



Environmental risk factors for non-Hodgkin's lymphoma: umbrella review and comparison of meta-analyses of summary and individual participant data

Xiaoting Shi ¹, Haoran Zhuo,¹ Yuxuan Du,² Kate Nyhan ^{1,3}, John Ioannidis ⁴, Joshua D Wallach ¹

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For numbered affiliations see end of article.

Correspondence to: Dr Joshua D Wallach, Department of Environmental Health Sciences, Yale School of Public Health, New Haven, Connecticut, USA; joshua.wallach@yale.edu

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ABSTRACT

OBJECTIVES To summarise the range, strength, and validity of reported associations between environmental risk factors and non-Hodgkin's lymphoma, and to evaluate the concordance between associations reported in meta-analyses of summary level data and meta-analyses of individual participant data.

DESIGN Umbrella review and comparison of meta-analyses of summary and individual participant level data.

DATA SOURCES Medline, Embase, Scopus, Web of Science Core Collection, Cochrane Library, and Epistemonikos, from inception to 23 July 2021.

ELIGIBILITY CRITERIA FOR SELECTING STUDIES

English language meta-analyses of summary level data and of individual participant data evaluating associations between environmental risk factors and incident non-Hodgkin's lymphoma (overall and subtypes). **DATA EXTRACTION AND SYNTHESIS** Summary effect estimates from meta-analyses of summary level data comparing ever versus never exposure that were adjusted for the largest number of potential confounders were re-estimated using a random effects model and classified as presenting evidence that was non-significant, weak ($P < 0.05$), suggestive ($P < 0.001$ and > 1000 cases), highly suggestive ($P < 0.000001$ and > 1000 cases), largest study reporting a significant association, or convincing ($P < 0.000001$, > 1000 cases, largest study reporting a significant association, $I^2 < 50\%$, 95% prediction interval excluding the null value, and no evidence of small study effects and excess significance bias) evidence. When the same exposures, exposure contrast levels, and outcomes were evaluated in meta-analyses of summary level data and meta-analyses of individual participant data from the International Lymphoma Epidemiology (InterLymph) Consortium, concordance in terms of direction, level of significance, and overlap of 95% confidence intervals was examined. Methodological quality of the meta-analyses of summary level data was assessed by the AMSTAR 2 tool.

RESULTS We identified 85 meta-analyses of summary level data reporting 257 associations for 134 unique environmental risk factors and 10 subtypes of non-Hodgkin's lymphoma nearly all (79, 93%) were classified as having critically low quality. Most associations (225, 88%) presented either non-significant or weak evidence. The 11 (4%) associations presenting highly suggestive evidence were primarily for autoimmune or infectious disease related risk factors. Only one association, between history of coeliac disease and risk of non-Hodgkin's lymphoma, presented convincing evidence. Of 40 associations reported in meta-analyses of summary level data that were also evaluated in InterLymph meta-analyses of individual participant data, 22 (55%) pairs were in the same direction, had the same level of statistical significance, and had overlapping 95% confidence intervals; 28 (70%) pairs had summary effect sizes from the meta-analyses of individual participant data that were more conservative.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Observational studies have suggested that environmental risk factors, including clinical, occupational, and lifestyle exposures, might be associated with the risk of developing non-Hodgkin's lymphoma
- ⇒ With many observational studies evaluating the impact of environmental risk factors on non-Hodgkin's lymphoma, dozens of systematic reviews and meta-analyses of summary and individual participant level data have focused on synthesising evidence and identifying potential risk factors
- ⇒ Little is known about the range, strength, and validity of associations between environmental risk factors and non-Hodgkin's lymphoma reported in meta-analyses; or the concordance between meta-analyses of summary level data and meta-analyses of individual participant data evaluating the same associations

WHAT THIS STUDY ADDS

- ⇒ This umbrella review suggests that although a wide range of environmental risk factors for non-Hodgkin's lymphoma have been evaluated in meta-analyses, most meta-analyses of summary level data are low quality and present either non-significant or weak associations
- ⇒ Overall, only half of the associations evaluated in both meta-analyses of summary level data and of individual participant data were in the same direction, had the same level of statistical significance, and had overlapping 95% confidence intervals
- ⇒ Several associations, primarily those for autoimmune and infectious disease related risk factors, presented either highly suggestive or convincing evidence.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

- ⇒ This umbrella review highlights the need for improving not only primary studies but also evidence synthesis in evaluations of environmental risk factors and non-Hodgkin's lymphoma
- ⇒ Umbrella reviews should critically evaluate how their findings relate to existing meta-analyses of individual participant data, focusing on the impact of different methods, populations, and other characteristics

CONCLUSION This umbrella review suggests evidence of many meta-analyses of summary level data reporting weak associations between environmental risk factors and non-Hodgkin's lymphoma. Improvements to primary studies as well as evidence synthesis in evaluations of environmental risk factors and non-Hodgkin's lymphoma are needed.

REVIEW REGISTRATION NUMBER PROSPERO CRD42020178010.

Introduction

Non-Hodgkin's lymphoma, a lymphoid cancer that originates in white blood cells called lymphocytes, is the ninth leading cause of cancer death among both men and women.¹ The disorder accounts for nearly 90% of all lymphomas² and is the most common haematological malignancy in the world.³ Although non-Hodgkin's lymphoma can be broadly categorised into two major groups (ie, B cell, or T cell or natural killer cell lymphomas), it represents a diverse group of malignant disorders with dozens of subtypes.⁴ Evidence suggests that non-Hodgkin's lymphoma is more common among older adults, men, and people with a first degree relative with the disorder.^{5 6} However, despite substantial efforts to identify risk factors over the past few decades, the exact causes of non-Hodgkin's lymphoma are unknown.⁵

Epidemiological studies have suggested that environmental risk factors, including physical, natural, chemical, clinical, biological, psychosocial, occupational, and lifestyle factors, are associated with the risk of developing non-Hodgkin's lymphoma. In particular, several prominent risk factors proposed in the literature include viruses (eg, Epstein-Barr virus infection),⁷ autoimmune diseases (eg, Sjogren's syndrome, coeliac disease, and rheumatoid arthritis),⁸⁻¹⁰ and immune dysregulation (ie, patients with a history of organ transplantation, acquired immunodeficiency syndromes (HIV/AIDS), or immunosuppressive medication treatment).^{5 6 11} However, given that these exposures and conditions are relatively rare,¹¹ a broad range of additional environmental risk factors, including exposure to insecticides,¹² red and processed meat consumption,¹³ and hair dye,¹⁴ have been evaluated and proposed as potential risk factors.

As a result of the large number of observational studies evaluating the impact of environmental risk factors on non-Hodgkin's lymphoma, dozens of systematic reviews and meta-analyses of summary level data have focused on synthesising evidence and identifying the most promising risk factors. Moreover, the International Lymphoma Epidemiology (InterLymph) Consortium,¹⁵ a group of investigators who pool data from their completed or ongoing case-control studies of non-Hodgkin's

lymphoma, have published multiple meta-analyses of individual participant data evaluating associations between various environmental risk factors and the disorder.^{8 16 17} Although these meta-analyses of individual participant data contain thousands of non-Hodgkin's lymphoma cases and are strengthened by their ability to use raw data that are harmonised across multiple studies, they do not include evidence from case-control and cohort studies conducted by investigators outside of the InterLymph Consortium. Therefore, meta-analyses of summary level data and those of individual participant data evaluating the same associations between environmental risk factors and non-Hodgkin's lymphoma can sometimes lead to discordant results and conclusions.

To provide an overview of the range, strength, and validity of reported associations between environmental risk factors and non-Hodgkin's lymphoma, we conducted an umbrella review of the evidence across published systematic reviews and meta-analyses. In addition to summarising the results, determining hints of biases, and assessing the quality of reviews, we evaluated the consistency between all associations reported in both meta-analyses of summary level data and InterLymph meta-analyses of individual participant data.

Methods

We conducted an umbrella review on the reported associations between environmental risk factors and the risk of non-Hodgkin's lymphoma. Umbrella reviews are used to systematically identify and evaluate evidence reported in published systematic reviews and meta-analyses.^{18 19} Our study protocol was pre-registered on the international prospective register of systematic reviews (CRD42020178010) and posted on Open Science Framework (<https://osf.io/6g2ev/>).

Database searches

Working with an experienced medical librarian (KN), we developed and performed a comprehensive search of multiple databases: Medline (Ovid), Embase (Ovid), Scopus, Web of Science Core Collection (as licensed at Yale University), Cochrane Library, and Epistemonikos from inception to 24 July 2020 (online supplemental eTable 1 in supplemental file 1). In each database, we used three concepts: non-Hodgkin's lymphoma, risk factors, and the study designs of interest (meta-analyses, systematic reviews, and pooled analyses). The search strategy for non-Hodgkin's lymphoma was based on the search strategy used in a published review.²⁰ The study design search strategy used elements from a published search filter.²¹ We used database limits to exclude conference papers and meeting abstracts. No language limits were used. Duplicate records were removed in EndNote, the Yale Reference

Deduplicator, and Covidence. No citation chaining was conducted.

On 24 July 2020, we ran searches in each database and identified 14 753 references. After removing duplications in EndNote and Covidence, 8025 unique records were uploaded for screening. On 23 July 2021, all searches were rerun and duplicates removed, and 969 additional unique records were added to Covidence for manual screening. In total, our search retrieved 8994 unique records across all databases.

Eligibility criteria

We included English language systematic reviews, meta-analyses of summary level data (ie, those using effect estimates reported in individual studies), and meta-analyses of individual participant data of observational studies evaluating associations between environmental risk factors and incident non-Hodgkin's lymphoma (overall or any subtypes, online supplemental eTable 2 in supplemental file 1). We considered all non-genetic factors, including physical, natural, chemical, biological, psychosocial, occupational, and lifestyle factors that can affect a person's health, as environmental risk factors.²² Systematic reviews and meta-analyses were excluded if they primarily focused on genetic risk factors; evaluated risk factors for patients' treatment, relapse, remission, or prognosis; or examined non-Hodgkin's lymphoma as a risk factor for other diseases (online supplemental eText 1 in supplemental file 1). Two reviewers (XS and HZ) independently screened the titles and abstracts and then full text versions of potentially eligible articles. Any disagreements or uncertainties were discussed with a third reviewer (JDW).

Data extraction

Data extraction was performed independently by two reviewers (XS and HZ), and a third reviewer (JDW) arbitrated all potential discrepancies. For each systematic review and meta-analysis, we recorded the first author, year of publication, article title, journal of publication, study design, population, examined exposures and their definitions, and examined outcomes and their definition (ie, non-Hodgkin's lymphoma or subtypes). For all meta-analyses of summary level data, we identified each unique exposure-outcome association and recorded the number of studies included, total sample size, number of cases, and study specific adjusted relative risk estimates (eg, relative risks, hazard ratios, or odds ratios) and corresponding 95% confidence intervals. For studies that considered multiple exposure contrast levels, control groups, or confounders, we prioritised the effect estimates comparing ever versus never exposure that were adjusted for the largest number of potential confounders. When comparisons between ever versus never exposures were not reported, we recorded the effect estimates

comparing the highest versus lowest levels of exposures. When multiple meta-analyses of summary level data were identified for the same environmental risk factor, we selected the effect estimates that were based on the largest number of component studies.

For systematic reviews with unique associations that were not investigated in meta-analyses of summary level data, we recorded the number of studies identified, the reasons why meta-analyses were not performed, and the main conclusions. Lastly, for all meta-analyses of individual participant data, one author (JDW) identified the exposures, non-Hodgkin's lymphoma subtypes, and number of non-Hodgkin's lymphoma cases for all nominally significant ($P < 0.05$) associations, and any associations that were also evaluated in meta-analyses of summary level data.

Quality assessment

Four reviewers (XS, HZ, YD, and JDW) evaluated the quality of all meta-analyses of summary level data using A MeaSurement Tool to Assess Systematic Reviews (AMSTAR) 2.²³ Any discrepancies were discussed and resolved by consensus. Based on the suggested rating scheme,²³ the overall confidence in the results of the meta-analyses of summary level data were classified as high, moderate, low, or critically low. We did not examine the quality of meta-analyses of individual participant data.

Statistical analysis

Firstly, we used a random effects model, which allows for unexplained heterogeneity between studies on the effect of interest, and estimated the variance between studies using the DerSimonian and Laird estimator. When summary effect estimates were reported without a corresponding P value, we used the 95% confidence intervals to calculate the P value using a previously described method.²⁴ Next, we categorised the strength of the reported associations across five levels (table 1), following previously established methodology.^{25–28} All associations with $P > 0.05$ were classified as non-significant. Associations with $P < 0.05$ and fewer than 1000 cases were classified as weak. Associations with $P < 0.001$ and at least 1000 cases were classified as suggestive. For associations with $P < 0.000001$, at least 1000 cases, and $P < 0.05$ for the largest component study, we sequentially evaluated 95% prediction intervals, presence of small study effects (Egger regression asymmetry test),²⁹ and evidence of excess significance using the Ioannidis test.³⁰ Prediction intervals provide a potential range of the true effect and incorporate the uncertainty of whether the observed effect will arise in future studies.^{31 32} $P < 0.1$ for Egger's test suggests the presence of small study effects

Table 1 | Grading criteria for evidence categories from meta-analyses of summary level data included in review. Evidence relates to the strength of associations between environmental risk factors and risk of non-Hodgkin's lymphoma

Strength of association	Description*
Convincing	Highly significant association ($P < 0.000001$) At least 1000 cases of non-Hodgkin's lymphoma Low or moderate proportion of total variability due to variability between studies ($I^2 < 50\%$) 95% prediction interval excluding the null value Largest study reporting a nominally significant result ($P < 0.05$) No evidence of small study effects No evidence of excess significance bias
Highly suggestive	Highly significant association ($P < 0.000001$) At least 1000 non-Hodgkin's lymphoma cases Largest study reporting a nominally significant result ($P < 0.05$)
Suggestive	At least 1000 non-Hodgkin's lymphoma cases Significant association ($P < 0.001$)
Weak	Nominally significant association ($P < 0.05$)
Non-significant	Non-significant associations ($P > 0.05$)

*P value for the association from a random effects model.

(ie, small studies are more prone to report larger or more significant results while larger studies tend to report more conservative results). The Ioannidis test estimates whether the observed number of studies with nominally significant ($P < 0.05$) results in a meta-analysis differs from the expected number of studies with nominally significant studies.³⁰ Associations with 95% prediction intervals including the null, significant Egger's test ($P < 0.1$), or evidence of excess significance were classified as highly suggestive. Associations with 95% prediction intervals excluding the null, non-significant Egger's test ($P > 0.1$), and no evidence of excess significance were classified as convincing. We did the statistical analysis using the metagen package in R version 4.1.0. (online supplemental eTable 3 in supplemental file 1).

Concordance between meta-analyses of summary level data and InterLymph meta-analyses of individual participant data

When the same exposures, exposure contrast levels, and non-Hodgkin's lymphoma subtypes were examined in meta-analyses of summary level data and InterLymph meta-analyses of individual participant data, two authors (XS and JDW) determined whether the effect estimates were in the same direction, had overlapping 95% confidence intervals, or had the same level of significance ($P < 0.05$ or $P \geq 0.05$). Associations with all three criteria fulfilled were classified as fully concordant. Lastly, we determined how often meta-analyses of summary level data included at least a third of the same component studies as the InterLymph meta-analyses of individual participant data.

Patient and public involvement

We did not involve patients or members of the public when designing the question and study, interpreting the results, or drafting the manuscript; they were not involved in the dissemination plans of this research.

Results

Literature search

Among 16 438 records identified through the literature search, 7444 were excluded as duplicates, leaving 8994 titles and abstracts for initial screening (figure 1). We excluded 7970 records based on the title and abstract, and screened 1024 at the full text stage for inclusion. After excluding 904 records at the full text stage (online supplemental eTable 1 in supplemental file 2), our searches identified 85 meta-analyses of summary level data evaluating 134 unique environmental risk factors and eight systematic reviews evaluating eight unique risk factors (online supplemental eFigure 1 and eText 2 in supplemental file 1 and online supplemental eTable 2 in supplemental file 2). In addition, we identified 27 meta-analyses of individual participant data (online supplemental eTable 2 in online supplemental file 2), of which 24 (89%) were conducted by the InterLymph Consortium. More than one meta-analysis of summary level data was identified for 44 (44/134, 33%) risk factors (online supplemental eTable 4 in supplemental file 1). Among the meta-analyses of summary level data selected based on the largest number of component studies, about half were also the most recently published (25/44, 57%).

Methodological quality

The vast majority of the 85 meta-analyses of summary level data had overall confidence ratings of low (three, 4%) or critically low (79, 93%) according

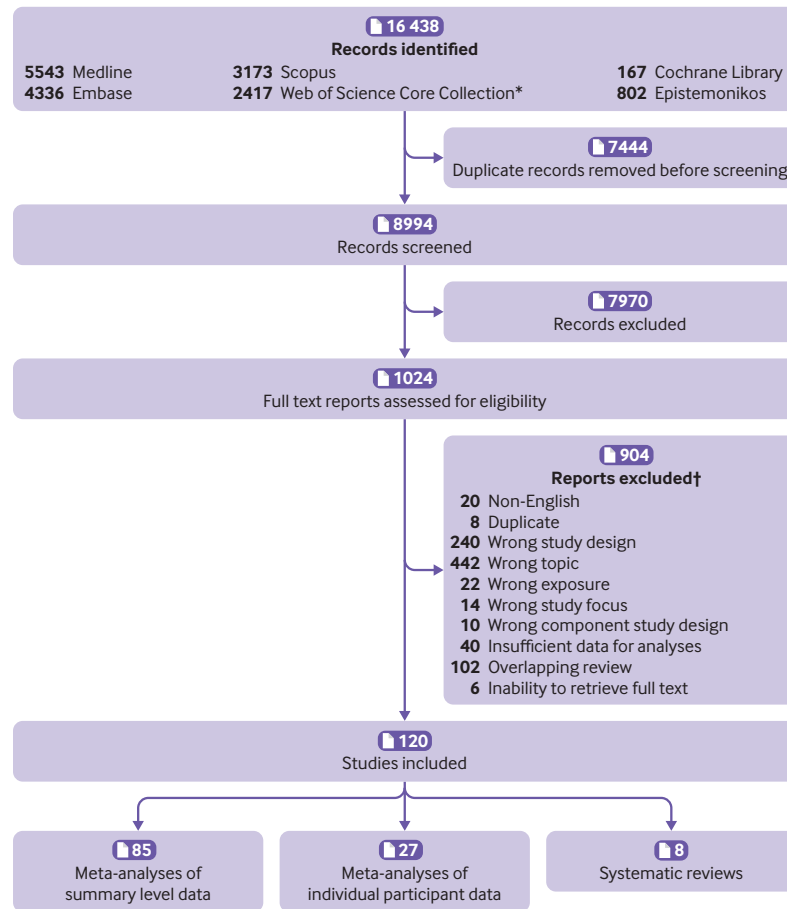


Figure 1 | Study selection flowchart. *Web of Science Core Collection as licensed at Yale; indexes are Science Citation Index Expanded (SCI-EXPANDED), Social Science Citation Index (SSCI), Arts and Humanities Citation Index (A&HCI), Conference Proceedings Citation Index - Science (CPCI-S), Conference Proceedings Citation Index - Social Science & Humanities (CPCI-SSH), Book Citation Index - Science (BKCI-S), Book Citation Index - Social Science & Humanities (BKCI-SSH), Emerging Sources Citation Index (ESCI), Current Chemical Reactions (CCR EXPANDED), and Inded Copernicus (IC) (timespan=all years). Wrong study design=the examined study was not a systematic review, meta-analysis of summary or individual participant data; wrong topic=the examined review did not examine non-Hodgkin's lymphoma or its subtypes as an outcome, the study did not examine the impact of an environmental exposure on the risk of non-Hodgkin's lymphoma development; wrong exposure=the examined risk factor does not meet the definition of environmental risk factor in the present study; wrong study focus=the review did not examine the impact of an exposure on the risk of developing non-Hodgkin's lymphoma; wrong component study design=the review did not synthesise observational study data; insufficient data for analyses=the review included fewer than three component studies; overlapping review=a larger review was identified for the same association

to the AMSTAR 2 tool. Two (2%) meta-analyses had moderate ratings of overall confidence in the results.^{33 34} Only one (1%) meta-analysis, evaluating the association between tuberculosis and risk of non-Hodgkin's lymphoma, had an overall confidence rating of high (online supplemental eTable 3 in supplemental file 2).³⁵ The most common unfulfilled critical domains of the AMSTAR 2 tool were incomplete justification of excluded studies (74, 87%) and missing or no information about preregistered protocols (72, 85%).

Meta-analyses of summary level data

Among the 257 associations reported in the meta-analyses of summary level data, 124 and 133 evaluated the impact of environmental risk factors on the risk of non-Hodgkin's lymphoma overall and

non-Hodgkin's lymphoma subtypes, respectively. Non-Hodgkin's lymphoma subtypes included follicular lymphoma (43, 17%); diffuse large B cell lymphoma (35, 14%); chronic lymphocytic leukaemia or small lymphocytic lymphoma (31, 12%); T cell lymphoma (12, 5%); B cell lymphoma (four, 2%); marginal zone lymphoma (two, 1%); endemic Burkitt lymphoma (one, 0.4%); Burkitt lymphoma (one, 0.4%); and primary cutaneous lymphoma (one, 0.4%). The most common exposure categories were dietary factors (90, 35%), medical histories and comorbidities (54, 21%), chemicals and pesticides (42, 16%), lifestyle factors (29, 11%), drugs, vaccinations, and medical procedures (30, 12%), and occupational (12, 5%). The median number of component studies per meta-analysis of summary level data was 5 (interquartile range 4-10).

The median number of non-Hodgkin's lymphoma cases, among the 64 (75%) meta-analyses reporting this information, was 1533 (interquartile range 482-5872).

Credibility criteria

After re-estimating the 257 associations using a random effects DerSimonian and Laird estimator and applying the credibility criteria, 145 (56%) were classified as presenting non-significant evidence (online supplemental eTable 4 in supplemental file 2). Eighty (31%) nominally significant ($P < 0.05$) associations were classified as presenting weak evidence; and 20 (8%) significant associations ($P < 0.001$), based on analyses with at least 1000 non-Hodgkin's lymphoma cases, were classified as presenting suggestive evidence. Only 12 (5%) associations were classified as presenting highly suggestive or convincing evidence, with a P value less than 0.000001, at least 1000 cases, and a P value less than 0.05 for the largest component study. The 11 highly suggestive associations were between a history of renal transplantation, rheumatoid arthritis, primary Sjogren's syndrome, systemic lupus erythematosus, tuberculosis, hepatitis B virus, hepatitis C virus, and teaching as an occupation and the risk of non-Hodgkin's lymphoma; as well as between coeliac disease and risk of T cell lymphoma, hepatitis B virus and B cell lymphoma, and hepatitis C virus and diffuse large B cell lymphoma and the risk of non-Hodgkin's lymphoma (table 2).

One association between history of coeliac disease and risk of non-Hodgkin's lymphoma (odds ratio 2.61, 95% confidence interval 2.04 to 3.33; 110 245 non-Hodgkin's lymphoma cases from eight individual studies) was classified as presenting convincing evidence. Although the association had a P value of less than 0.000001, at least 1000 cases, a nominally significant result for the largest component study, low or moderate proportion of total variability due to variability between studies ($I^2 < 50\%$), a 95% prediction interval excluding the null, and no evidence of small study effects, we were unable to conduct the Ioannidis test owing to the incomplete information reported about the component studies. Across all the 112 nominally significant associations, 63 (56%) had relative risk values between 0.67 and 1.50.

Systematic reviews

We identified eight systematic reviews without quantitative synthesis with eight unique associations that were not investigated by meta-analyses of summary level data (online supplemental eText 2 in supplemental file 1).

Meta-analyses of individual participant data

We identified 27 meta-analyses of individual participant data, of which 24 were from the InterLymph Consortium. The 24 InterLymph meta-analyses of individual participant data reported 715 nominally

significant ($P < 0.05$) associations. Of these, 116 and 21 associations were based on analyses with at least 1000 non-Hodgkin's lymphoma cases and had $P < 0.001$ and $P < 0.000001$, respectively (table 3 and online supplemental eTable 5 in supplemental file 2). Overall, the unique suggestive exposures categories were alcohol consumption on risk of diffuse large B cell lymphoma, marginal zone lymphoma, and non-Hodgkin's lymphoma; history of Sjogren's syndrome on risk of diffuse large B cell lymphoma, marginal zone lymphoma, and non-Hodgkin's lymphoma; recreational sun exposure on risk of diffuse large B cell lymphoma, follicular lymphoma, and non-Hodgkin's lymphoma; and history of hepatitis C virus on risk of diffuse large B cell lymphoma, marginal zone lymphoma, and non-Hodgkin's lymphoma.

Although the three non-InterLymph meta-analyses of individual participant data examined five associations not reported in systematic reviews and/or meta-analyses of the summary level data, none was nominally significant. These associations included fish eaters and risk of non-Hodgkin's lymphoma,³⁶ vegetarians and vegans and risk of non-Hodgkin's lymphoma,³⁶ maternal age at the time of the child's birth and risk of non-Hodgkin's lymphoma,³⁷ paternal age at the time of the child's birth and risk of non-Hodgkin's lymphoma,³⁷ and leisure time physical activity and risk of non-Hodgkin's lymphoma.³⁸

Consistency between meta-analyses of summary level data and InterLymph meta-analyses of individual participant data

Forty associations reported in meta-analyses of summary level data were also evaluated in InterLymph meta-analyses of individual participant data (online supplemental eTable 6 in supplemental file 2 and online supplemental eFigure 1 in supplemental file 1). While 22 (55%) associations evaluated the impact of environmental risk factors on the risk of non-Hodgkin's lymphoma overall, the other half (18, 45%) focused on various non-Hodgkin's lymphoma subtypes (chronic lymphocytic leukaemia or small lymphocytic lymphoma, five (13%); diffuse large B cell lymphoma, five (13%); follicular lymphoma, four (10%); T cell lymphoma, three (8%); marginal zone lymphoma, one (3%)).

Overall, 22 (55%) of 40 of the associations reported in meta-analyses of summary level data that were also evaluated in InterLymph meta-analyses of individual participant data were in the same direction, had the same level of significance, and had overlapping 95% confidence intervals. We identified 10 (25%) pairs that had effect estimates where both significantly increased, three (8%) where they were both significantly decreased, seven (18%) where they were both non-significantly increased, and two (5%) where they were both non-significantly decreased ($\kappa = 0.37$, online supplemental eTable 6 in

Table 2 | Environmental risk factors for non-Hodgkin's lymphoma reported in meta-analyses of summary level data with convincing and highly suggestive evidence

Environmental risk factor	Level of comparison	Outcome	Study type	Author year	No of primary studies	No of cases	Effect measure	Random effects summary effect size (95% CI)	P random*	Largest study in the meta-analysis nominally significant (P<0.05)	I ² (%)	95% PI	Small study effect	Strength of association†
Renal transplantation														
Renal transplantation	Transplant recipients v general population	NHL	SRMA	Wang 2018	6	770	SIR	10.66 (8.54 to 13.31)	3.44×10 ⁻⁸⁶	Yes	80.2	NA	NA	Highly suggestive
Autoimmune diseases														
Rheumatoid arthritis	Patients v general population	NHL	SRMA	Simon 2015	16	1531	SIR	2.26 (1.82 to 2.81)	8.42×10 ⁻¹³	Yes	96	NA	NA	Highly suggestive
Primary Sjogren's syndrome	Patients v general population	NHL	SRMA	Liang 2014	11	12 325	Risk ratio	13.76 (8.53 to 18.99)	1.62×10 ⁻³⁴	Yes	58.8	NA	NA	Highly suggestive
Systemic lupus erythematosus	Patients v general population	NHL	MA	Cao 2015	12	166	Risk ratio	5.4 (3.75 to 7.77)	1.99×10 ⁻¹⁸	Yes	74.3	NA	NA	Highly suggestive
Coeliac disease	Patients v general population	NHL	SRMA	Tio 2012	8	110 245	Odds ratio	2.61 (2.04 to 3.33)	9.32×10 ⁻¹⁴	Yes	23.4	1.57 to 4.33	No	Convincing
Coeliac disease	Patients v general population	TCL	SRMA	Tio 2012	5	35 358	Odds ratio	15.84 (7.85 to 31.94)	6.90×10 ⁻¹⁴	Yes	55.5	NA	NA	Highly suggestive
Infectious diseases														
Tuberculosis	Patients v general population	NHL	SRMA	Leung 2020	8	2390	Risk ratio	1.61 (1.34 to 1.94)	6.76×10 ⁻⁷	Yes	50.2	NA	NA	Highly suggestive
Hepatitis B virus	Infected v non-infected	NHL	SRMA	Li 2018	58	53 714	Odds ratio	2.50 (2.2 to 2.83)	6.33×10 ⁻⁴²	Yes	77.9	NA	NA	Highly suggestive
Hepatitis B virus	Infected v non-infected	BCL	SRMA	Li 2018	20	>1000	Odds ratio	2.46 (1.97 to 3.07)	1.24×10 ⁻¹⁴	Yes	62.9	NA	NA	Highly suggestive
Hepatitis C virus	Infected v non-infected	NHL	SRMA	Masanone 2019	27	33 077	Odds ratio	3.36 (2.4 to 4.72)	7.92×10 ⁻¹²	Yes	88	NA	NA	Highly suggestive
Hepatitis C virus	Patients v general population	DLBCL	MA	DalMaso 2006	8	1020	Risk ratio	2.65 (1.88 to 3.74)	4.98×10 ⁻⁸	Yes	39	1.46 to 5.81	No	Highly suggestive
Occupation														
Teacher	Teacher v non-teachers	NHL	MA	Boffetta 2007	19	>1000	Risk ratio	1.47 (1.34 to 1.61)	1.60×10 ⁻¹⁵	Yes	76	NA	NA	Highly suggestive

PI=prediction interval; NHL=non-Hodgkin's lymphoma; SRMA=systematic review and meta-analysis; SIR=standardised incidence ratio; NA=not available; TCL=T cell lymphoma; MA=meta-analyses; TCL=T cell lymphoma; BCL=B cell lymphoma; DLBCL=diffuse large B cell lymphoma.

*P value for summary effect estimates using a random effects DerSimonian and Laird estimator.

†P<0.1 for Egger's test suggests the presence of small study effects.

‡Strength of association using the criteria listed in [table 1](#).

Table 3 | Suggestive risk factors and protective factors identified in 24 meta-analyses of individual participant data from the International Lymphoma Epidemiology Consortium looking at 715 nominally significant associations between environmental factors and risk of developing non-Hodgkin's lymphoma

Subtype of non-Hodgkin's lymphoma	At least 1000 cases of non-Hodgkin's lymphoma and P<0.001 for associations	At least 1000 cases of non-Hodgkin's lymphoma and P<0.000001 for associations
Chronic lymphocytic leukaemia or small lymphocytic lymphoma	Years since quitting cigarette smoking, printing pressmen	None
Chronic lymphocytic leukaemia or small lymphocytic lymphoma, prolymphocytic leukaemia, mantle cell lymphoma	Adult infectious mononucleosis	None
Diffuse large B cell lymphoma	Alcohol*, any atopic disorder*, allergy*, B and T cell activating autoimmune diseases, hepatitis C virus, hay fever*, recreational sun exposure*, socioeconomic status (high v low)*, body mass index as young adult (25 to <30), rheumatoid arthritis, blood transfusion*, weight	History of B cell activating autoimmune disease, Sjogren's syndrome, hepatitis C virus, body mass index as young adult (% >25), years since quit cigarette smoking, age at first alcohol consumption (20-29 years v non-drinker)*, current alcohol consumption status as of about 2 years before diagnosis or interview*
Follicular lymphoma	Blood transfusions*, body mass index as young adult (%>25+), recreational sun exposure*, history of cigarette smoking (women), current cigarette smoking, university and higher education teachers*, male height (100% v 60%), any atopic disorder*	None
Marginal zone lymphoma	Systemic lupus erythematosus, hepatitis C virus, peptic ulcer, wine	History of B cell activating autoimmune disease, Sjogren's syndrome
Hairy cell leukaemia	Current cigarette smoking	None
Non-Hodgkin's lymphoma	Hormone replacement therapy*, systemic lupus erythematosus, hepatitis C virus, allergy*, food allergy*, hay fever*, blood transfusion*, height, alcohol consumption*, recreational hair dye use*, socioeconomic status (high v low)*, secondary Sjogren's syndrome, childhood measles*	Sjogren's syndrome; history of B cell activating autoimmune disease; hay fever; body mass index as young adult (%>25); recreational sun exposure (% quartile 3-quartile 4, hours/week)*; recreational hair dye use (% quartile 3-quartile 4 hours/week); beer, wine, and liquor*

*These were protective risk factors.

supplemental file 2 and online supplemental eFigure 1 in supplemental file 1).

The 13 associations where the meta-analyses of the summary level data and meta-analyses of individual participant data effect estimates were both significantly increased or decreased were for history of smoking and risk of T cell lymphoma; history of drinking and risk of non-Hodgkin's lymphoma, diffuse large B cell lymphoma, and follicular lymphoma; history of primary Sjogren's syndrome and risk of non-Hodgkin's lymphoma; history of systemic lupus erythematosus and risk of non-Hodgkin's lymphoma; history of coeliac disease and risk of non-Hodgkin's lymphoma, T cell lymphoma, and diffuse large B cell lymphoma; and history of hepatitis C virus and risk of non-Hodgkin's lymphoma, diffuse large B cell lymphoma, marginal zone lymphoma, and chronic lymphocytic leukaemia or small lymphocytic lymphoma. We identified 28 (70%) pairs where the effect sizes from the meta-analyses of individual participant data were more conservative than the effect sizes from the meta-analyses of summary level data.

Four suggestive associations reported in meta-analyses of summary level data were also evaluated in the InterLymph meta-analyses of individual participant data. Of these associations, three from meta-analyses of individual participant data had

effect estimates in the same direction, had P values less than 0.001, and were based on analyses with at least 1000 non-Hodgkin's lymphoma cases (ie, history of psoriasis and risk of non-Hodgkin's lymphoma, history of Herpes Zoster and risk of non-Hodgkin's lymphoma, and history of farming as an occupation and risk of non-Hodgkin's lymphoma). Eight highly suggestive associations reported in meta-analyses of summary level data were also evaluated in InterLymph meta-analyses of individual participant data. Of these, seven associations from the meta-analyses of individual participant data had effect estimates in the same direction, had P values less than 0.000001, and were based on analyses with at least 1000 non-Hodgkin's lymphoma cases (ie, history of rheumatoid arthritis and risk of non-Hodgkin's lymphoma, history of primary Sjogren's syndrome and risk of non-Hodgkin's lymphoma, history systemic lupus erythematosus and risk of non-Hodgkin's lymphoma, history of coeliac disease and risk of non-Hodgkin's lymphoma and T cell lymphoma, history of tuberculosis and risk of non-Hodgkin's lymphoma, and history of hepatitis C virus and risk of non-Hodgkin's lymphoma).

We identified 19 (48%) pairs where the meta-analyses of summary level data included at least a third of the same component studies as the InterLymph meta-analyses of individual participant

data. No difference was seen in terms of concordance (direction, significance of summary effect estimates, and overlapping 95% confidence intervals) between meta-analyses of summary level data that included at least a third versus fewer than a third of the same component studies as the meta-analyses of individual participant data (12/19 (63%) v 10/21 (48%), $P=0.32$).

Discussion

Principal findings

In this umbrella review, we evaluated the range, strength, and validity of reported associations between environmental risk factors and non-Hodgkin's lymphoma across 85 meta-analyses of published observational studies. Overall, we identified 257 associations for 134 unique environmental risk factors and 10 non-Hodgkin's lymphoma subtypes. The vast majority of the associations, including those evaluating various dietary, clinical, lifestyle, chemical, and occupational exposures, were classified as having either non-significant or weak evidence. Only 5% of the associations, primarily those for autoimmune and infectious disease related risk factors, presented either highly suggestive or convincing evidence. When the same associations were evaluated in meta-analyses of summary level data and InterLymph meta-analyses of individual participant data, only half were in the same direction, had the same level of statistical significance, and had overlapping 95% confidence intervals. Overall, effect sizes from meta-analyses of individual participant data were more conservative.

This umbrella review suggests evidence of many low quality meta-analyses of summary level data reporting weak associations between environmental risk factors and non-Hodgkin's lymphoma. These findings highlight the need for improving not only primary studies but also evidence synthesis in this field. Moreover, given that many of the assessed risk factors are correlated, simultaneous consideration of multiple risk factors will be useful to understand which ones have the strongest, independent effects on non-Hodgkin's lymphoma risk.

Context of primary findings

Although a wide range of environmental exposures have been evaluated and proposed as potential risk factors for non-Hodgkin's lymphoma, our evaluation suggests that the only highly suggestive or convincing exposures proposed in meta-analyses of summary level data and meta-analyses of individual participant data are related to autoimmune and infectious diseases. In particular, the prominent risk factors related to autoimmune disease include history of coeliac disease, rheumatoid arthritis, primary Sjogren's syndrome, and systemic lupus erythematosus. Although the exact mechanisms behind these associations remains unclear, many

autoimmune disorders are characterised by chronic inflammation,^{39–41} which could intensify B cell or T cell activation and promote the development of lymphoma.^{42–43} Previous studies have also suggested that the dysfunction of some protein families, such as Fas ligand and tumour necrosis factor, and the interplay between various immune cells, could be potential mechanisms.⁴⁴ However, the temporality of these associations is unclear, with studies reporting that autoimmune diseases can occur during lymphoma.^{45–46}

Associations between viral and bacterial infections and non-Hodgkin's lymphoma risk have been suggested for several decades.^{2 5 6 47 48} Different hypotheses for hepatitis C related lymphomagenesis have been proposed. For instance, chromosomal aberrations, including chromosome t(14;18) translocation, have been found to be associated with mixed cryoglobulinemia, a disorder most commonly caused by hepatitis C infection and that can evolve into lymphoproliferative disorders.^{49–51} Furthermore, genetic variations, including interleukin 10 polymorphisms, have also been proposed as a pathway between hepatitis C infection and non-Hodgkin's lymphoma susceptibility and development.⁵² Similar to risk factors related to autoimmune disease, whether these associations are driven by disease status, drug treatment use, or disease-treatment interactions is unclear.^{53–57} Considering how rare many of these autoimmune and infectious disease related exposures are, future efforts are necessary to determine the impact of multiple environmental as well as non-environmental risk factors simultaneously.^{5 6}

Among 40 associations evaluated by both meta-analyses of summary level data and InterLymph meta-analyses of individual participant data, only half were in the same direction, had the same level of statistical significance, and had overlapping 95% confidence intervals. Unlike meta-analyses of summary level data, meta-analyses of individual participant data tend to focus on studies with more homogeneous designs and patient populations. Furthermore, meta-analyses of individual participant data can allow for better harmonisation of data across studies, more advanced one stage meta-analytical approaches, and analyses accounting for many exposure categories and potential confounders.^{58 59} Although the InterLymph meta-analyses of individual participant data are particularly robust owing to the large number of non-Hodgkin's lymphoma cases and subtypes considered, meta-analyses of individual participant data without systematic reviews can exclude evidence from high quality case-control or cohort studies. For instance, the InterLymph analyses only included evidence from completed and ongoing case-control studies from consortium members.

Furthermore, the InterLymph findings might be difficult to disentangle, with at least 700 nominally significant associations among thousands of analyses conducted across different subtypes of non-Hodgkin's lymphoma and exposure levels (eg, different type or dosage of alcohol consumption). In the future, the consistency between meta-analyses of summary level data and meta-analyses of individual participant data will need to be monitored, especially because about half of the meta-analyses of summary level data had at least a third of the same component studies as the meta-analyses of individual participant data. In addition, authors of meta-analyses should carefully evaluate whether any external studies can and should be included in their syntheses. We also observed that more than two thirds of the effect sizes were more conservative in the InterLymph meta-analyses of individual participant data than in the meta-analyses of summary level data. This observation might reflect greater selective reporting bias in the studies available in the literature than in a set of studies participating in a consortium.

Our study suggests that nearly all meta-analyses of summary level data evaluating associations between environmental risk factors and risk of non-Hodgkin's lymphoma could be classified as having critically low quality according to the AMSTAR 2 tool. Previous umbrella reviews focused on the associations between environmental risk factors and health outcomes have noted similar concerns. However, the proportion of non-Hodgkin's lymphoma reviews with low or critically low quality is higher than what has been observed among umbrella reviews for inflammatory bowel diseases,⁶⁰ attention deficit or hyperactivity disorder,⁶¹ eating disorders,⁶² early childhood caries,⁶³ physical activity for academic achievement,⁶⁴ and physical therapy for tendinopathy.⁶⁵ These findings might not be surprising considering recent concerns about the mass production of systematic reviews.^{66,67} Authors should also critically evaluate how their findings relate to existing meta-analyses of individual participant data, focusing on the impact of different methods, populations, and other characteristics.

Limitations of the study

Our umbrella review had several limitations. First, we did not identify potential environmental risk factors that were only examined in individual observational studies. Our objective was to identify and summarise the associations that were reported by the meta-analyses of summary level data, which already covered a wide space of diverse associations. Second, we did not evaluate the quality of individual studies included in the meta-analyses of summary level data, the impact that individual studies have on the overall heterogeneity, the magnitude of the associations, or the potential role that residual or unmeasured confounding could have on associations. Individual

risk-of-bias evaluations are outside the scope of umbrella reviews, and it is the expectation that meta-analyses have already conducted these quality assessments. Third, we considered meta-analyses that included cohort and case-control studies, and our assessments did not prioritise reviews of certain study designs or look at differences across different study designs. Considering that certain non-Hodgkin's lymphoma subtypes are rare, case-control studies might often be the most realistic study design to evaluate exposure histories.

Fourth, although umbrella reviews provide a comprehensive summary of the associations reported in meta-analyses, the validity of the summary effect estimates depends on the quality of the individual meta-analyses. Although we attempted to standardise associations using a random effects DerSimonian and Laird estimator, we did not evaluate or re-conduct the literature searches for all potential associations between exposure and outcome. Different approaches can affect the width of the confidence intervals (ie, Wald *v* Hartung-Knapp-Sidik-Jonkman). In our evaluation, these differences were unlikely to affect the associations that were classified as highly suggestive or convincing. Given that the Hartung-Knapp-Sidik-Jonkman method has been found to outperform the standard DerSimonian and Laird method in certain scenarios, future meta-analyses should consider this approach in their analyses.^{68–70}

Fifth, we did not calculate I^2 , 95% prediction intervals, Egger's test, and excess significance test for non-significant and nominally significant associations. Given the large number of associations identified, we prioritised these calculations for associations where these values were necessary to determine the strength of associations using the previously established classification system.¹⁹ Other tests might be more appropriate (eg, Peter's test *v* Egger's test to examine small study effects⁷¹) and I^2 values should not be used to make inferences about heterogeneity, because it does not measure heterogeneity directly but rather the proportion of total variability due to variability between studies.⁷² However, we used the same approaches as previous umbrella reviews.^{25,61}

Sixth, when summary effect estimates of multiple exposure contrast levels were reported, we also focused on the risk estimates comparing ever versus never exposure (or comparing the highest *v* lowest levels of exposures). Although we did not consider all potential contrast levels and dose-response relations, our objective was to provide a universal overview of the associations between examined risk factors and non-Hodgkin's lymphoma. Specific dose-response relations might nevertheless exist for certain associations, and they would need to be examined on a case-by-case basis.

Seventh, we only identified the nominally statistically significant associations among the thousands of associations reported in InterLymph meta-analyses

of individual participant data. Eight, by excluding non-English language reviews, we could have missed additional potential associations; however, we used the same approach as previous umbrella reviews that focused on risk factors for health outcome(s).^{60 73}

Ninth, meta-analyses of individual participant data and meta-analyses of summary level data can have different strengths and limitations, and our evaluation did not focus on comparing the potential quality of these types of studies. We also did not focus on the impact of different methods, populations, or other characteristics when comparing the consistency of the results between the two study types. Tenth, umbrella reviews are also not intended to provide information about the likelihood that associations are causal. Lastly, when multiple meta-analyses of summary level data evaluated the same exposures and outcomes, we selected the association based on the largest number of included studies. Although this approach does not ensure that the highest quality meta-analyses are selected, this methodology has been used by previous umbrella reviews.^{25 73–75}

Conclusion

In this large scale umbrella review, we identified dozens of meta-analyses evaluating associations between environmental risk factors and non-Hodgkin's lymphoma. However, the vast majority of meta-analyses of summary level data were low quality and presented either non-significant or weak evidence. When the same associations were evaluated in meta-analyses of summary level data and meta-analyses of individual participant data, only half were in the same direction, had the same level of statistical significance, and had overlapping 95% confidence intervals. Although several associations, primarily those for risk factors related to autoimmune and infectious diseases, presented either highly suggestive or convincing evidence, these findings highlight the need for improving not only primary studies but also evidence synthesis in evaluations of environmental risk factors and of non-Hodgkin's lymphoma.

AUTHOR AFFILIATIONS

¹Department of Environmental Health Sciences, Yale School of Public Health, New Haven, CT, USA

²Department of Health Policy and Management, Yale School of Public Health, New Haven, CT, USA

³Harvey Cushing/John Hay Whitney Medical Library, Yale University, New Haven, CT, USA

⁴Department of Medicine, of Epidemiology and Population Health, of Biomedical Data Science, and of Statistics, and Meta-Research Innovation Center at Stanford (METRICS), Stanford University, Stanford, CA, USA

Twitter Joshua D Wallach @JoshuaDWallach

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Contributors XS and JDW originally conceived this study. XS, JI, and JDW designed this study. XS, HZ, YD, KN, and JDW acquired the data. XS and YD conducted the statistical analysis. XS and JDW and drafted the manuscript. XS, JPAI, and JDW participated in the interpretation of the data. All authors and critically revised the manuscript for important intellectual content. XS and JDW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. JDW provided supervision. JDW is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. **Transparency:** The lead author (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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ORCID iDs

Xiaoting Shi <http://orcid.org/0000-0002-5256-0646>

Kate Nyhan <http://orcid.org/0000-0001-5397-2303>

John Ioannidis <http://orcid.org/0000-0003-3118-6859>

Joshua D Wallach <http://orcid.org/0000-0002-2816-6905>

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