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

Supplementary materials summary

Supplement 1

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

eTable 1: Search strategy

Database searches, 2021-07-23

Searches on the Ovid platform can be rerun at https://tools.ovid.com/ovidtools/launcher.html

Ovid MEDLINE(R) ALL <1946 to July 22, 2021>		
1	[Xiaoting Shi]	0
2	[concept two: SRs]	0
3	(systematic adj4 review).ti.	160473
4	systematic review.pt.	162162
5	Cochrane Database of Systematic Reviews.jn. and review.pt.	13658
6	[approach c: based on Lee 2012]	0
7	medline.tw. or systematic review.ti. or meta-analysis.pt. or pubmed.tw.	357483
8	[from our previous searches]	0
9	(pooled analysis or pooled analyses).mp.	11737
10	(metaanalysis or meta-analysis).af.	220100
11	[NHL concept]	0
12	neoplasms/ or lymphoma/ or exp lymphoma, non-hodgkin/	589505
13	[alternative based on https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004024.pub2/appendices#CD004024-sec1-0011]	0
14	*Lymphoma/	36024
15	*hematologic neoplasms/	10823
16	lymphom*.mp.	258573

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17	non-hodgkin*.mp.	58024
18	nonhodgkin*.mp.	136
19	(non adj1 hodgkin*).mp.	58025
20	nhl.mp.	13936
21	(hemato* adj1 malign*).mp.	26969
22	(haemato* adj1 malign*).mp.	5497
23	(hemato* adj1 neoplas*).mp.	16617
24	(haemato* adj1 neoplas*).mp.	415
25	or/12,14-24	721711
26	risk/ or protective factors/ or risk factors/	999994
27	(risk* or protective factor*).mp.	2899716
28	26 or 27	2899716
29	or/3-10	423179
30	25 and 28 and 29	5543
Embase <1974 to 2021 July 22>		
1	[NHL concept]	0
2	neoplasm/ or lymphoma/ or lymphatic system tumor/ or exp nonhodgkin lymphoma/	672631
3	*Lymphoma/	45821
4	hematologic malignancy/	35985
5	lymphom*.mp.	350480
6	non-hodgkin*.mp.	60548
7	nonhodgkin*.mp.	62197
8	(non adj1 hodgkin*).mp.	60551

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9	nhl.mp.	25440
10	(hemato* adj1 malign*).mp.	63015
11	(haemato* adj1 malign*).mp.	9491
12	(hemato* adj1 neoplas*).mp.	4590
13	(haemato* adj1 neoplas*).mp.	689
14	or/2-13	821814
15	exp risk/ or protection/	2714952
16	(risk* or protective factor*).mp.	4327584
17	15 or 16	4368125
18	[study design concept]	0
19	(systematic adj4 review).ti.	191826
20	Cochrane Database of Systematic Reviews.jn. and review.pt.	11247
21	medline.tw. or systematic review.ti. or pubmed.tw.	380127
22	(pooled analysis or pooled analyses).mp.	19038
23	(metaanalysis or meta-analysis).af.	327799
24	or/19-23	563188
25	14 and 17	155988
26	limit 25 to meta analysis	3382
27	limit 25 to systematic review	3023
28	25 and 24	6739
29	26 or 27 or 28	7272
30	limit 29 to conference abstract status	2936
31	29 not 30	4336

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Scopus	((TITLE-ABS-KEY (lymphom* OR non-hodgkin* OR (non W/1 hodgkin*) OR nhl OR ((hemato* OR haemato*) W/1 (malign* OR neoplas*)))) AND (TITLE-ABS-KEY (risk* OR protective-factor*))) AND (TITLE-ABS-KEY ((systematic W/4 review) OR medline OR pubmed OR "pooled analysis" OR "pooled analyses" OR metaanalysis OR meta-analysis)) AND (EXCLUDE (DOCTYPE , "cp"))	3173
Web of Science Core Collection	TS=(lymphom* OR non-hodgkin* OR (non NEAR/1 hodgkin*) OR nhl OR ((hemato* OR haemato*) NEAR/1 (malign* OR neoplas*))) AND TS=(risk* OR protective-factor*) AND TS=((systematic NEAR/4 review) OR medline OR pubmed OR "pooled analysis" OR "pooled analyses" OR metaanalysis OR meta-analysis)	
	Refined by excluding the Web of Science document types proceedings papers and meeting abstracts	2417
Cochrane Library		
ID	Search	Hits
#1	((systematic NEAR/4 review)):ti OR (systematic review):pt OR (medline or pubmed or "pooled analysis" or "pooled analyses" or metaanalysis or meta-analysis):ti,ab,kw (Word variations have been searched)	29396
#2	MeSH descriptor: [Neoplasms] this term only	6376
#3	MeSH descriptor: [Lymphoma] this term only	1369
#4	MeSH descriptor: [Lymphoma, Non-Hodgkin] explode all trees	2056
#5	MeSH descriptor: [Hematologic Neoplasms] this term only	466
#6	(lymphom* or non-hodgkin* or nonhodgkin* or (non NEAR/1 hodgkin*) or nhl or (hemato* NEAR/1 malign*) or (haemato* NEAR/1 malign*) or (hemato* NEAR/1 neoplas*) or (haemato* NEAR/1 neoplas*)):ti,ab,kw	14144
#7	#2 or #3 or #4 or #5 or #6	20192
#8	(risk* or (protective NEAR/1 factor*)):ti,ab,kw	253910
#9	MeSH descriptor: [Risk] this term only	3322
#10	MeSH descriptor: [Protective Factors] this term only	135
#11	MeSH descriptor: [Risk Factors] this term only	24955
#12	#8 or #9 or #10 or #11	253910

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#13	#1 and #7 and #12	273
	Limited to reviews (not trials)	167
Epistemonikos		
SR filter	(title:(lymphoma*) OR abstract:(lymphoma*)) AND (title:(risk* OR protective) OR abstract:(risk* OR protective))	736
broad synthesis filter	(title:(lymphoma*) OR abstract:(lymphoma*)) AND (title:(risk* OR protective) OR abstract:(risk* OR protective))	24
no filter	(title:(lymphoma*) OR abstract:(lymphoma*)) AND (title:(risk* OR protective) OR abstract:(risk* OR protective)) AND (title:("pooled analysis" OR "pooled analyses") OR abstract:("pooled analysis" OR "pooled analyses"))	42

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eTable 2: NHL subtypes

Category	Subtypes	Eligibility as NHL
Mature B-cell neoplasms	Chronic lymphocytic leukemia/small lymphocytic lymphoma	Yes
	Monoclonal B-cell lymphocytosis*	No
	B-cell prolymphocytic leukemia	Yes
	Splenic marginal zone lymphoma	Yes
	Hairy cell leukemia	Yes
	Splenic B-cell lymphoma/leukemia, unclassifiable	Yes
	Splenic diffuse red pulp small B-cell lymphoma	Yes
	Hairy cell leukemia-variant	Yes
	Lymphoplasmacytic lymphoma	Yes
	Waldenström macroglobulinemia	Yes
	Monoclonal gammopathy of undetermined significance (MGUS), IgM*	No
	μ heavy-chain disease	No
	γ heavy-chain disease	No
	α heavy-chain disease	No
	Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*	No
	Plasma cell myeloma	No
	Solitary plasmacytoma of bone	No
	Extraosseous plasmacytoma	No
	Monoclonal immunoglobulin deposition diseases*	No
	Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)	Yes
	Nodal marginal zone lymphoma	Yes
	Pediatric nodal marginal zone lymphoma	Yes
	Follicular lymphoma	Yes
	In situ follicular neoplasia*	Yes
	Duodenal-type follicular lymphoma*	Yes
	Pediatric-type follicular lymphoma*	Yes

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Category	Subtypes	Eligibility as NHL
	Large B-cell lymphoma with IRF4 rearrangement*	Yes
	Primary cutaneous follicle center lymphoma	Yes
	Mantle cell lymphoma	Yes
	In situ mantle cell neoplasia*	Yes
	Diffuse large B-cell lymphoma (DLBCL), NOS	Yes
	Germinal center B-cell type*	Yes
	Activated B-cell type*	Yes
	T-cell/histiocyte-rich large B-cell lymphoma	Yes
	Primary DLBCL of the central nervous system (CNS)	Yes
	Primary cutaneous DLBCL, leg type	Yes
	EBV+ DLBCL, NOS*	Yes
	EBV+mucocutaneous ulcer*	No
	DLBCL associated with chronic inflammation	Yes
	Lymphomatoid granulomatosis	No
	Primary mediastinal (thymic) large B-cell lymphoma	Yes
	Intravascular large B-cell lymphoma	Yes
	ALK+ large B-cell lymphoma	Yes
	Plasmablastic lymphoma	Yes
	Primary effusion lymphoma	Yes
	HHV8+DLBCL, NOS*	Yes
	Burkitt lymphoma	Yes
	Burkitt-like lymphoma with 11q aberration*	Yes
	High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements*	Yes
	High-grade B-cell lymphoma, NOS*	Yes
	B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma	Yes
	Double hit/triple hit lymphoma	Yes
	T-cell prolymphocytic leukemia	Yes
	T-cell large granular lymphocytic leukemia	Yes

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Category	Subtypes	Eligibility as NHL
Mature T and NK neoplasms	Chronic lymphoproliferative disorder of NK cells	Yes
	Aggressive NK-cell leukemia	Yes
	Systemic EBV+ T-cell lymphoma of childhood*	Yes
	Hydroa vacciniforme–like lymphoproliferative disorder*	Yes
	Adult T-cell leukemia/lymphoma	Yes
	Extranodal NK-/T-cell lymphoma, nasal type	Yes
	Enteropathy-associated T-cell lymphoma	Yes
	Monomorphic epitheliotropic intestinal T-cell lymphoma*	Yes
	Indolent T-cell lymphoproliferative disorder of the GI tract*	No
	Hepatosplenic T-cell lymphoma	Yes
	Subcutaneous panniculitis-like T-cell lymphoma	Yes
	Mycosis fungoides	Yes
	Sézary syndrome	Yes
	Primary cutaneous CD30+ T-cell lymphoproliferative disorders	Yes
	Lymphomatoid papulosis	No
	Primary cutaneous anaplastic large cell lymphoma	Yes
	Primary cutaneous γδ T-cell lymphoma	Yes
	Primary cutaneous CD8+aggressive epidermotropic cytotoxic T-cell lymphoma	Yes
	Primary cutaneous acral CD8+T-cell lymphoma*	Yes
	Primary cutaneous CD4+small/medium T-cell lymphoproliferative disorder*	No
	Peripheral T-cell lymphoma, NOS	Yes
	Angioimmunoblastic T-cell lymphoma	Yes
	Follicular T-cell lymphoma*	Yes
	Nodal peripheral T-cell lymphoma with TFH phenotype*	Yes
	Anaplastic large-cell lymphoma, ALK+	Yes
	Anaplastic large-cell lymphoma, ALK−*	Yes
	Breast implant–associated anaplastic large-cell lymphoma*	Yes

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Category	Subtypes	Eligibility as NHL
	Acute lymphoblastic leukaemia (ALL)	No

Footnotes:
*Changes from the 2008 classification.
NOS: not otherwise specified
Information source: 2016 WHO classification of mature lymphoid neoplasms (https://pubmed.ncbi.nlm.nih.gov/26980727/)

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eTable 3: R code

Below is the R code example for the association between Behcet disease and NHL
read in data_Behcet Disease
meta1 = read_excel("RR_effect_sizes_Behcet Disease_#4206.xlsx")
head(meta1)
conduct main analysis
meta2<-metagen(meta1$LNRR,meta1$SE, sm="R",studlab=paste(lastname,publication_year)
,data=meta1,method.bias="Egger",prediction = TRUE,
level.predict =0.95)
summary(meta2)
create forest plot, funnel plot
forest(meta2)
funnel(meta2)
meta2$pval.random
conduct egger's test
metabias(meta2,method.bias="Egger",plotit=TRUE, correct= TRUE, k=3)

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eTable 4: Overlapping meta-analyses of summary level data

Environmental risk factors	Largest review (First author, year)	Number of overlapping meta-analyses	Number of primary studies in the largest meta-analyses	Most recent (Y/N)	Highest impact factor one (Y/N)
Dietary factors					
Red meat	Yang 2015	4	18	N	N
Processed meat	Yang 2015	4	18	N	N
White meat/poultry	Dong 2017	3	10	N	N
Fish	Caini 2016	3	11	N	N
Fruit and vegetable	Chen 2013	2	4	N	Y
Fruit	Chen 2013	2	13	N	Y
Vegetable	Chen 2013	2	13	N	Y
Eggs	Caini 2016	2	10	N	N
Total dairy products	Wang 2016	2	7	Y	Y
Milk	Wang 2016	3	16	N	Y
Cheese	Wang 2016	2	10	Y	Y
Vitamin D	Lu 2014	2	6	N	N
Drugs, vaccinations and procedures					
Aspirin	Ye 2015	2	10	Y	Y
Non-steroidal anti-inflammatory drugs	Ye 2015	2	13	Y	N
Statin	Ye 2017	3	9	Y	Y

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Environmental risk factors	Largest review (First author, year)	Number of overlapping meta-analyses	Number of primary studies in the largest meta-analyses	Most recent (Y/N)	Highest impact factor one (Y/N)
Non-dietary lifestyle factors					
Physical activity	Davies 2020	3	17	Y	Y
Hair dye	Qin 2019	2	16	Y	N
Petrochemical exposure	Jephcote 2020	2	9	Y	Y
Maternal smoking	Antonopoulos 2011	2	7	N	Y
Ever smoking	Sergentanis 2013	2	33	Y	N
Ever drinking	Tramacere 2012	3	29	N	Y
Heavy drinking	Tramacere 2012	2	6	N	Y
Medical history and comorbid diseases					
Rheumatoid arthritis	Simon 2015	2	17	Y	N
Primary Sjogren's syndrome	Liang 2014	2	11	Y	Y
Systemicl lupus erythematosus	Cao 2015	3	12	N	N
Psoriasis	Vaengebjerg 2020	3	8	Y	Y
Type 1 diabetes	Wang 2020	2	3	Y	N
Celiac disease	Tio 2012	2	8	Y	Y
Systemic sclerosis	Zhang 2013	2	4	Y	N

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Environmental risk factors	Largest review (First author, year)	Number of overlapping meta-analyses	Number of primary studies in the largest meta-analyses	Most recent (Y/N)	Highest impact factor one (Y/N)
Asthma	Yang 2017	2	15	Y	Y
Type 2 diabetes	Castillo 2012	8	21	N	N
Overweight	Larsson 2007	11	16	N	Y
Obesity	Larsson 2007	11	16	N	Y
Hepatitis B virus	Li 2018	5	58	N	N
Hepatitis C virus	Masarone 2019	4	27	Y	Y
Chemicals and pesticides					
Benzene	Kane 2010	4	24	Y	N
Polychlorinated biphenyls	Catalani 2019	3	30	Y	N
Trichloroethylene	Scott 2011	3	17	N	N
Glyphosate	Boffetta 2021	4	6	Y	N
2,4-Dichlorophenoxyacetic acid	Smith 2017	3	11	Y	Y
Occupation					
Female flight attendant	Buja 2006	4	3	Y	N
Farmer	Boffetta 2007	4	50	Y	N
Firefighter	Jalilian 2019	3	14	Y	Y
Petroleum refinery worker	Schnatter 2018	2	16	Y	N
Y=Yes; N=No.					

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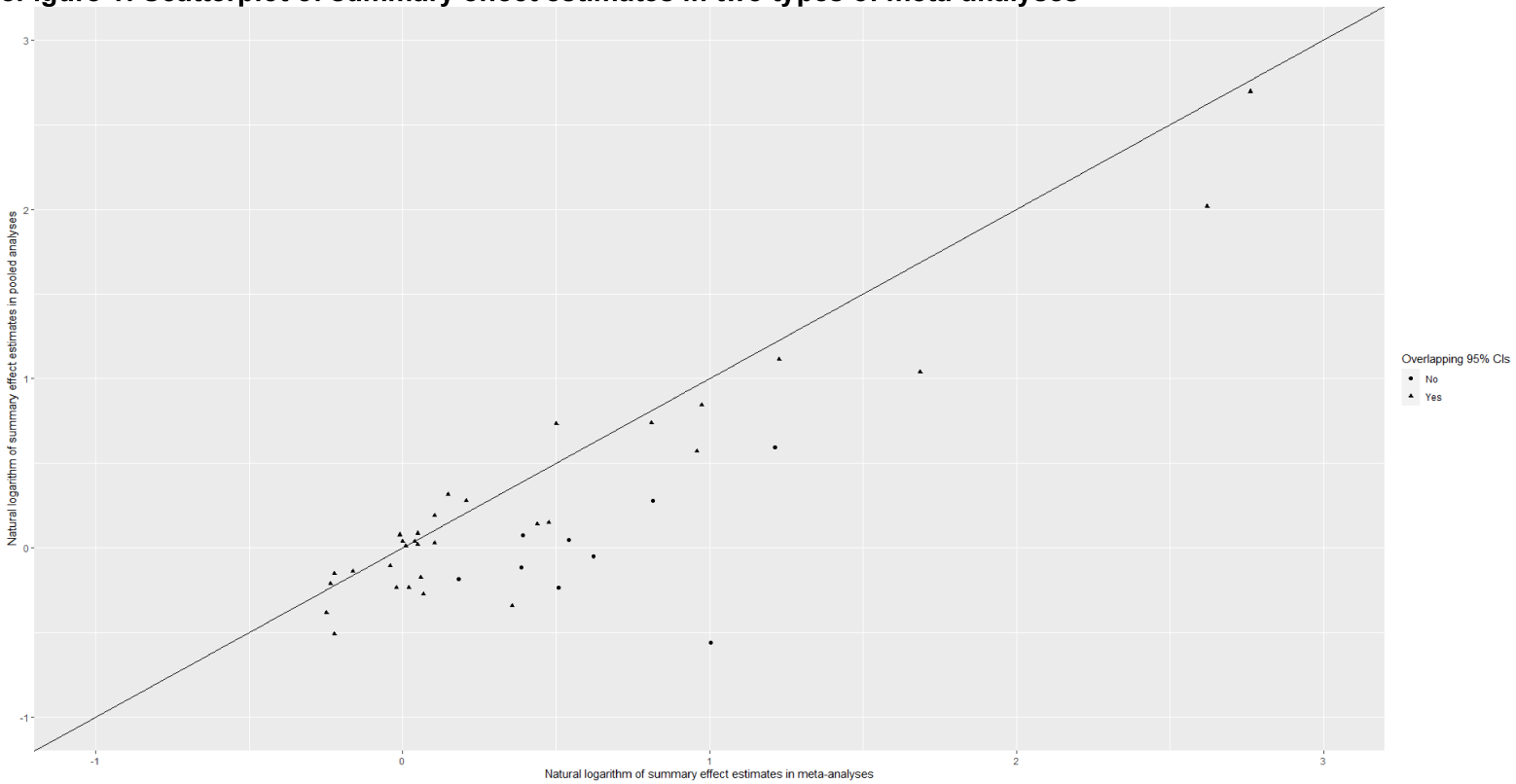
eFigure 1: Scatterplot of summary effect estimates in two types of meta-analyses



eFigure 1: Scatterplot of summary effect estimates in meta-analyses of summary level data and meta-analyses of individual participant data (pooled analyses) reporting the same associations between environmental risk factors and non-Hodgkin lymphoma

CI=confidence interval.

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eText 1: Eligibility criteria

Eligibility criteria for systematic reviews and (or) meta-analyses

General inclusion criteria

Language: English only.

Study types: Systematic review and (or) meta-analysis (referred as '*Review studies*' in the following contents).

Study designs included in review studies: Observational epidemiological studies[1].

Study subjects: Human only[2].

General exclusion criteria

Review studies that:

1. Focus on **genetic risk factors**[3] for non-Hodgkin lymphoma (NHL)
2. Focus on **biomarkers**[4] for NHL
3. Focus on risk factors for **treatment, relapse, remission, or prognosis** on NHL patients
4. Examine **NHL as a risk factor** for other diseases
5. Focus on cancer, hematological cancers, lymphoma, or any broader spectrum of diseases, but **fail to provide specific data for NHL**[5]
6. Only include **experimental** studies
7. Focus on NHL as a **metastasis/secondary cancer** of other primary cancers
8. Focus on NHL in a particular population but **fail to provide detailed information on environmental risk factors**[6]
9. Investigate the **prevalence/incidence** of NHL

[1] Cohort studies or case control studies only
[2] Review studies mixed with human and animal subjects will be checked in details at full text screening stage
[3] Including genetic polymorphisms, family history/familial aggregation
[4] Any substance, structure, or process that can be measured in the body or its products that can influence or predict the incidence of outcome or disease. Ref: http://www.inchem.org/documents/ehc/ehc/ehc222.htm (accessed 24th April, 2020)
[5] This may be unclear at the title-abstract screening, therefore when in doubt, two researchers will send it on to the full text screening
[6] For example, NHL in indigenous population, or men who have sex with men (MSM)

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Besides the aforementioned eligibility criteria, based on our definition of environmental risk factors, personal medical history and comorbidities (excluding metastasis of tumors) will be considered eligible in our study. In addition to the 8th General exclusion criteria, studies focus on NHL on a particular occupational population would be included since occupation can act as proxy for certain environmental exposures.

Study types, exposures and outcome definition

Systematic reviews and (or) Meta-analyses of summary level data and individual participant data:

The eligible study types in our study are systematic reviews (SRs), meta-analyses (MAs), systematic reviews and meta-analyses (SRMAs) or pooled analyses. To be eligible, SRs and SRMAs must have performed a systematic search in at least one bibliographic database. SRs, MAs and SRMAs should clearly define themselves as systematic reviews and(or) meta-analyses [1,2]. For SRs in particular, we will only include exposure-outcome relationships (i.e., associations) that have not been investigated in MAs or SRMAs.

In terms of pooled analyses, the primary goal for including pooled analyses in our study is to incorporate the valuable pooled information of individual level data from scientific institutes on NHL and its subtypes, such as The International Lymphoma Epidemiology Consortium (InterLymph[7]) [3] and to add to the evidence for meta-analyses on certain risk factors.

Environmental risk factors:

We define environmental risk factors as a broad concept of non-genetic factors, including physical, natural, chemical, biological, psychosocial, occupational, and lifestyle factors that can affect a person's health, as environmental risk factors.[4]

Outcome of interest:

Our study outcome is non-Hodgkin lymphoma, including its subtypes (**eTable 2 in Supplement 1**). The classification of NHL subtypes was consulted and confirmed by an epidemiologist on NHL from InterLymph consortia.
We will identify with the definition/diagnostic criteria of NHL from the original review studies.

References

1. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. *Syst Rev.* 2017;6(1):245.

[7] An open scientific forum for epidemiologic research in non-Hodgkin's lymphoma and a group of international investigators who have completed or have ongoing case-control studies and who discuss and undertake research projects that pool data across studies or otherwise undertake collaborative research. Ref: https://epi.grants.cancer.gov/interlymph/ (accessed 24th April, 2020)

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2. Faggion CM, Jr., Diaz KT. Overview authors rarely defined systematic reviews that are included in their overviews. *J. Clin. Epidemiol.* 2019;109:70-79.
3. Morton LM, Sampson JN, Cerhan JR, et al. Rationale and Design of the International Lymphoma Epidemiology Consortium (InterLymph) Non-Hodgkin Lymphoma Subtypes Project. *J. Natl. Cancer Inst. Monogr.* 2014;2014(48):1-14.
4. Prüss-Ustün A, van Deventer E, Mudu P, et al. Environmental risks and non-communicable diseases. *BMJ.* 2019;364:l265.

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eText 2: Systematic reviews without quantitative synthesis

Systematic reviews

We identified 8 systematic reviews without quantitative synthesis with 8 unique associations that were not investigated by meta-analyses of the published literature (Supplement). Among them, 6 (75.0%) concluded that there were weak or non-statistically significant associations between the examined risk factors (Omega-3 fatty acids,[1] sugar intake,[2] artificial sweetener consumption,[3] hazardous waste,[4] preterm birth,[5] and prenatal/postnatal Diagnostic X-rays and childhood[6]) and NHL risk. Two (25%) additional systematic reviews suggested possible associations between Gaucher disease[7] and NHL risk and breast implants and anaplastic large cell lymphoma risk.[8] Half (4, 50.0%) of the systematic reviews outlined that quantitative analyses were not conducted due to high levels of heterogeneity and/or a small number of eligible studies.[1,3,6,7] The remaining 4 (50.0%) systematic reviews did not provide any reasons for not conducting quantitative analyses.[2,4,5,8]

Exclusion reasons

Among the 1024 records screened at the full text level, 904 were excluded, mostly because they were for the wrong topic (442, 48.9%), they had the wrong study design (240, 26.5%), or they were not the largest meta-analysis of the published literature for a specific association (102, 11.3%).

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References

1. MacLean CH, Newberry SJ, Mojica WA, Khanna P, Issa AM, Suttorp MJ, Lim YW, Traina SB, Hilton L, Garland R, Morton SC. Effects of omega-3 fatty acids on cancer risk: a systematic review. Jama. 2006 Jan 25;295(4):403-15.

2. Makarem N, Bandera EV, Nicholson JM, Parekh N. Consumption of sugars, sugary foods, and sugary beverages in relation to cancer risk: a systematic review of longitudinal studies. Annual review of nutrition. 2018 Aug 21;38:17-39.

3. Mishra A, Ahmed K, Froghi S, Dasgupta P. Systematic review of the relationship between artificial sweetener consumption and cancer in humans: analysis of 599,741 participants. International journal of clinical practice. 2015 Dec;69(12):1418-26.

4. Fazzo L, Minichilli F, Santoro M, Ceccarini A, Della Seta M, Bianchi F, Comba P, Martuzzi M. Hazardous waste and health impact: a systematic review of the scientific literature. Environmental Health. 2017 Dec;16(1):1-1.

5. Paquette K, Coltin H, Boivin A, Amre D, Nuyt AM, Luu TM. Cancer risk in children and young adults born preterm: A systematic review and meta-analysis. PloS one. 2019 Jan 4;14(1):e0210366.

6. Schulze-Rath R, Hammer GP, Blettner M. Are pre-or postnatal diagnostic X-rays a risk factor for childhood cancer? A systematic review. Radiation and environmental biophysics. 2008 Jul;47(3):301-12.

7. Arends M, van Dussen L, Biegstraaten M, Hollak CE. Malignancies and monoclonal gammopathy in G aucher disease; a systematic review of the literature. British journal of haematology. 2013 Jun;161(6):832-42.

8. Kim B, Roth C, Chung KC, Young VL, van Busum K, Schnyer C, Mattke S. Anaplastic large cell lymphoma and breast implants: a systematic review. Plastic and reconstructive surgery. 2011 Jun 1;127(6):2141-50.