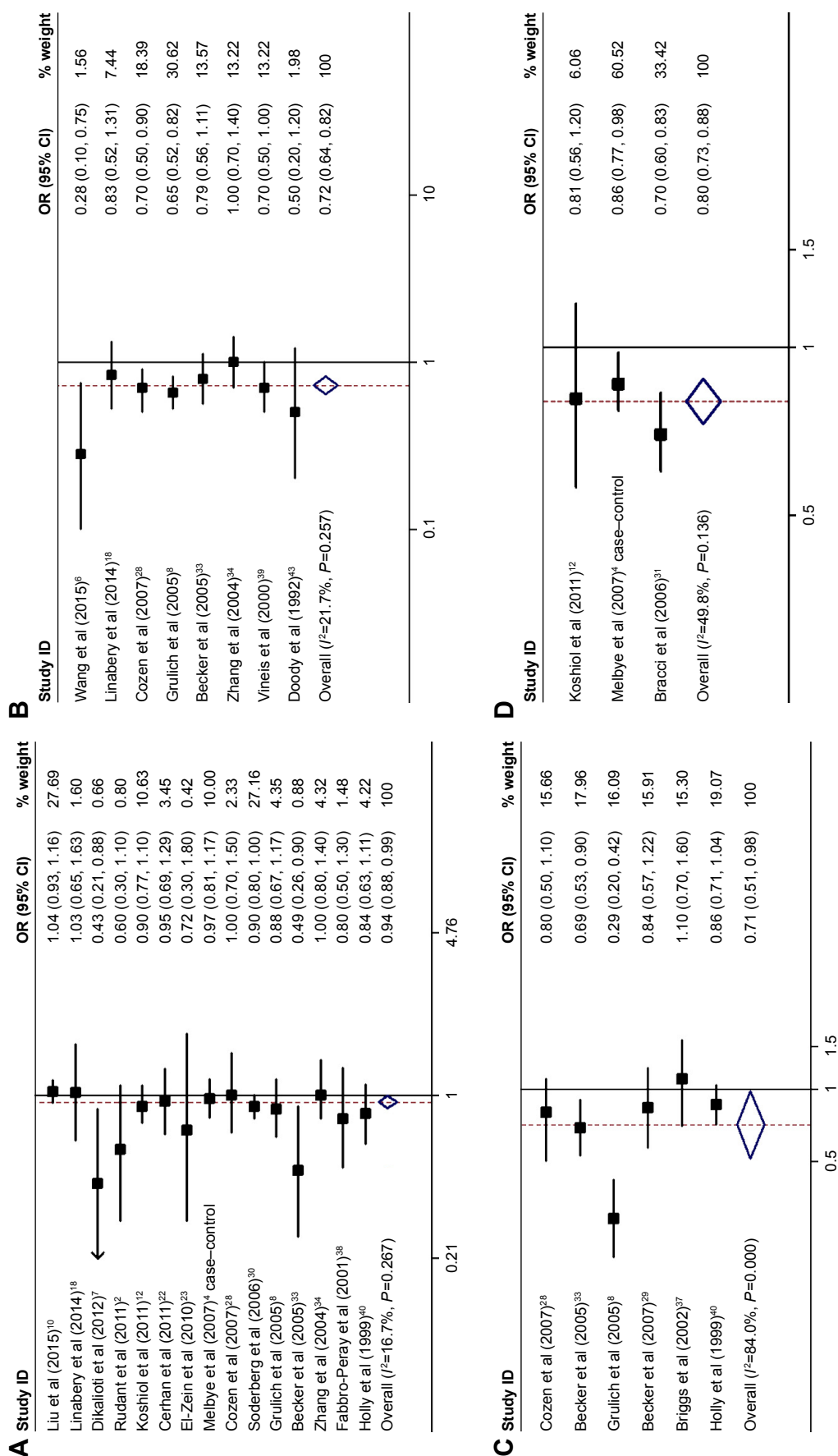


Figure 3 Association between several specific allergic conditions and the risk of NHL.

Notes: Weights are from random-effects analysis. **(A)** Pooled analysis of studies on asthma. **(B)** Pooled analysis of studies on hay fever. **(C)** Pooled analysis of studies on food allergy. **(D)** Pooled analysis of studies on allergic rhinitis.

Abbreviations: CI, confidence interval; NHL, non-Hodgkin's lymphoma; OR, odds ratio.

Table 2 Association between history of specific allergic conditions and the risk of NHL

Allergic conditions	Number of studies	Pooled OR/RR (95% CI)	Heterogeneity	
			I ² (%)	P-value
Asthma	15	0.94 (0.88–0.99)	16.7	0.267
Hay fever	8	0.72 (0.64–0.82)	21.7	0.257
Food allergy	6	0.71 (0.51–0.98)	84.0	<0.001
Allergic rhinitis	3	0.80 (0.73–0.88)	49.8	0.136
Dust allergy	3	0.85 (0.73–1.00)	0	0.614
Eczema	15	0.99 (0.81–1.21)	82.8	<0.001
Hives	4	1.67 (1.37–2.04)	48.2	0.122
IgE level	4	0.86 (0.49–1.49)	84.5	<0.001
Insect allergy	2	0.94 (0.64–1.37)	0	0.682
Animal allergy	3	0.83 (0.58–1.17)	58.5	0.088
Medicine allergy	5	1.06 (0.89–1.25)	64.6	0.023

Note: The OR/RR of individual study was pooled with a random-effects model if there was significant heterogeneity, otherwise a fixed-effects model was used.

Abbreviations: CI, confidence interval; NHL, non-Hodgkin's lymphoma; OR, odds ratio; RR, relative risk.

cohort studies, especially prospective cohort studies, are warranted to clarify this question.

There has long been interest in the relationship between allergic conditions and the risk of malignancy. Previous studies have indicated that the association between allergic conditions and the risk of cancer was different according to cancer site and types of allergic conditions. A meta-analysis of 10 case-control studies suggested a reduction in the risk of pancreatic cancer in population with allergic conditions.⁵¹ Further analyses demonstrated that hay fever and allergy to animals, but not asthma or other allergies, reduced the risk of pancreatic cancer.⁵¹ Previous meta-analysis has also indicated an association between allergic conditions and

Table 3 Association between history of allergic conditions and the risk of NHL according to the type of NHL and geographic region

Factor	Number of studies	Pooled OR/RR (95% CI)	Heterogeneity	
			I ² (%)	P-value
NHL type				
B-cell NHL	8	0.74 (0.59–0.92)	73.3	<0.001
T-cell NHL	3	0.70 (0.52–0.94)	0	0.520
DLBCL	8	0.85 (0.75–0.97)	0	0.791
FL	9	0.94 (0.77–1.15)	51.1	0.037
MZL	2	0.56 (0.27–1.16)	29.5	0.234
LPL	2	0.38 (0.14–1.04)	0	0.419
Geographic region				
USA and Canada	15	0.87 (0.74–1.03)	90.6	<0.001
Europe	20	0.91 (0.81–1.02)	65.3	<0.001
Others	2	1.86 (0.35–9.89)	98.7	<0.001

Note: The OR/RR of individual study was pooled with a random-effects model if there was significant heterogeneity, otherwise a fixed-effects model was used.

Abbreviations: CI, confidence interval; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; MZL, marginal zone lymphoma; NHL, non-Hodgkin's lymphoma; OR, odds ratio; RR, relative risk.

the risk of head and neck cancers.⁵² In the present analysis, we observed a negative association with the risk of NHL for several allergic conditions, including hay fever, asthma, food allergy, and allergic rhinitis. An increased risk of NHL for hives was also suggested. However, the associations were mainly found in case-control studies but not in cohort studies. Few studies have been conducted to explore the risk of NHL in relation to allergic conditions according to race/ethnicity. Erber et al²⁵ investigated the association between common immune-related factors and the risk of NHL, suggesting that the association was limited to certain ethnic groups. Another study also supported a role for race-related differences in genes regulating immune/inflammatory response.¹² Our pooled analysis also demonstrated that hay fever (pooled OR = 0.71, 95% CI 0.54–0.93) and food allergy (pooled OR = 0.54, 95% CI 0.33–0.88) were significantly associated with the risk of HL, though null association was observed for any allergic condition.

There has been plenty of research investigating the role of allergic conditions in malignancy, while the mechanisms remain unclear. According to the “cancer immunosurveillance hypothesis”, people with allergic conditions may have an activated response of immune system, which promotes the ability to eradicate premalignant cells and, thus, reduced the risk of lymphomas.⁵³ Besides, Immunoglobulin E (IgE) can bind to cell surface IgE receptors, CD23 and FcεRI, which engage several types of antitumor effector cells.⁵⁴ Moreover, other blood cells associated with allergic diseases, such as eosinophils and mast cells, have been indicated to play a role in eliminating tumor cells.^{54,55} In contrast, for individuals with allergic conditions, antigenic stimulation may lead to a chronic inflammation and stimulate cell growth, which may increase the risk of malignancies.⁵ The mechanisms of allergic conditions on NHL and HL are complicated and unclear; thus, further studies are warranted to explore this issue.

One of the advantages of the current study is the large sample size, which increased the statistical power to evaluate the association between allergic conditions and the risk of NHL. However, there are also some limitations in this study. First, though most of the studies involved in this analysis were adjusted for other known risk factors of NHL or HL, the confounders might be different across the included studies and it is possible that the control of confounders is inadequate. This may lead to exaggeration or underestimation in the risk estimates in the current study. Second, most of the included studies used self-report for the diagnosis of allergic conditions, which might not be accurate enough. In addition, few studies reported the risk of lymphoma in

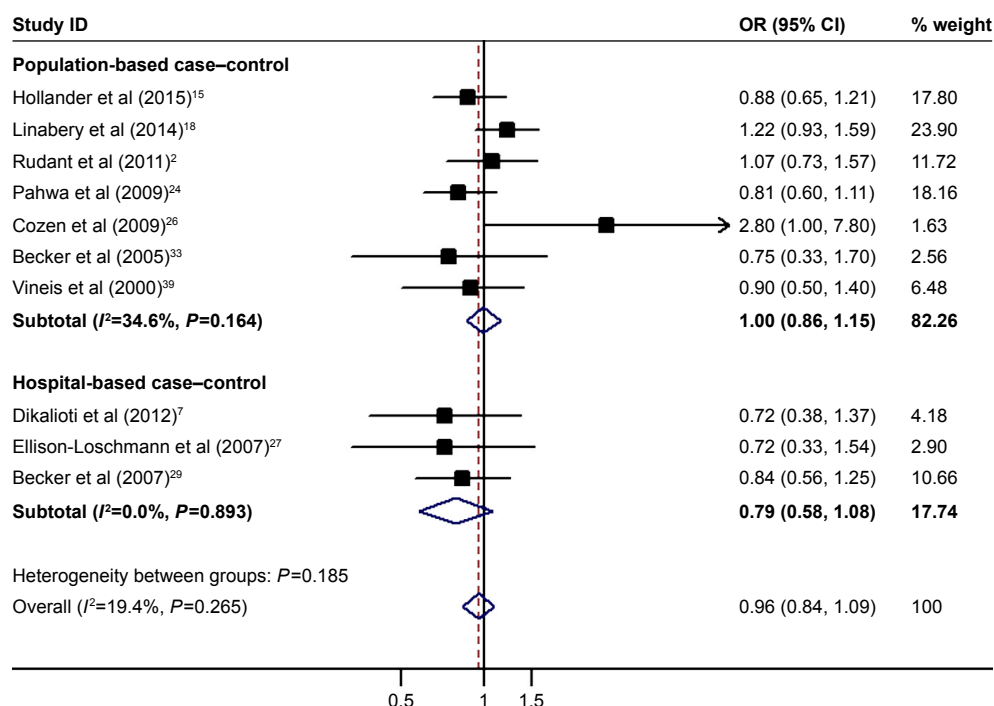


Figure 4 Association between history of allergic conditions and the risk of HL.
Abbreviations: CI, confidence interval; HL, Hodgkin's lymphoma; OR, odds ratio.

multiple allergic conditions, which may need further evaluation. Finally, most of the included studies were conducted in Europe and North America and the participants enrolled were mainly Caucasian population. Thus, the pooled results should be interpreted with caution for other population.

Conclusion

History of any allergic condition was not significantly associated with the risk of NHL or HL. Several specific allergic conditions, including asthma, hay fever, food allergy, and

allergic rhinitis, might be associated with a reduced risk of NHL, while individuals with hay fever or food allergy may have a reduced risk of HL. Further large-scale prospective cohort studies are warranted to clarify the association between history of allergic diseases and the risk of lymphoma.

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Disclosure

The authors report no conflicts of interest in this work.

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Table 4 Association between history of allergic conditions and the risk of HL according to the type of allergic conditions and geographic region

Factor	Number of studies	Pooled OR/RR (95% CI)	Heterogeneity	
			I ² (%)	P-value
Allergic conditions				
Hay fever	3	0.71 (0.54–0.93)	57.5	0.095
Food allergy	2	0.54 (0.33–0.88)	0	0.916
Asthma	7	0.99 (0.83–1.18)	0	0.693
Eczema	4	1.21 (0.80–1.83)	56.1	0.077
Geographic region				
USA and Canada	3	1.16 (0.73–1.83)	73.1	0.024
Europe	9	0.95 (0.82–1.10)	0	0.563

Note: The OR/RR of individual study was pooled with a random-effects model if there was significant heterogeneity, otherwise a fixed-effects model was used.

Abbreviations: CI, confidence interval; HL, Hodgkin's lymphoma; OR, odds ratio; RR, relative risk.

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