Fecha de recepción: enero 27 de 2019
Fecha de aceptación: octubre 15 de 2019

ARTÍCULO ORIGINAL

DOI: https://doi.org/10.14482/sun.36.1.616.238

Association Between Cold Exposure and Asthma: Systematic Review and meta-analysis, 1965-2015

Asociación entre la exposición al frío y el asma: revisión sistemática y meta-análisis, 1965-2015

Germán Zuluaga Ramírez[1], Iván Sarmiento Combariza[2], Juan Pimentel González[3], Neil Andersson[4]

[1] Director, Grupo de Estudios en Sistemas Tradicionales de Salud (GESTS), Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario. gzuluaga@cemi.org.co. Orcid: 0000-0001-5715-9133. https://scienti.colciencias.gov.co/cvlac/visualizador/generarCurriculoCv.do?cod_rh=0000211664

[2] Candidato a doctor en Medicina Familiar. Department of Family Medicine, McGill University. ivan.sarmiento@mail.mcgill.ca. Orcid: 0000-0003-2871-1464. http://scienti.colciencias.gov.co:8081/cvlac/visualizador/generarCurriculoCv.do?cod_rh=0001016156

[3] Candidato a doctor en Medicina Familiar. Department of Family Medicine, McGill University. juan.pimentel@mail.mcgill.ca. Orcid: 0000-0002-6842-3064. http://scienti.colciencias.gov.co:8081/cvlac/visualizador/generarCurriculoCv.do?cod_rh=0001474877

[4] Director, CIET-PRAM, Department of Family Medicine, McGill University. Orcid: 0000-0003-1121-6918

Correspondencia: Germán Zuluaga Ramírez, Calle 12 # 3A – 21 (Cota, Cundinamarca, +57 (1) 8776310, gzuluaga@cemi.org.co - Escuela de Medicina y Ciencias de la Salud, Universidad del Rosario. Calle 12C No. 6-25 - Bogotá D.C. Colombia.

ABSTRACT

Objectives: to conduct a systematic review and a meta-analysis of observational and experimental studies that explore the relation between asthma and cold exposure.

Materials and methods: systematic review of experimental and observational studies published up to August 2015 in Pubmed, Embase and Lilacs. Two researchers selected studies that measured the occurrence of asthma in individuals exposed to different environmental temperatures. A meta-analysis used RevMan 5.3's random effects model to calculate a summary weighted Odds Ratio with 95% confidence intervals, and a sensitivity analysis identified the influence of each study. Subsequent subgroup analyses identified summary measures by type of cold exposure and study design. Additional analysis measured heterogeneity and risk of bias.

Results: we found 86 studies measuring the relation between cold exposure and asthma. We included 11.6% (10/86) of the studies in the meta-analysis and found an association between *cold exposure* and *asthma* with all the studies (ORw 2.0 95%CI 1.28-3.14), with the subgroup of experimental studies (ORw 3.8 IC95% 1.70-8.86), and with cold environmental air (ORw 1.59 IC95% 1.10-2.30). The studies had high risk of bias and statistical heterogeneity [I^2: 63.1% (27%-81.4%)].

Conclusions: the results support the hypothesis of an association between asthma and cold exposure. This study encourages to explore the concepts proposed by traditional medicine to establish its benefits on prevention and care of respiratory diseases, such as asthma.

Key words: Respiratory health, asthma, cultural factors, traditional medicine, intercultural epidemiology.

RESUMEN

Objetivos: realizar una revisión sistemática y meta-análisis de estudios observacionales y experimentales que exploren la relación entre asma y exposición al frío

Materiales y Métodos: revisión sistemática de estudios experimentales y observacionales publicados hasta agosto de 2015 en Pubmed, Embase y Lilacs. Dos investigadores seleccionaron estudios midiendo la ocurrencia de asma tras la exposición a diferentes temperaturas ambientales. Usando un modelo de efectos aleatorios en RevMan 5.3, un meta-análisis calculó un resumen de Odds Ratio ponderado con intervalos de confianza de 95%. Un análisis de sensibilidad identificó la influencia de cada estudio. Análisis de subgrupo identificaron las medidas de resumen de acuerdo a tipo de exposición al frío y diseño de estudio. Finalmente, medimos heterogeneidad y riesgo de sesgos.

Resultados: encontramos 86 estudios explorando la relación entre la exposición al frío y el asma. Incluimos 11.6% (10/86) de los estudios en el meta-análisis y encontramos una asociación entre la exposición al frío y asma en todos los estudios (ORw 2.0 95%CI 1.28-3.14), en el subgrupo de estudios experimentales (ORw 3.8 IC95% 1.70-8.86), y aire frío ambiental (ORw 1.59 IC95% 1.10-2.30). Los estudios tienen alto riesgo de sesgos y heterogeneidad [I^2: 63.1% (27%-81.4%)].

Conclusiones: los resultados apoyan la hipótesis de una asociación entre asma y exposición al frío. Este estudio invita a explorar los conceptos de la medicina tradicional para la prevención y cuidado de enfermedades respiratorias.

Palabras clave: Salud respiratoria, asma, factores culturales, medicina tradicional, epidemiología intercultural.

INTRODUCTION

Asthma is an inflammatory respiratory illness affecting between 5-16% of the population around the world; (1) it has also been on the rise since the second half of the 20th century, especially in industrialized countries.(2) The mechanism behind the illness and the reasons for its rise have not been completely specified. However, some risk factors have been identified, such as genetics,(3) taking certain medicines,(4) environmental factors,(5) and other lifestyle-related factors, such as nutrition.(6)

In the traditions of several cultures and traditional health systems, the concepts of *cold* and *heat* are considered one of the most important factors for health, and they emphasize the importance of cold exposure as a cause or a risk factor of inflammatory respiratory processes, especially asthma. In the Afro-Colombian Pacific tradition, water and air exposure are causes of disease, due to their link to cold and humidity.(7) In the Bolivian plateau, Aymara medicine considers that illnesses caused by cold are counteracted by hot remedies and conversely.(8) Some authors in Colombia report medicinal plants that fall in the cold and hot categories in indigenous,(9) rural *mestizo*(9) and even urban communities.(10)

In Chinese traditional medicine, cold is a pathogenic factor, and a *cold syndrome* is considered to include all illnesses caused by cold pathogenic energy, or by a decrease in yang and an excess of yin.(11) In ancient Ayurveda traditional medicine, the concept of *virya* refers to the effect of heat and cold transmitted by substances that are ingested; the hot and cold properties give these substances a therapeutic quality.(12) One of the transgressions in the cosmic rhythm that leads to disease is *osha vata*, which is cold and dry.(12)

The concept of cold has endured in popular concepts and beliefs. In English, the word *cold* simultaneously refers to lower temperatures and to an illness, which points to the same meaning the word *resfrío* used to have in Spanish before the term *gripe* (flu) was introduced. In popular imagination, there is still a belief that cold causes or worsens respiratory illnesses.

Traditional care is a peripheral aspect and almost nonexistent in the management guidelines of respiratory diseases,(13–15) although the cultural dimension has significant impact on monitoring and treatment of asthma.(16)

Several studies highlight the persistence and importance of classical concepts of cold and heat in traditional medicine and their role in explaining the occurrence of asthma, even in highly urbanized countries such as the United States.(17) For example, a study reports that 76% of Hispanic mothers in New York recognize the importance of keeping their children sheltered to prevent asthma attacks. Similarly, they attributed asthma attacks in school to exposure to cold air.(16) Other studies report that these concepts persist, and urban communities share the same concepts in countries such as Puerto Rico, Mexico, Guatemala, Singapore, Malaysia and China.(18,19)

We have not found systematic review or meta-analysis studies, which explored the association between cold exposure and asthma. This study sought to conduct a systematic review and a meta-analysis of observational and experimental studies that explore the relation between asthma and cold exposure.

METHODS

Inclusion criteria

Systematic review with meta-analysis of observational and experimental studies among humans of all ages, published or non-published, based on the Cochrane Collaboration(20) and Centre for Reviews Dissemination guidelines.(21) We excluded studies that did not assess the association among individuals (ecological studies). For the meta-analysis, we included only the studies that reported sample size, characteristics of the exposition and the outcome, and frequency of asthma among exposed and non-exposed.

The protocol of this systematic review is available in the repository of the *Universidad del Rosario's* research fund under the registration number QDN_B0002 and is accessible from the Research Director of the *Universidad del Rosario* under reasonable request (direccion.investigacion@urosario.edu.co).

The outcome variable was *asthma*. We defined asthma occurrence as a clinical asthma diagnosis by a doctor(22), the mechanical spirometry test and positive reversibility with a bronchodilator,(22) bronchial stimulus testing with methacholine(23) or prostaglandins,(24) exercise-induced bronchoconstriction,(25) or prostaglandins,(24) exercise-induced bronchoconstriction,(25) IgE antibody levels for allergy patients,(26) questionnaires, genetics tests or a combination of two or more methods. We included any of the following possibilities: prevalence of asthma, asthma incidence (new cases and crisis or exacerbation), severity, emergency room visits due to asthma attacks, and hospitalization for asthma.

The exposure variable was *cold*. The operational definition for this term is not precise, especially if we consider that it is a physical-chemical characteristic that is not often considered in physiology, biochemistry and physiopathology. The search strategy included the following variables: environmental air (outdoor/indoor), inhaled air (controlled exposure), food and drink, lower body temperature (skin), and two or more of the above. We consider cold when studies explicitly contrast any of these variables with a group exposed to higher temperature and the other exposed to low temperature.

Search methods to identify studies

We carried out an electronic search of publications in English, Spanish and Portuguese without time restrictions, up to 11 August 2015, in the following databases: PubMed, Embase, Lilacs and the Cochrane Central Register of Controlled Trials. The search used standard descriptors (MeSH, Emtree and DeCS) and free text words. Additionally, we performed a manual search for potentially relevant articles among the bibliographic references of the selected articles.

Two independent researchers (IS and JP) reviewed the titles and abstracts of all the articles identified in the first stage of the search, to identify potentially relevant sources. Once the articles were identified, both researchers applied the inclusion criteria (Additional file 1) and data-extraction criteria separately (Additional file 2). Possible differences were solved by consensus. These two criteria were piloted in a random sample with 10% of the studies, which allowed the instrument to be fine-tuned.

Data collection and analysis

We performed a first analysis to identify general characteristics of the studies, including year of publication, country in which it was carried out, study type, asthma diagnosis method, asthma occurrence measurement, exposure measurement and covariates.

Quantitative information was analyzed using RevMan 5.3's meta-analysis module.(27) The statistical analysis was based on the random effects model, considering the diversity of criteria for exposure and reported categories of asthma among included studies.

For the general occurrence relation (any type of cold exposure and any asthma category), we obtained the summary weighted Odds Ratio (ORw) and its 95% confidence intervals (95%CI), including data collected from all the references which met the inclusion criteria, independently whether they were observational or experimental studies. We also performed a subgroup analysis by type of cold exposure, reported categories of asthma, and study design.

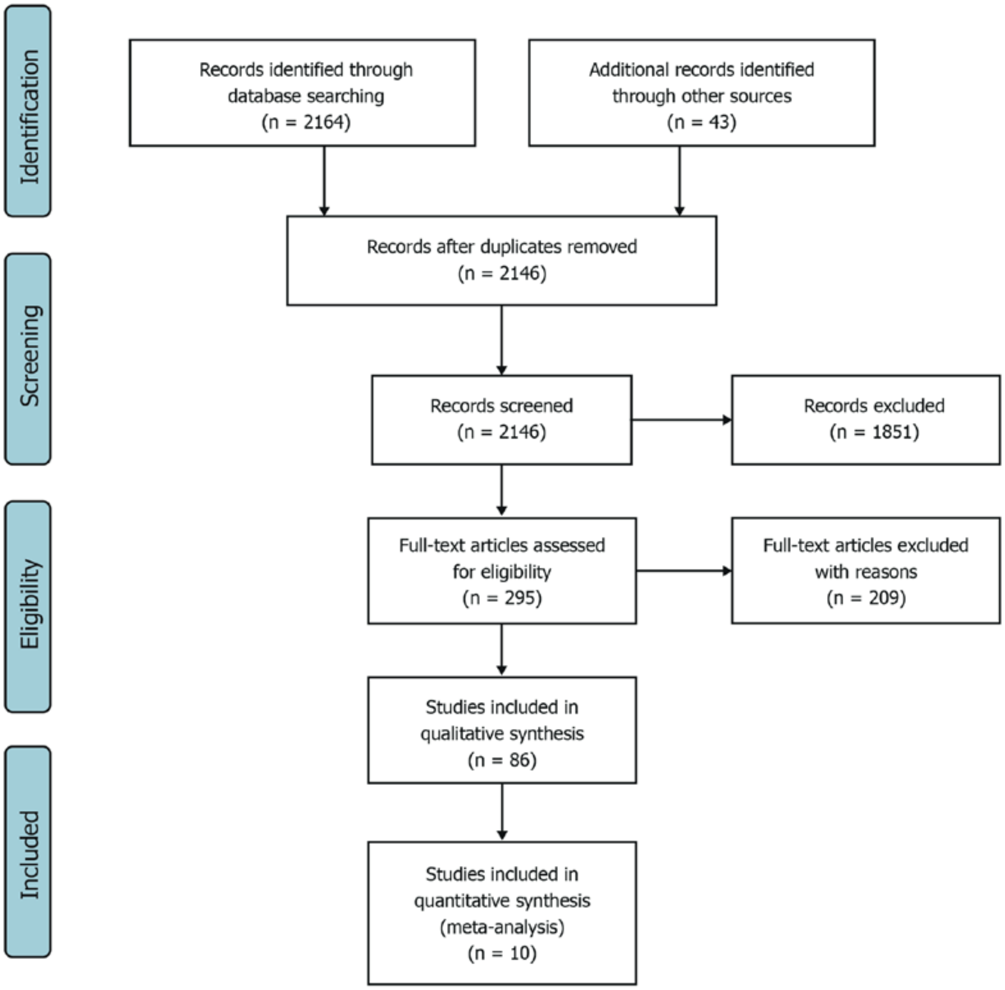
We performed the risk of bias assessment using the categories proposed by the Cochrane collaboration: sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other elements.(20) We used the RevMan 5.3's risk of bias form.(27) The risk of bias was assessed using a funnel plot, keeping in mind the small number of studies and the use of OR as a measure of association, which makes the results less reliable; we did not apply statistical tests for funnel plot asymmetry.(20)

We carried out a sensitivity analysis to identify the influence of each study, replicating the meta-analysis and eliminating one of the included studies at each step.(28) The heterogeneity analysis for the studies used the I^2 statistical test from the RevMan 5.3 software, which expresses the level of inconsistency, obtained through the formula that combines Q (statistical chi-squared) with the number of degrees of freedom. When I^2 had a value above 50%, it is considered that there is substantial heterogeneity.(28)

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines,(29) both the flowchart and checklist, were followed during the preparation of this review (Additional file 4).

RESULTS

The search strategy yielded 2164 potential studies. The bibliographical references yielded other 43 studies. After removing duplicated records, we obtained a total of 2146 studies. After reviewing the titles and abstracts, we obtained 295 studies. Some 59.4% (116/295) had information related to the contrast between asthma occurrence and cold exposure, although they were excluded due to their ecologic designs. Applying the inclusion criteria yielded 86 studies (Additional file 3). Finally, the data-extraction criteria yielded 10 studies for meta-analysis, as seen in Figure 1.



Fuente: Adapted from the freely available form at http://prisma-statement.org

Figure 1. Flowchart of the study selection process

Characteristics of included studies for data extraction

Applying the data extraction criteria to 86 studies and 11 references (12.8%) yielded data about associations, although without providing details regarding the sample size or the frequency of exposed and non-exposed. We communicated with the authors via e-mail and received responses from two of them, who stated they did not have the data available; there was no reply from the rest. Of the 86 studies, 11.6% (10/86) met all the inclusion criteria for meta-analysis (Table 1 shows the characteristics of the 10 included studies).(30–39)

Table 1. Characteristics of 10 included studies

Study	Year	Country	Study type	n	OR	95%CI	Exposure	Outcome	Diagnosis
Hyrkas	2014	Finland	Cross-sectional	1623	1,22	0.67 – 2.21	Environmental air: cold weather	Prevalence: physician-diagnosed asthma, use of asthma medication, asthma-related symptoms	Self-reported (questionnaire)
Langdeau	2004	Canada	Cross-sectional	698	0,94	0.59 – 1.51	Environmental air: cold air inhaled during outdoors exercise	Prevalence: physician-diagnosed asthma or self-reported asthma	Clinical and self-reported
Gurkan	2002	Turkey	Case control	236	2,56	1.34 – 4.87	Environmental air: cold weather	Hospitalization: physician-diagnosed asthma	Clinical
Yang	1998	Taiwan	Case control	330	1,32	0.76 – 2.29	Environmental air: air-conditioned	Prevalence: physician-diagnosed asthma	Clinical
Helenius	1998	Finland	Experimental	80	3,58	0.94 – 13.6	Environmental air: exercise challenge test at sub-zero temperature during the winter	Incidence: exercise induced asthma	Spirometry and self-reported
Carlsen	1998	Norway	Experimental	58	3,4	1.19 – 9.70	Environmental air: treadmill run while inhaling cold air	Incidence: exercise induced asthma	Clinical and spirometry

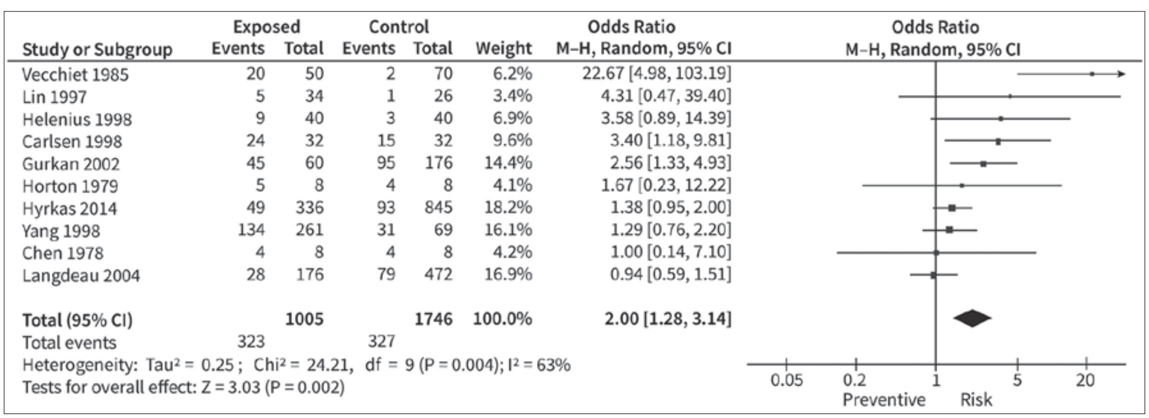
Continúa...

Study	Year	Country	Study type	n	OR	95%CI	Exposure	Outcome	Diagnosis
Lin	1997	Taiwan	Experimental	60	4,31	0.54 – 34.4	Drinks: drinking ice water	Incidence: cold-drinks induced asthma	Clinical and spirometry
Vecchiet	1985	Italy	Experimental	120	22,67	6.9 – 74.10	Cooling: cold stimulus on the chest wall	Incidence: cold-induced bronchospasm	Spirometry
Horton	1979	USA	Experimental	16	1,67	0.22 – 12.20	Combination: body cooling using cold showers and wind	Incidence: cold-induced asthma	Clinical and spirometry
Chen	1978	USA	Experimental	8	1	0.37 – 2.66	Combination: exposition of the wet body to high wind generated by a fan	Severity: cold-induced asthma	Clinical and spirometry

Fuente: Created by the authors.

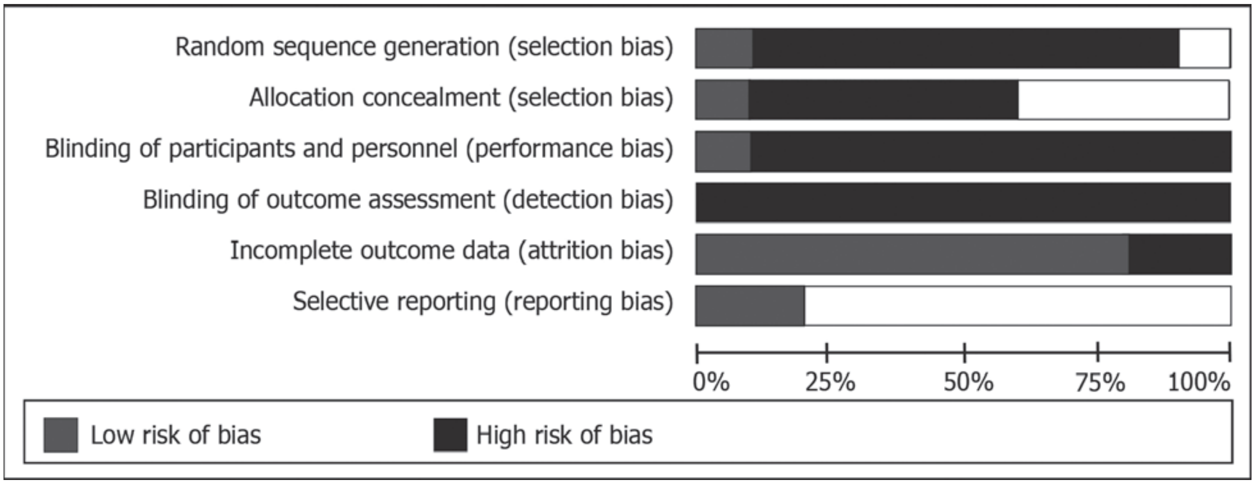
Intervention effects

The summary measurement with the random effects model (Figure 2) shows that a subject exposed to cold is more likely to have asthma (ORw 2.0 95%CI 1.28-3.14). A quality assessment showed that the level of evidence has a high risk of bias (Figures 3 and 4).



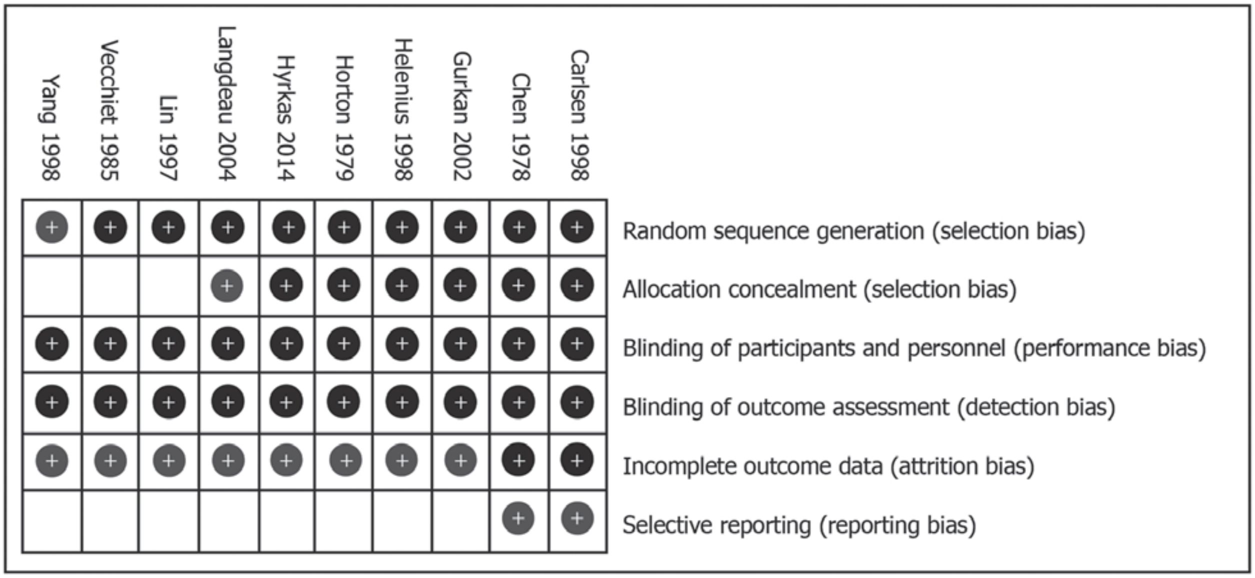
Fuente: Created by the authors.

Figure 2. Forest plot of the association between cold and asthma: random effects model



Fuente: Created by the authors.

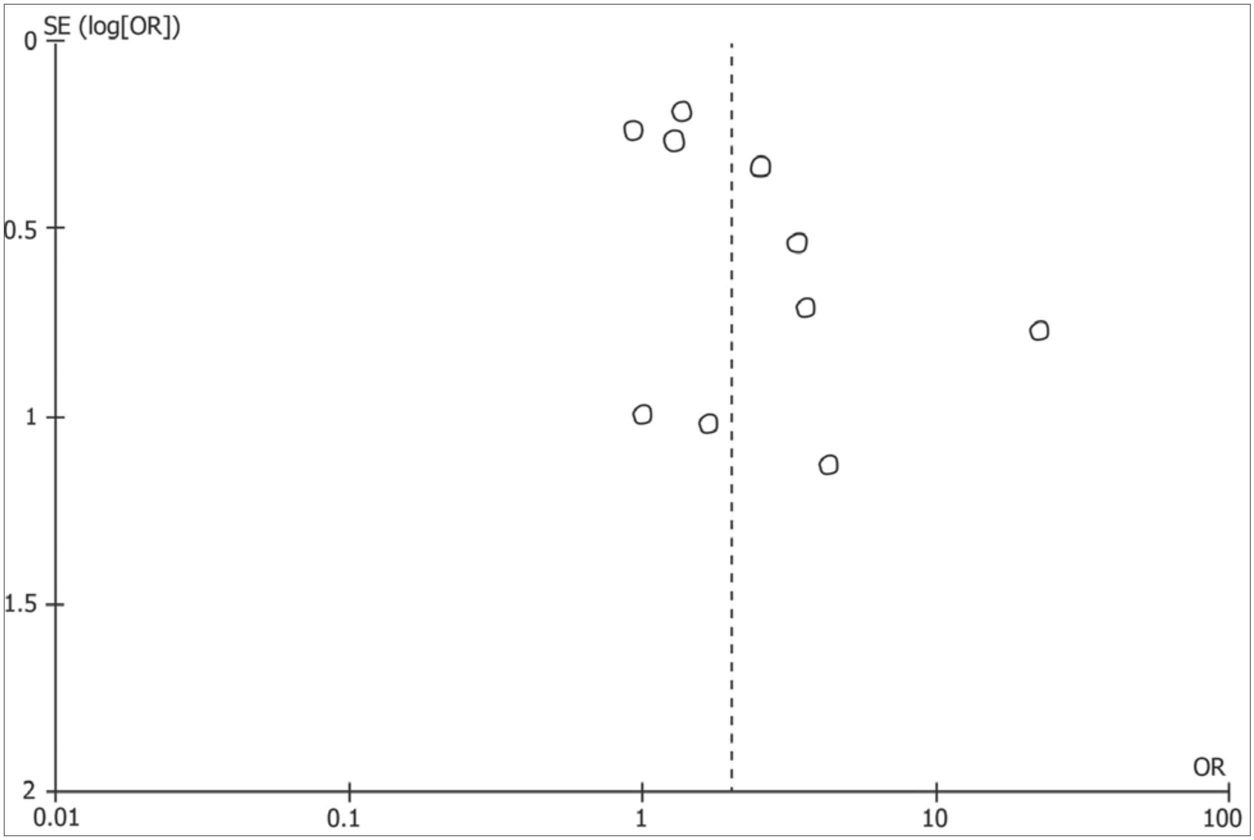
Figure 3. Risk of bias for studies included in meta-analysis



Fuente: Created by the authors.

Figure 4. Risk of bias for studies included in meta-analysis - Summary

As seen in the funnel plot (Figure 5), the ten included studies have evident publication bias. Considering the low number of studies and the use of OR as a measure of effect, we did not carry out a statistical test.



Fuente: Created by the authors.

Figure 5. Funnel plot of publication bias

The Revman 5.3 software yielded the I^2 statistical heterogeneity: 63.1% (27%-81.4%). We carried out a sensitivity analysis, successively removing one study at a time. At no point did the summary measurement lose statistical significance (Table 2). The Hyrkäs(30) study produced the highest increment of the summary measurement when removed, while the one by Vecchiet caused the highest reduction.(31)

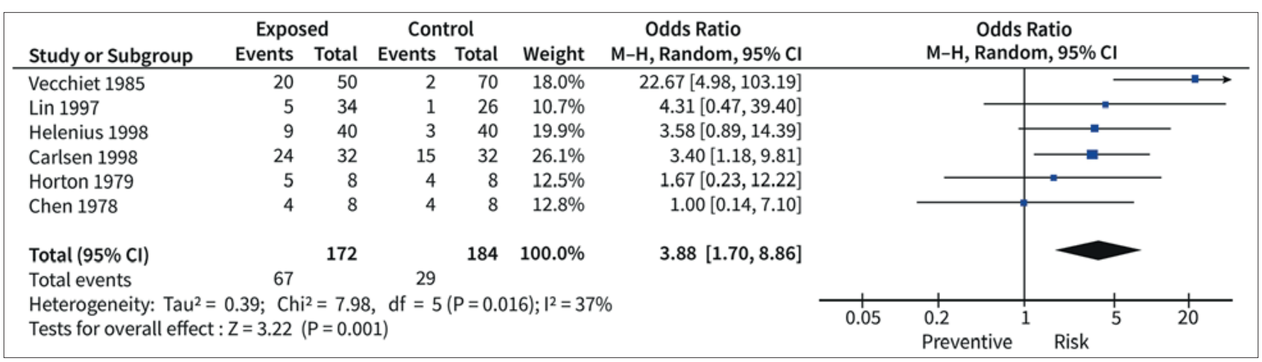
Table 2. Sensitivity analysis

Excluded study	ORw	95%CI
Value with all studies	**2**	**1.28-3.14**
Increased effect of risk		
Hyrkas 2014	2,3	1.29-4.09
Yang 1998	2,26	1.32-3.88
Chen 1978	2,09	1.30-3.34
Horton 1979	2,04	1.27-3.27
Decreased effect of risk		
Lin 1997	1,96	1.23-3.10
Helenius 1998	1,92	1.20-3.07
Carlsen 1998	1,89	1.18-3.03
Gurkan 2002	1,94	1.18-3.20
Langdeau 2004	2,34	1.43-3.83
Vecchiet 1985	1,56	1.14-2.14

Fuente: Created by the authors.

Subgroup meta-analysis

Regarding the study design, 6 of the 10 were experimental. Random effects model showed that a person *exposed to cold* is 3.8 times more likely to have asthma, compared to a person not exposed (ORp 3.8 95%CI 1.7-8.86) as shown in Figure 6.



Fuente: Created by the authors.

Figure 6. Forest plot of the association between cold and asthma of experimental studies: random effects model

With regards to the *exposure categories*, 6 of the 10 studies contrasted environmental air (outdoor/indoor) and the random effects model showed that the asthma risk for a person *exposed to cold environmental air* was 1.6 times higher compared with a non-exposed person (ORw 1.59 95%CI 1.1-2.3). In relation to the outcome, 5 of the 10 studies contrasted cold with *asthma incidence* (new cases and crisis or exacerbation) and the random effects model showed that a person exposed to cold had 4.7 times the risk of asthma incidence, compared to a non-exposed person (ORw 4.73 95%CI 2.06-10.85). Also, 3 of the 10 studies contrasted cold with *asthma prevalence* and the random effects model showed that the association between cold and asthma prevalence could be explained by chance (ORw 1.12 95%CI 0.82-1.52).

DISCUSSION

The meta-analysis showed an association between cold exposure and asthma for experimental studies (ORw 3.8 95%CI 1.7-8.86) and for all the studies (ORw 2.0 95%CI 1.28-3.14). The sensitivity analysis showed that none of the 10 studies changed the statistical significance. The subgroup analysis showed that *cold environment* exposure is a risk factor for asthma (ORw 1.59 95%CI 1.1-2.3) and that cold exposure is a risk factor for *asthma incidence* (ORw 4.73 95%CI 2.06-10.85).

Cold exposure has been described by some clinical management guides as a precipitating or aggravating factor of asthma, without specifying the mechanism behind it(13,40). The 2014 Gina guide includes the word *cold*, defined as the common cold, for symptoms associated to respiratory infections and as an aggravating factor for coughs. It also defines *cold air* as a triggering factor and recommends that athletes avoid exercise in very cold climates.(22) Another study also concluded that cold air induces ventilation disturbances in asthma patients.(41)

Despite probable evidence, asthma diagnosis, prevention and treatment guides do not suggest controlling cold exposure. We only found one study that recommends considering the role of climate in management plans: "It is important to understand how local weather patterns influence asthma attendance in general practice so that asthma management plans might include specific advice to adjust medication according to the local weather."(42)

A working group composed of pediatricians and general practitioners in the Asia-Pacific region, stressed the importance of expanding the evidence on the practices of traditional medicine for the treatment of asthma in pediatric population, as part of one of the six challenges for primary care asthma in this region.(43)

Quality of evidence and study limitations

Quality assessment in the 10 studies included in the meta-analysis showed a high risk of bias. We found no randomized trials or cohort studies. Six of the studies were experimental, all made in the past century, with little rigor in control and randomization.

We found a high level of heterogeneity among studies (I^2 test: 63.1%). The operational definition of asthma is not precise, and the means of diagnosing and including cases varied greatly between studies. Also, the operational definition of exposure also varied; it included diverse categories, such as body cooling by water or drinks and cooling by exposure to environmental air. The funnel chart showed an evident publication bias in all ten included studies.

We could not detect a specific association between asthma and exposure to cold food or drinks, lowering body temperatures, or cold-water showers. We were also unable to detect an association between cold exposure and other asthma related outcomes, such as prevalence, mortality, absence from school, seeking emergency healthcare services and hospitalization. The reason for this limitation was the absence of at least two studies that explored these associations.

Most studies were performed in first-world countries or in temperate countries, which makes it difficult to assess likely associations with geographic, economic and climatic conditions in equatorial countries. All the studies showed a weak covariance analysis to determine possible effect modifiers and confounders. There are few studies exploring the relation between asthma and altitude and other geo-climatic effects.(44) Most studies related to cold exposure and respiratory illnesses have been carried out in temperate countries, with a predominating measure of the seasonal variable, without taking into account, for example, that during the hotter months of late spring and summer respiratory illnesses can be associated to the presence of pollen(45) or to the use and abuse of air-conditioning, while during the colder months of late-autumn and winter the association is confounded by heating,(46) winter sports,(47) or higher concentrations of microbial agents in closed quarters.(5) Cold exposure can also be confounded by air contamination due to fine particles such as sulfur dioxide,(48, 49) or by the presence of dust mites and mold.(50) Finally, research on cold exposure and respiratory illnesses has been predominantly done through ecological studies, which do not assess individual subject associations.

CONCLUSIONS

The systematic review and meta-analysis of the few available studies, which showed a high risk of bias and a high level of statistical heterogeneity, showed that cold exposure –particularly cold environments– is a risk factor for asthma. Although better evidence is needed, this study encourages to explore the concepts proposed by the traditional medicine to establish its benefits on the prevention and care of respiratory diseases, such as asthma.

Funding: *Fondo de Investigación de la Universidad del Rosario* and the Secretariat of Health of Cota, Cundinamarca (2014 to 2015)..

Authors' contributions: GZ designed the study, analysed the data and drafted the manuscript. IS and JP applied the criteria for inclusion and data extraction to collect the articles for meta-analysis, solving differences by consensus. Also supported the data analysis and contributed to the manuscript. NA supervised the data analysis and contributed to data analysis and write-up. GZ, IS, JP, and NA had access to the data and all authors had final responsibility for the decision to submit for publication. All authors read and approved the final manuscript.

List of abbreviations

CI95%: 95% confidence intervals

DeCS: Health Sciences Descriptors

MeSH: Medical Subject Headings

ORw: weighted Odds Ratio

DECLARATIONS

Ethics approval and consent to participate

Not applicable.

Availability of data and material

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

GZ, IS and JP report grants from Universidad del Rosario's research fund, during the conduct of the study. The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors declare that they have no competing interests.

Acknowledgements

Francisco Laucirica translated the manuscript from Spanish into English, Elizabeth Nava gave academic guidance during the design of the systematic review, and Ana María Zuluaga designed the figures. The Centro de Investigación de Enfermedades Tropicales and the Traditional Health Systems Studies Group supported the project as part of their effort to promote intercultural epidemiology.

REFERENCES

1. Martinez FD, Vercelli D. Asthma. *Lancet*. 2013;382(9901):1360–72. Doi: 10.1016/S0140-6736(13)61536-6.

2. Eder W, Ege MJ, von Mutius E. The Asthma Epidemic. *N Engl J Med*. 2006;355(21):2226–35. Doi: 10.1056/NEJMra054308.

3. Belsky DW, Sears MR, Hancox RJ, Harrington H, Houts R, Moffitt TE, et al. Polygenic risk and the development and course of asthma: an analysis of data from a four-decade longitudinal study. *Lancet Respir Med*. 2013;1(6):453–61. Doi: 10.1016/S2213-2600(13)70101-2.

4. Rosenow EC. Drug-induced pulmonary disease. *Disease-a-Month*. 1994;40(5):258–310. Doi: 10.1016/0011-5029(94)90025-6.

5. Dick S, Friend A, Dynes K, AlKandari F, Doust E, Cowie H, et al. A systematic review of associations between environmental exposures and development of asthma in children aged up to 9 years. *BMJ Open*. 2014;4(11):e006554. Doi: 10.1136/bmjopen-2014-006554.

6. Thornley S, Stewart A, Marshall R, Jackson R. Per capita sugar consumption is associated with severe childhood asthma: an ecological study of 53 countries. *Prim Care Respir J*. 2011;20(1):75–8. Doi: 10.4104/pcrj.2010.00087.

7. Cifuentes A. Salud y culturas médicas tradicionales. In: P. Leyva, editor. Colombia Pacífico. Bogotá: Fonde FEN; 1993.

8. Fernández G, Albó X, Pinto E, Zalles J. Medicos y yatiris: salud e interculturalidad en el altiplano aymara. Cuadernos de Investigación no. 51 [Internet]. Albó X, editor. La Paz, Bolívia: CIPCA, ESA; 1999. 276 p. (Cuadernos de investigación).

9. Reichel-Dolmatoff G, Reichel-Dolmatoff A. Nivel de salud y medicina popular en una aldea mestiza colombiana. *Rev Colomb Antropol*. 1959;7.

10. Monje CA, Salazar MO. La práctica de la medicina tradicional en niveles socio-económicos bajos en áreas urbanas del departamento del Huila. Neiva, Colombia: Universidad Surcolombiana, Cesco; 1980.

11. Lu H. Chinese natural cures. Black Dog & Leventhal; 2006.

12. Svoboda R. Ayurveda, medicina milenaria de la India. Barcelona, España: Ediciones Urano; 1995.

13. Ministerio de Salud y Protección Social. Guía de práctica clínica para el diagnóstico, atención integral y seguimiento de niños y niñas con diagnóstico de Asma. Bogotá, Colombia; 2013. (Guías de práctica clínica). Report No.: GPC-2013-01.

14. Serugendo A, Kirenga B, Hawkes M, Nakiyingi L, Worodria W, Okot-Nwang M. Evaluation of asthma control using Global Initiative for Asthma criteria and the Asthma Control Test in Uganda. *Int J Tuberc Lung Dis*. 2014;18(3):371–6.

15. Szefler SJ. Advances in pediatric asthma in 2014: Moving toward a population health perspective. *J Allergy Clin Immunol*. 2015;135(3):644–52.

16. Bearison DJ, Minian N, Granowetter L. Medical management of asthma and folk medicine in a Hispanic community. *J Pediatr Psychol*. 2002;27(4):385–92.

17. Pachter LM, Weller SC, Baer RD, de Alba García JEG, Trotter RT, Glazer M, et al. Variation in asthma beliefs and practices among mainland Puerto Ricans, Mexican-Americans, Mexicans, and Guatemalans. *J Asthma*. 2002;39(2):119–34. Doi: 10.1081/JAS-120002193.

18. Harwood A. The Hot-Cold Theory of Disease: Implications for Treatment of Puerto Rican Patients. *JAMA*. 1971;216(7):1153–8. Doi: 10.1001/jama.1971.03180330029005.

19. Connett GJ, Lee BW. Treating childhood asthma in Singapore: when West meets East. *BMJ Br Med J* (International Ed. 1994;308(6939):1282.

20. The Cochrane Collaboration. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [Internet]. Higgins JP, Green S, editors. 2011.

21. Tacconelli E. Systematic reviews: CRD's guidance for undertaking reviews in health care. *Lancet Infect Dis*. 2010;10(4):226. Doi: 10.1016/S1473-3099(10)70065-7.

22. Global Initiative for Asthma. Pocket guide for Asthma Management and Prevention [Internet]. *Global Initiative for Asthma*. 2014. 1-28 p.

23. Fruchter O, Yigla M. Bronchodilator response after negative methacholine challenge test predicts future diagnosis of asthma. *J Asthma*. 2009;46(7):722–5. Doi: 10.1080/02770900903067903.

24. Lewis RA, Tattersfield AE. Cold-Induced Bronchoconstriction: Interaction with Prostaglandin-Induced Bronchoconstriction. *Clin Sci*. 1980;59(3):12P.1-12P. Doi: 10.1042/cs059012P.

25. Stensrud T, Berntsen S, Carlsen K-H. Exercise capacity and exercise-induced bronchoconstriction (EIB) in a cold environment. *Respir Med*. 2007;101(7):1529–36. Doi: 10.1016/j.rmed.2006.12.011.

26. Merino M, Aranguren J, Callén M, Elorz J, Etxebarría A. *Guía de práctica clínica sobre asma*. Osakidetka/Servicio Vasco de Salud; 2005.

27. The Nordic Cochrane Centre, The Cochrane Collaboration. *Review Manager (RevMan)*. Copenhagen; 2014.

28. L'Abbé KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Ann Intern Med*. 1987;107(2):224–33.

29. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ*. 2015;349(jan02 1):g7647–g7647. Doi: 10.1136/bmj.g7647.

30. Hyrkäs H, Jaakkola MS, Ikäheimo TM, Hugg TT, Jaakkola JJK. Asthma and allergic rhinitis increase respiratory symptoms in cold weather among young adults. *Respir Med*. 2014;108(1):63–70. Doi: 10.1016/j.rmed.2013.10.019.

31. Vecchiet L, Flacco L, Marini I, Marchionni A, Gatto MR, D'Autilio A. Effects of cold stimulus of the chest wall on bronchial resistance. *Respiration*. 1985;47(4):253–9.

32. Langdeau J-B, Turcotte H, Thibault G, Boulet L-P. Comparative prevalence of asthma in different groups of athletes: a survey. *Can Respir J*. 2004;11(6):402–6.

33. Gurkan F, Davutoglu M, Bilici M, Dagli A, Haspolat K. Asthmatic children and risk factors at a province in the southeast of Turkey. *Allergol Immunopathol (Madr)*. 2002;30(1):25–9. Doi: 13027471.

34. Yang CY, Lin MC, Hwang KC. Childhood asthma and the indoor environment in a subtropical area. *Chest*. 1998;114(2):393–7.

35. Helenius IJ, Tikkanen HO, Haahtela T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. *Br J Sports Med*. 1998;32(2):125–9.

36. Carlsen KH, Engh G, Mørk M, Schrøder E. Cold air inhalation and exercise-induced bronchoconstriction in relationship to metacholine bronchial responsiveness: different patterns in asthmatic children and children with other chronic lung diseases. *Respir Med*. 1998;92(2):308–15.

37. Lin YZ, Hsieh KH. Asthma induced by ice water ingestion in ethnic Chinese asthmatic children: a challenge. *Pediatr Allergy Immunol*. 1997;8(1):11–6.

38. Horton DJ, Chen WY. Effects of breathing warm humidified air on bronchoconstriction induced by body cooling and by inhalation of methacholine. *Chest*. 1979;75(1):24–8.

39. Chen WY, Horton DJ. Airways obstruction in asthmatics induced by body cooling. *Scand J Respir Dis*. 1978;59(1):13–20.

40. Escribano Montaner A, Ibero Iborra M, Garde Garde J, Gartner S, Villa Asensi JR, Pérez Frías J. Protocolos terapéuticos en el asma infantil. In: Neumología y Alergia Asociación Española de Pediatría. Asociación Española de Pediatría, Sociedad Española de Inmunología Clínica y Alergia Pediátrica; 2003. p. 187–209. (Protocolos de la AEP).

41. Hodgson WC, Cotton DJ, Werner GD, Cockcroft DW, Dosman JA. Relationship between bronchial response to respiratory heat exchange and nonspecific airways reactivity in asthmatic patients. *Chest*. 1984;85(4):465–70.

42. Kljakovic M, Salmond C. A model of the relationship between consultation behaviour for asthma in a general practice and the weather. *Clim Res*. 1998;10:109–13. Doi: 10.3354/cr010109.

43. Jusuf L, Hsieh CT, Abad L, Chaiyote W, Chin WS, Choi YJ, et al. Primary care challenges in treating paediatric asthma in the Asia-Pacific region. *Prim Care Respir J*. 2013;22(3):360–2. Doi: 10.4104/pcrj.2013.00069.

44. Seys SF, Daenen M, Dilissen E, Van Thienen R, Bullens DMA, Hespel P, et al. Effects of high altitude and cold air exposure on airway inflammation in patients with asthma. *Thorax*. 2013;68(10):906–13. Doi: 10.1136/thoraxjnl-2013-203280.

45. Gonzalez-Barcala FJ, Aboal-Viñas J, Aira MJ, Regueira-Méndez C, Valdes-Cuadrado L, Carreira J, et al. Influence of pollen level on hospitalizations for asthma. *Arch Environ Occup Health*. 2013;68(2):66–71. Doi: 10.1080/19338244.2011.638950.

46. Howden-Chapman P, Pierse N, Nicholls S, Gillespie-Bennett J, Viggers H, Cunningham M, et al. Effects of improved home heating on asthma in community dwelling children: randomised controlled trial. *BMJ*. 2008;337(sep23 1):a1411–a1411. Doi: 10.1136/bmj.a1411.

47. Carlsen K-H. Sports in extreme conditions: The impact of exercise in cold temperatures on asthma and bronchial hyper-responsiveness in athletes. *Br J Sports Med*. 2012;46(11):796–9. Doi: 10.1136/bjsports-2012-091292.

48. Gehring U, Wijga AH, Brauer M, Fischer P, de Jongste JC, Kerkhof M, et al. Traffic-related Air Pollution and the Development of Asthma and Allergies during the First 8 Years of Life. *Am J Respir Crit Care Med*. 2010;181(6):596–603. Doi: 10.1164/rccm.200906-0858OC.

49. Sheppard D, Eschenbacher WL, Boushey HA, Bethel RA. Magnitude of the interaction between the bronchomotor effects of sulfur dioxide and those of dry (cold) air. *Am Rev Respir Dis*. 1984;130(1):52–5. Doi: 10.1164/arrd.1984.130.1.52.

50. Pulimood TB, Corden JM, Bryden C, Sharples L, Nasser SM. Epidemic asthma and the role of the fungal mold Alternaria alternata. *J Allergy Clin Immunol*. 2007;120(3):610–7. Doi: 10.1016/j.jaci.2007.04.045.