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RESEARCH ARTICLE

Interrelationships between Atopic Disorders in Children: A Meta-Analysis Based on ISAAC Questionnaires

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Abstract

Purpose

To study the prevalence and interrelationship between asthma, allergic rhinitis and eczema using data obtained from ISAAC questionnaires.

Method

The Medline, Pubmed Publisher, EMBASE, Google Scholar and the Cochrane Controlled Clinical Trials Register databases were systematically reviewed to evaluate epidemiological data of children with atopic disorders. To study these interrelationships, a new approach was used. Risk ratios were calculated, describing the risk of having two different atopic disorders when the child is known with one disorder.

Results

Included were 31 studies, covering a large number of surveyed children (n=1,430,329) in 102 countries. The calculated worldwide prevalence for asthma, eczema and allergic rhinitis is 12.00% (95% CI: 11.99-12.00), 7.88% (95% CI: 7.88-7.89) and 12.66% (95% CI: 12.65-12.67), respectively. The observed prevalence [1.17% (95% CI: 1.17-1.17)] of having all three diseases is 9.8 times higher than could be expected by chance. For children with asthma the calculated risk ratio of having the other two disorders is 5.41 (95% CI: 4.76-6.16), for children with eczema 4.24 (95% CI: 3.75-4.79), and for children with allergic rhinitis 6.20 (95% CI: 5.30-7.27). No studied confounders had a significant influence on these risk ratios.

Conclusions

Only a minority of children suffers from all three atopic disorders, however this co-occurrence is significantly higher than could be expected by chance and supports a close relationship of these disorders in children. The data of this meta-analysis supports the hypothesis that there could be a fourth distinct group of children with all three disorders. Researchers and clinicians

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might need to consider these children as a separate group with distinct characteristics regarding severity, causes, treatment or prognosis.

Background

Eczema, asthma and allergic rhinitis are common atopic disorders among children, making it an important public health problem worldwide. The prevalences of these three disorders show variability at regional and even at country level [1–4]. Despite this variability, there seems to be a close relationship between these disorders. In a triad of events that include eczema, asthma and allergic rhinitis, eczema is often the first disorder to evolve. A biologically plausible pathway to explain this cascade was proposed by Burgess et al [5]. As a result of a defective skin barrier in children with eczema, an epicutaneous sensitization to an allergen can take place resulting in T-helper type 2 memory cells; these cells can migrate to nasal and bronchial lymphoid tissue. When the airways become exposed to the same allergen, this might cause asthma and/or allergic rhinitis symptoms to evolve. However, in practice, the number of patients following this classic 'atopic march' seems to vary considerably [6, 7], only partially explaining the interrelationships.

The International Study of Asthma and Allergies in Childhood (ISAAC) was established in 1991 and formally closed in December 2012. The ISAAC study was divided into three phases. The purpose was to assess the worldwide prevalence of asthma, allergic rhinitis and eczema in children in the open population and to obtain possible risk factors that could influence these three disorders using a standardized questionnaire [8–10]. This makes ISAAC a reliable data source to use when studying the interrelationship of atopic diseases in children aged 6–7 and 13–14 years. Although non-ISAAC research groups (i.e. non-official ISAAC studies) also published data using ISAAC questionnaires, the official ISAAC reviews do not include these latter data in their analyses.

The primary aim of this review is to calculate the worldwide prevalence in children of asthma, allergic rhinitis, eczema, and of having all three disorders, using data obtained with ISAAC questionnaires and to examine interrelationships between these disorders using risk ratios. Risk ratios will describe the risk of having two different atopic disorders when the child is known with one disorder. A secondary aim is to analyze whether these risk ratios and prevalences are influenced by potential confounders such as study period, age, sex, continent, and use of the original English-language ISAAC questionnaire.

Methods

The protocol of this review is described below.

Search strategy

An extensive literature search was performed in Medline (OvidSP), Pubmed Publisher, EMBASE, Google Scholar and the Cochrane Controlled Clinical Trials Register. Two complementary search strategies were used for optimal article retrieval. The first strategy, focusing on the three atopic disorders, combined the following items: "Child" AND "Epidemiology" AND "Asthma" AND "Allergic rhinitis" AND "Eczema". The second strategy, focusing on ISAAC studies, used additional items and different Boolean operators: "Child" AND "Epidemiology" AND ("Asthma" OR "Allergic rhinitis" OR "Eczema") AND ("ISAAC" OR "International Study of Asthma and Allergies").

The full search strategies can be found in S1 Appendix. Since ISAAC started in 1991, only full-text articles published after 1991 were considered; there was no language restriction. The search was completed on February 2, 2015. A reference check was made on all articles finally included.

Study selection

Studies (n>100) with a cross-sectional or cohort design, including youngsters aged 0–18 years, recruited in the open population (e.g. schools) were included. Studies using the ISAAC questionnaire, performed by both official and non-official ISAAC research groups, were included if the studies presented data on the prevalence of all three atopic diseases and their interrelationships.

One reviewer (EA) commenced the selection of studies, initially based on title and abstract. To check for any missed inclusions by the first reviewer, a random selection of 50% of the articles was independently checked by second reviewers (DP, JW, AB, NR, HM). This check showed that the first reviewer did not exclude any potentially relevant articles.

Of the abstracts selected, the full-text articles were retrieved. Two reviewers (EA and NR) independently performed the full-text selection using a standardized form based on the above-mentioned inclusion criteria. Studies were excluded if they only presented aggregated worldwide data, or when double inclusion of the data could not be ruled out. Disagreement was resolved in a consensus meeting or with the help of a third independent reviewer (DP). Authors of the studies were contacted regarding missing data.

Quality assessment

To minimize the risk of information bias, the quality of the included studies was assessed by two independent reviewers (DP and AB). Disagreement was resolved in a consensus meeting.

ISAAC used the same standardized method in ISAAC phase 1 and 3. Methodological differences between these phases were studied [11] and it was concluded that the ISAAC methodology was replicated to a high degree by the majority of the study centers. This showed that the ISAAC protocol is robust and that working in accordance with this protocol implied substantial generalizability. Any important violations of this protocol were, therefore, identified in order to assess quality (Table 1).

The present review includes only those articles that used the ISAAC questionnaires. This questionnaire has been translated into various languages by regional coordinators of ISAAC, using a consistent protocol that was evaluated by Ellwood et al. [12]. Use of a validated questionnaire was also considered an important quality item and was part of the quality assessment (Table 1).

The above mentioned violations and the use of the original questionnaire or not could potentially influence the comparability of ISAAC and non-ISAAC studies. For this reason we performed a meta-regression analyses in order to evaluate if these violation would influence our outcomes (prevalence and RR).

Data extraction

Two reviewers (EA/JW and DP) independently extracted data from the included studies. A standardized digital form was used to record study design, participants, official ISAAC study or not, and outcome measures. In view of the outcome measures, the total number of participants and the number of participants with asthma (As), eczema (Ec), allergic rhinitis (AR) and of As+Ec, As+AR, Ec+ AR and As+Ec+AR were extracted. These numbers were then entered in the Review Manager (RevMan) Computer program (Version 5.1. Copenhagen: The Nordic

Table 1. Study characteristics and quality assessment.

Article	ISAAC	No. analyzed*	Age range (years)	% Males	Response rate	Study year	Continent	English Question.	Violation protocols†
Ait-Khaled 2007 [13] ‡	Yes	4,123	13–14	58.3	99.1	1996–1999	Africa	No	None
Asher 2001 [14]	Yes	18,569/19,023	6-7/13-14	50.6/46.7	91.2/92.6	1992–1993	Oceania	Yes	None
Austin 1999 [15]	Yes	27,507	12–14	49.2	85.9	1995	Europe	Yes	6
Bröms 2013 [16]	No	4,886	1–6	50,7	67,5	2002	Europe	No	1, 2, 3, 4, 6
Cibella 2011 [17]	No	2,150	10–17	49.2	87.8	2005–2006	Europe	No	2, 3, 6, 7
Civelek 2010 [18]	No	5,664	9–11	50.9	91.3	2005–2006	Europe	No	3
Duggan 2012 [19]	No	1,474/1,535	6–9	47.3/47.9	74.8/76.2	2002/2007	Europe	Yes	3, 6, 7
Eder 1998 [20]	Yes	3,672/3,371	6-8/12-15	51.0/51.0	88.2/85.1	1995	Europe	No	3, 6
Falade 2004 [21]	Yes	1,312	6–7	46.8	73.3	1995	Africa	Yes	6, 7
Futamura 2011 [22]	No	27,389	6–14	47.2	74.4	2005	Asia	No	3, 6
Ghaffari 2012 [23]	No	1,818	7–12	65.0	91.0	2010	Asia	No	3, 4, 5, 7
Hailu 2003 [24]	No	3,365	13–14	40.1	98.4	1997	Africa	No	None
Hong 2012 [25]	No	31,201	0–13	51.1	82.1	2010	Asia	No	3, 4, 5, 6
Janahi 2006 [26]	No	3,283	6–14	52.3	93.8	2003–2004	Asia	No	3, 5
Lamnisos 2013 [27]	No	4,569/5,587	7-8/13-14	50,0/49,8	56,8/68,1	2007–2009	Europe	No	2, 3, 6
Liao 2005 [28]	No	7,040	6–8	51.5	89.4	2002	Asia	No	3, 6
Liao 2009 [29]	No	4,622	6–8	53.2	79.1	2007	Asia	No	3, 6
Mallol 2012 [30]	Yes	388,453/796,368	6-7/13-14	50.3/49.3	-	2000–2003	World	Yes/No	6
Manning 1997 [31]	Yes	3,148	13–14	46.0	92.1	1995	Europe	Yes	None
Marinho 2007 [32]	No	815	5	54.7	67.3	1998–2002?	Europe	Yes	1, 2, 3, 5, 6, 7
Martin Fernández 2004 [33]	Yes	3,018	13–14	51.4	100.0	<2002?	Europe	No	None
Musharrafieh 2009 [34]	No	3,115	13–14	48.6	-	2005	Asia	No	2, 6
Nwaru 2013 [35]	No	2,448	5	53.0	93.0	2001–2009	Europe	No	1, 2, 3, 7
Rahimi Rad 2007 [36]	No	3,000	13–14	50.0	98.3	2002–2003	Asia	No	None
Rahimi Rad 2008 [37]	No	2,999	6–7	48.4	94.4	2002–2003	Asia	No	7
Remes 1998 [38]	Yes	11,607	13–14	49.5	96.5	1994–1995	Europe	No	None
Robertson 1998 [39]	Yes	10,914/12,280	6-7/13-14	-	84.3/93.9	1993–1994	Oceania	Yes	6
Škvorc 2014 [40]	No	3,106	7–9	50,4	96,9	2005	Europe	No	3, 4
Wördemann 2006 [41]	No	398	5–13	48.0	100.0	2003–2004	North America	No	3, 4, 5, 7
Yao 2011 [42]	No	5,155	4–18	48.9	94.9	2007	Asia	No	3, 4, 5

(*Continued*)

Table 1. (*Continued*)

Article	ISAAC	No. analyzed*	Age range (years)	% Males	Response rate	Study year	Continent	English Question.	Violation protocols†
Ziyab 2014 [43]	No	1,345	10	50,7	92,4	1999	Europe	Yes	1, 2, 3, 5, 7

* Number of patients available for analysis

† 1) Recruitment at schools; 2) All schools or randomly selected; 3) Age groups 6–7 and 13–14 years; 4) Use of validated questionnaires; 5) questionnaires completed by parents (< 12 years old) or by adolescents themselves (≥ 12 years old); 6) Participation >90%; 7) N ≥3000

‡ Only two centers were included (Benslimane, Morocco; Conakry, Guinea.

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Cochrane Centre, The Cochrane Collaboration, 2011). This program provides risk ratios, 95% confidence intervals (CI) (using the Mantel-Haenszel test and random effects models) and the weight of every study. The extraction was limited to current symptoms (past 12 months) and data collected by written questionnaires. Study characteristics regarding gender, age, continent, validated (English) questionnaires, ISAAC/non-ISAAC study, number of participants, response rate, study period and ISAAC protocol violations were also collected. Data entry was additionally checked by two independent reviewers (AB, JW).

Statistical analyses

In order to calculate the mean prevalences, the studies were weighted for their number of participants. Risk ratios (RR) calculated by RevMan describe the risk of having two different atopic disorders when a child is known with one disorder. For example, if the RR for asthma is four, this would mean that a child with asthma has a fourfold risk of reporting eczema and allergic rhinitis in contrast to a child without asthma. Heterogeneity (I^2) was assessed using a random effects model.

For the study characteristics of this meta-analysis, a mixed-effects model was used for natural logarithm of the calculated RR for asthma, eczema and allergic rhinitis and for the prevalence of asthma, eczema, allergic rhinitis and having all three disorders. Initial models for these seven responses contained all covariates of interest as fixed effects: percentage of males, age, continent, ISAAC/non-ISAAC, number of participants, response rate, study period and the use of validated English questionnaires. The latter was chosen to explore the influence of using translations on the RR. Since not all studies provided data on the percentage of male participants and the response rate, and both variables did not have significant parameters in the complete case analysis, both variables were excluded from the models in order to be able to use all 57 studies for the meta regression. Some influential centers were removed from initial and final models using traditional measures: standardized residuals, DFFITS values, Cook's distance and hat values. All calculations were conducted in R with the metafor package (Wolfgang Viechtbauer (2010)). A p value of 0.01 was considered the limit of significance because of multiple testing (Bonferroni correction).

Results

Identification and selection of the literature

The combined search strategies resulted in 5,178 original abstracts. No articles were excluded because of language barriers but the majority (n = 3,607; 69.7%) did not meet the inclusion criteria, mainly because these articles did not present data on all three disorders or because ISAAC questionnaires were not used. We retrieved 1,571 full-text articles for detailed evaluation. Of these, another 1,533 studies were not included, mainly because the studies did not use

ISAAC questionnaires or because these articles did not present data on all three disorders. Finally 38 studies were initially included in this review for further analysis [2, 13–49] (Fig 1).

Description and final selection of studies

The ISAAC Phase 3 synthesis presented by Mallol et al. [30] covers a large number of surveyed children (n = 1,184,821). Four of the included ISAAC studies [45–48] were excluded because it is assumed that the data from these studies were already included by Mallol et al. [30]. The data presented by Song et al. [49] showed internal inconsistency and was therefore excluded. Furthermore, articles that only presented worldwide data (n = 2) [44, 50] were not used for the final analysis.

Finally, data from 31 studies were used, covering a large number of surveyed children (n = 1,430,329) in 102 different countries. Table 1 presents descriptive characteristics of the studies, including the results of the quality assessment. All officially acknowledged ISAAC studies, with the exception of one [38], used the same definition for asthma, eczema and allergic rhinitis. Non-ISAAC studies varied considerably in the definitions they used for the disorders.

Overall and regional difference in prevalence of atopic manifestations

The calculated worldwide prevalence for asthma, eczema and allergic rhinitis for children in the open population is 12.00% (95% CI: 11.99–12.00), 7.89% (95% CI: 7.88–7.89) and 12.66% (95% CI: 12.65–12.67), respectively. Fig 2 shows the prevalence per continent. None of the continents significantly influenced the worldwide prevalence of any one of the atopic disorders, neither did percentage of males, ISAAC/non-ISAAC, number of participants and the use of validated English questionnaires. There were significant negative associations between age and prevalence of eczema and between study period and prevalence of asthma. The worldwide observed prevalence of having all three diseases is 1.17% (95% CI: 1.17–1.17) and was not influenced by the above mentioned factors. If there would be no interrelationship at all between the three disorders, the expected worldwide prevalence of having all three disorders is only 0.12% (12.00%*7.89%*12.66%)). In the present review, the observed prevalence is 9.8 times higher than could be expected by chance, suggesting a close relationship between these disorders in children. It is remarkable that the prevalence of 'all three expected' is relatively consistent between the six continents (Fig 2).

Interrelationship between the atopic manifestations

Calculated RR for children with asthma, eczema and allergic rhinitis are presented in the Forest plots (Figs 3–5). If possible, the Forest plots provide a subdivision per article by continent and age. The overall RR for patients having asthma to also suffer from eczema and rhinitis is 5.41 (95% CI:4.76–6.16). For patients with eczema the RR is 4.24 (95% CI: 3.75–4.79) and for allergic rhinitis the RR is 6.20 (95% CI: 5.30–7.27). These risk ratios show a clear relationship of the three disorders. Additional analyses to examine whether RRs were influenced by covariates (percentage of males, age, continent, official ISAAC/non-ISAAC study, number of participants, response rate, study period and the use of validated English questionnaires) showed no significant effect on the calculated RR.

There is substantial heterogeneity (I^2 = 97–98%) between these studies. Subanalyses performed for different subgroups (percentage of males, age, continent, ISAAC/non-ISAAC, number of participants, response rate, study period) showed no major change in heterogeneity.

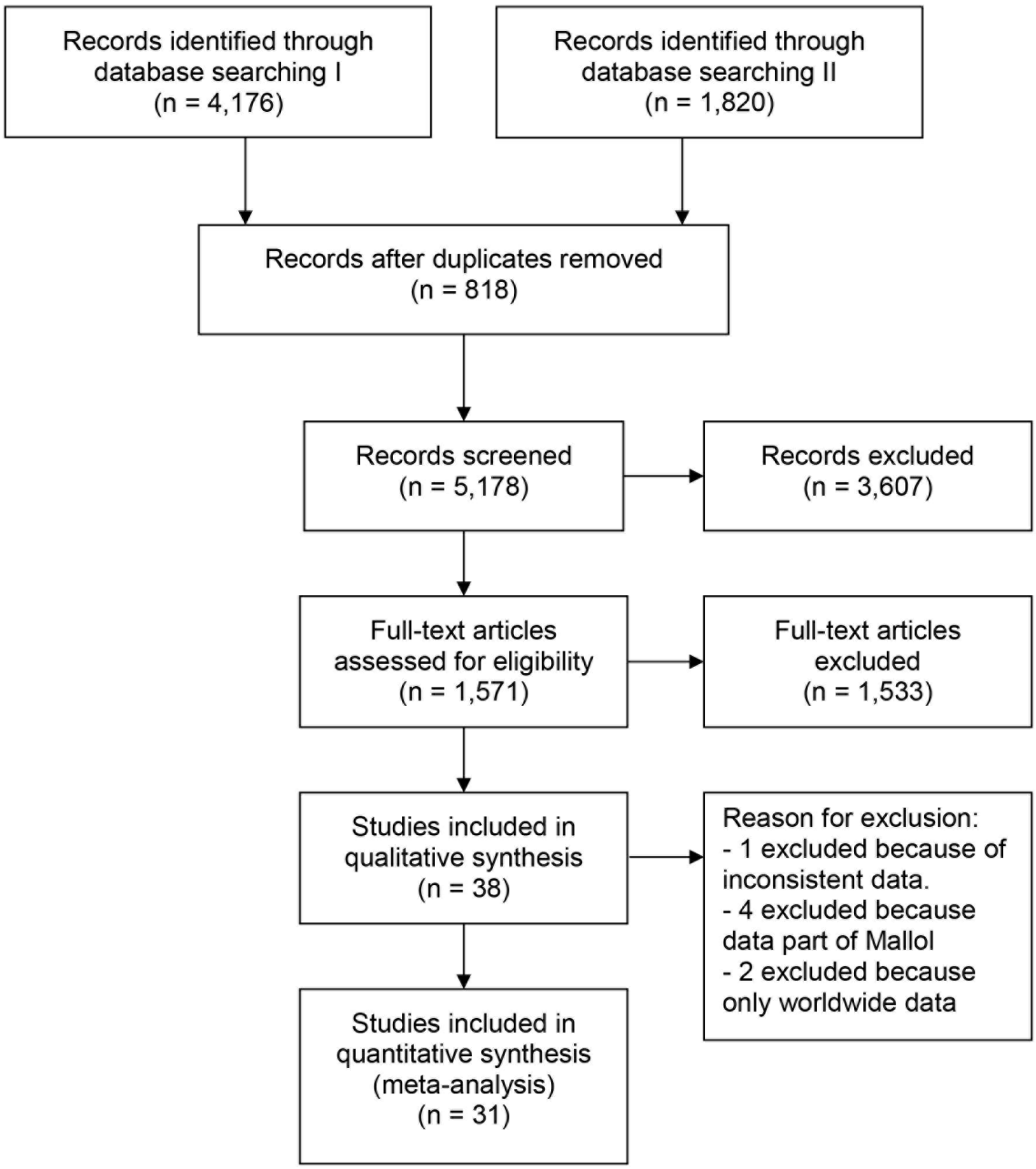

Fig 1. Flow diagram for selection of studies identified in the systematic review.

doi:10.1371/journal.pone.0131869.g001

Discussion

A comprehensive literature search retrieved data from 102 different countries, making this one of the largest meta-analysis of asthma, eczema and allergic rhinitis ever conducted. The calculated worldwide prevalence for asthma, eczema and allergic rhinitis for children in the open population is 12.0%, 7.9% and 12.7%, respectively. Overall this prevalence is higher than that presented earlier by Mallol et al [30]. None of the individual continents had a significant influenced on the worldwide prevalence of one of the atopic disorders.

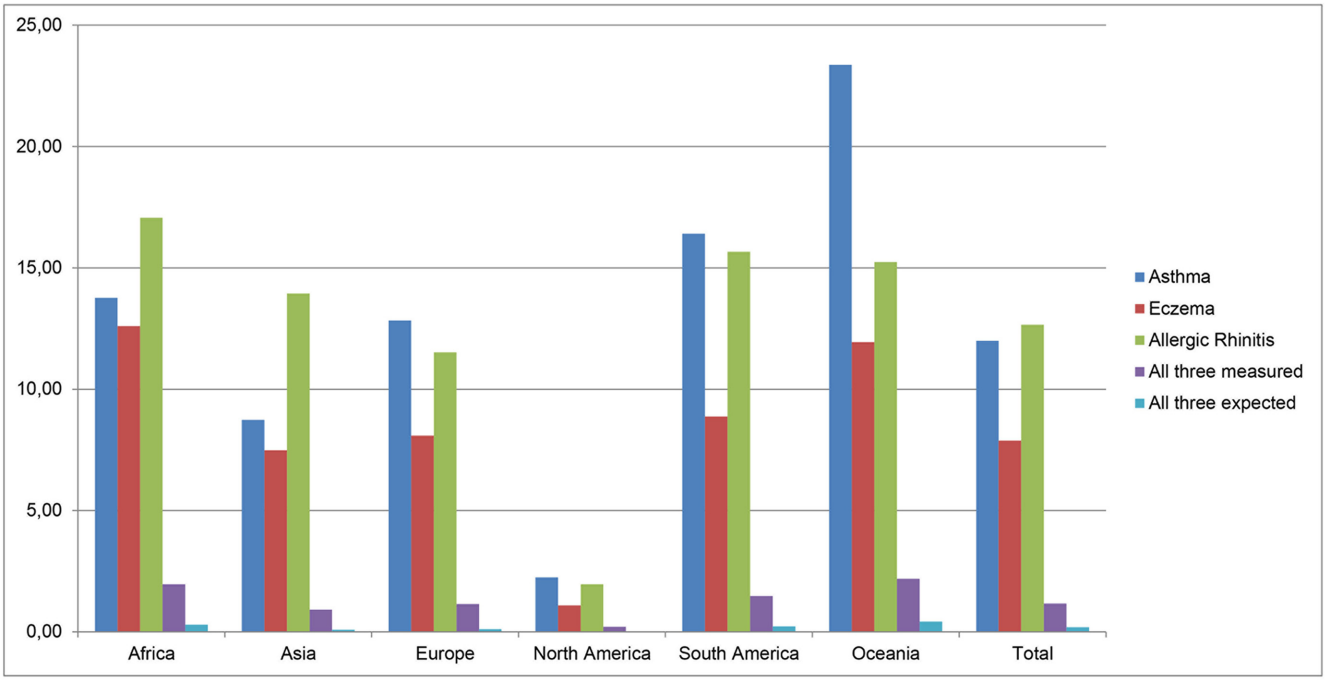

Fig 2. Prevalence (%) of the atopic disorders per continent.

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In this review, the observed prevalence of having all three disorders is 1.17% (95% CI: 1.17–1.18). This co-occurrence is substantially higher than could be expected by chance, based on the individual prevalence of each disorder (0.12%). This supports the hypothesis that there could be a fourth distinct group of children with all three disorders. A new and different way of looking at the interrelationships is by calculating RRs; the RRs presented in this review, describe the risk of having the other two atopic disorders when a child is known with one disorder. The RRs ranged from 4.24–6.20 and were not significantly influenced by any of the confounders investigated. Since all RR were > 1, this implies that the observed co-occurrence is not based on chance, but suggest a clear relationship between the disorders. Remarkably, the RR of eczema is low compared with the other two disorders; this might be because we used prevalence data based on having complaints in the past 12 months and not on lifetime prevalences. On average, eczema is seen in children at a younger age than those studied in this review, thereby resulting in a lower RR. This study also showed a significant decline in the prevalence of asthma when a child becomes older.

The wide variation in the prevalence of atopic diseases [1–4] has received considerable attention. Possible causes of these variations include (amongst others): genetics, use of paracetamol, use of antibiotics, breastfeeding, diet, body mass index, living in a rural area, and air pollution. However, none of these proposed factors fully explains this wide variation. Remarkably, when looking at the prevalence of having all three disorders, this wide variation does not occur to the same extent. In the present study, the limited degree of overlap between the three conditions (1.17%) was very similar to that reported by others [30, 50]. Asher et al. [44] even showed that this overlap has been relatively consistent over a period of seven years; for 6–7 year olds this overlap increased from 0.8% to 1.0% and for the 13–14 year olds the overlap increased from 1.1% to 1.3%. This consistency in prevalence also suggests that a fourth group of children with atopic disorders might exist. In addition to the three regularly described

Study or Subgroup	Weight	Risk Ratio M-H, Random, 95% CI
Ait-Khaled 2007 (MAR)	1.6%	8.85 [5.72, 13.69]
Ait-Khaled 2007 (GIN)	1.9%	4.65 [3.74, 5.78]
Asher 2001 (13-14yr)	1.9%	4.48 [3.89, 5.15]
Asher 2001 (6-7yr)	1.9%	6.45 [5.48, 7.60]
Austin 1999	2.0%	4.01 [3.63, 4.42]
Bröms 2013	1.8%	6.03 [4.56, 7.98]
Cibella 2011	1.0%	13.21 [5.18, 33.70]
Civelek 2010	1.9%	2.99 [2.33, 3.84]
Duggan 2012 (2002)	1.6%	6.95 [4.35, 11.10]
Duggan 2012 (2007)	1.7%	5.58 [3.78, 8.22]
Eder 1998 (12-15yr)	1.7%	6.38 [4.31, 9.44]
Eder 1998 (6-8yr)	1.6%	5.37 [3.32, 8.69]
Falade 2004	1.1%	7.23 [3.13, 16.70]
Futamura 2011	2.0%	3.05 [2.78, 3.34]
Ghaffari 2012	1.6%	3.20 [2.09, 4.89]
Hailu 2003	1.4%	29.45 [16.45, 52.72]
Hong 2012 (0-3yr)	1.9%	1.84 [1.46, 2.32]
Hong 2012 (10-13yr)	1.9%	3.04 [2.62, 3.53]
Hong 2012 (4-6yr)	1.9%	2.00 [1.67, 2.39]
Hong 2012 (7-9yr)	1.9%	2.70 [2.36, 3.09]
Janahi 2006	1.9%	3.87 [3.19, 4.70]
Lamnisos 2013 (13-14yr)	1.2%	16.84 [8.30, 34.14]
Lamnisos 2013 (7-8yr)	1.2%	5.23 [2.41, 11.35]
Liao 2005	1.9%	5.36 [4.27, 6.74]
Liao 2009	1.9%	4.02 [3.34, 4.83]
Mallol 2012 (AF; 13-14yr)	2.0%	3.84 [3.59, 4.11]
Mallol 2012 (AF; 6-7yr)	1.8%	7.82 [5.74, 10.66]
Mallol 2012 (AS; 13-14yr)	2.0%	5.70 [5.15, 6.31]
Mallol 2012 (AS; 6-7yr)	2.0%	5.89 [5.30, 6.55]
Mallol 2012 (EM; 13-14yr)	2.0%	5.27 [4.69, 5.93]
Mallol 2012 (EM; 6-7yr)	1.9%	9.91 [8.15, 12.04]
Mallol 2012 (IN; 13-14yr)	2.0%	10.58 [9.31, 12.03]
Mallol 2012 (IN; 6-7yr)	1.9%	13.75 [11.17, 16.93]
Mallol 2012 (N/E-E;13-14)	2.0%	7.06 [6.25, 7.97]
Mallol 2012 (N/E-EU; 6-7)	1.9%	9.24 [7.79, 10.97]
Mallol 2012 (NA; 13-14yr)	1.9%	57.71 [48.01, 69.38]
Mallol 2012 (NA; 6-7yr)	1.7%	7.32 [4.92, 10.89]
Mallol 2012 (OC; 6-7yr)	1.9%	5.53 [4.69, 6.51]
Mallol 2012 (OC; 13-14yr)	2.0%	3.39 [3.05, 3.76]
Mallol 2012 (SA; 13-14yr)	2.0%	3.87 [3.68, 4.07]
Mallol 2012 (SA; 6-7yr)	2.0%	4.65 [4.34, 4.99]
Mallol 2012 (W-EU; 13-14)	2.0%	5.83 [5.39, 6.29]
Mallol 2012 (W-EU; 6-7)	2.0%	8.09 [7.31, 8.96]
Manning 1997	1.7%	2.86 [1.98, 4.14]
Marinho 2007	1.3%	2.04 [1.05, 3.98]
Martin Fernández 2004	1.7%	3.44 [2.29, 5.18]
Musharrafieh 2009	1.9%	3.40 [2.86, 4.06]
Nwaru 2013	1.8%	3.91 [2.99, 5.11]
Rahimi Rad 2007	1.8%	9.82 [7.22, 13.35]
Rahimi Rad 2008	0.7%	6.55 [1.86, 23.07]
Remes 1998	1.9%	2.63 [2.27, 3.05]
Robertson 1998 (13-14yr)	1.9%	5.14 [4.28, 6.17]
Robertson 1998 (6-7yr)	1.9%	5.51 [4.38, 6.94]
Wördemann 2006	1.2%	6.22 [2.97, 13.04]
Yao 2011	1.9%	3.08 [2.41, 3.94]
Ziyab 2014	1.6%	5.97 [3.75, 9.51]
Škvorc 2014	1.7%	7.30 [5.04, 10.57]
Total (95% CI)	**100.0%**	**5.41 [4.76, 6.16]**
Total events		

Heterogeneity: Tau² = 0.22; Chi² = 2046.85, df = 56 (P < 0.00001); I² = 97%
Test for overall effect: Z = 25.79 (P < 0.00001)

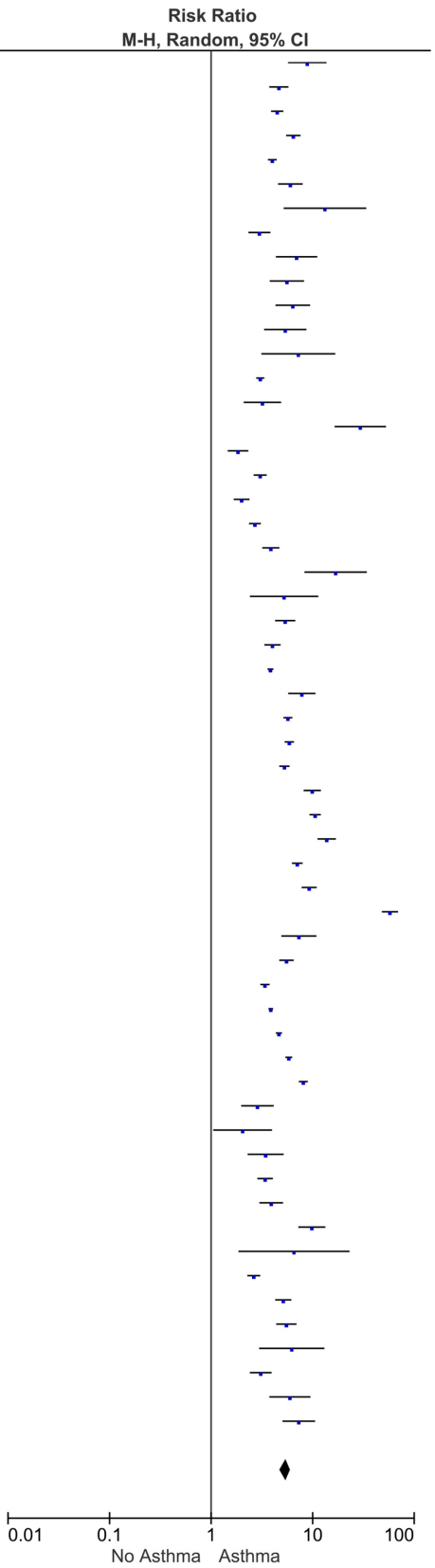

Fig 3. Forest plot of risk ratios for asthma.

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Study or Subgroup	Weight	Risk Ratio M-H, Random, 95% CI
Ait-Khaled 2007 (MAR)	1.5%	7.03 [4.41, 11.19]
Ait-Khaled 2007 (GIN)	1.8%	5.31 [4.23, 6.67]
Asher 2001 (13-14yr)	1.9%	2.81 [2.57, 3.07]
Asher 2001 (6-7yr)	1.9%	4.04 [3.60, 4.54]
Austin 1999	2.0%	3.29 [3.07, 3.52]
Bröms 2013	1.7%	4.41 [3.06, 6.36]
Cibella 2011	0.9%	11.61 [4.36, 30.91]
Civelek 2010	1.9%	2.70 [2.19, 3.35]
Duggan 2012 (2002)	1.8%	2.77 [2.07, 3.72]
Duggan 2012 (2007)	1.8%	2.88 [2.23, 3.73]
Eder 1998 (12-15yr)	1.7%	4.66 [3.39, 6.40]
Eder 1998 (6-8yr)	1.6%	3.86 [2.51, 5.95]
Falade 2004	1.0%	3.57 [1.55, 8.22]
Futamura 2011	1.9%	3.26 [2.96, 3.59]
Ghaffari 2012	1.6%	4.34 [2.93, 6.41]
Hailu 2003	1.3%	60.45 [31.51, 115.96]
Hong 2012 (0-3yr)	1.8%	1.55 [1.22, 1.96]
Hong 2012 (10-13yr)	1.9%	2.13 [1.79, 2.53]
Hong 2012 (4-6yr)	1.9%	1.52 [1.24, 1.86]
Hong 2012 (7-9yr)	1.9%	1.94 [1.65, 2.27]
Janahi 2006	1.9%	2.59 [2.16, 3.12]
Lamnisos 2013 (13-14yr)	1.4%	13.81 [7.82, 24.37]
Lamnisos 2013 (7-8yr)	1.3%	4.27 [2.21, 8.25]
Liao 2005	1.8%	3.95 [3.08, 5.08]
Liao 2009	1.8%	3.83 [2.94, 4.99]
Mallol 2012 (AF; 13-14yr)	2.0%	3.79 [3.55, 4.05]
Mallol 2012 (AF; 6-7yr)	1.8%	7.66 [5.67, 10.35]
Mallol 2012 (AS; 13-14yr)	1.9%	4.83 [4.41, 5.28]
Mallol 2012 (AS; 6-7yr)	1.9%	4.16 [3.76, 4.61]
Mallol 2012 (EM; 13-14yr)	1.9%	5.41 [4.86, 6.02]
Mallol 2012 (EM; 6-7yr)	1.9%	7.83 [6.69, 9.17]
Mallol 2012 (IN; 13-14yr)	1.9%	10.97 [9.82, 12.25]
Mallol 2012 (IN; 6-7yr)	1.9%	9.99 [8.49, 11.76]
Mallol 2012 (N/E-E;13-14)	1.9%	5.44 [4.92, 6.02]
Mallol 2012 (N/E-EU; 6-7)	1.9%	6.44 [5.57, 7.45]
Mallol 2012 (NA; 13-14yr)	1.9%	40.91 [35.46, 47.21]
Mallol 2012 (NA; 6-7yr)	1.8%	5.70 [4.24, 7.67]
Mallol 2012 (OC; 6-7yr)	1.9%	3.86 [3.39, 4.39]
Mallol 2012 (OC; 13-14yr)	1.9%	3.50 [3.20, 3.83]
Mallol 2012 (SA; 13-14yr)	2.0%	3.72 [3.56, 3.88]
Mallol 2012 (SA; 6-7yr)	2.0%	3.80 [3.59, 4.02]
Mallol 2012 (W-EU; 13-14)	2.0%	4.19 [3.95, 4.45]
Mallol 2012 (W-EU; 6-7)	2.0%	4.94 [4.53, 5.40]
Manning 1997	1.8%	1.85 [1.37, 2.49]
Marinho 2007	1.2%	1.01 [0.52, 1.98]
Martin Fernández 2004	1.7%	3.33 [2.31, 4.81]
Musharrafieh 2009	1.9%	3.45 [2.93, 4.07]
Nwaru 2013	1.4%	10.06 [5.94, 17.05]
Rahimi Rad 2007	1.8%	7.70 [6.02, 9.84]
Rahimi Rad 2008	0.8%	6.16 [2.19, 17.34]
Remes 1998	1.9%	2.05 [1.76, 2.40]
Robertson 1998 (13-14yr)	1.9%	3.18 [2.86, 3.54]
Robertson 1998 (6-7yr)	1.9%	2.93 [2.52, 3.41]
Wördemann 2006	1.8%	1.79 [1.32, 2.43]
Yao 2011	1.8%	2.65 [2.06, 3.40]
Ziyab 2014	1.6%	3.18 [2.14, 4.73]
Škvorc 2014	1.7%	4.93 [3.55, 6.86]
Total (95% CI)	**100.0%**	**4.24 [3.75, 4.79]**
Total events		

Heterogeneity: Tau² = 0.20; Chi² = 2530.29, df = 56 (P < 0.00001); I² = 98%
Test for overall effect: Z = 23.12 (P < 0.00001)

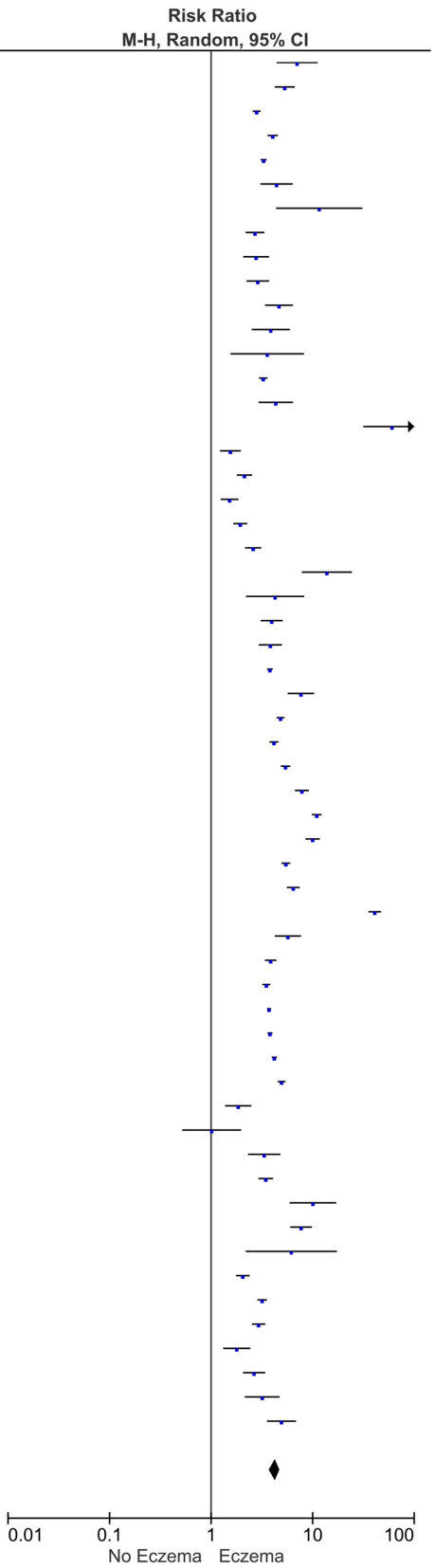

Fig 4. Forest plot of risk ratios for eczema.

doi:10.1371/journal.pone.0131869.g004

Study or Subgroup	Weight	Risk Ratio M-H, Random, 95% CI
Ait-Khaled 2007 (MAR)	1.4%	12.51 [6.22, 25.15]
Ait-Khaled 2007 (GIN)	1.9%	7.16 [5.47, 9.37]
Asher 2001 (13-14yr)	1.9%	3.92 [3.51, 4.37]
Asher 2001 (6-7yr)	1.9%	5.63 [5.05, 6.29]
Austin 1999	2.0%	4.28 [3.96, 4.62]
Bröms 2013	1.9%	7.31 [5.56, 9.62]
Cibella 2011	0.6%	22.27 [4.35, 114.09]
Civelek 2010	1.8%	3.26 [2.44, 4.36]
Duggan 2012 (2002)	1.6%	6.47 [3.92, 10.67]
Duggan 2012 (2007)	1.7%	8.02 [4.96, 12.97]
Eder 1998 (12-15yr)	1.6%	8.00 [4.68, 13.66]
Eder 1998 (6-8yr)	1.5%	8.98 [4.96, 16.25]
Falade 2004	1.3%	6.50 [2.85, 14.84]
Futamura 2011	1.9%	2.60 [2.33, 2.90]
Ghaffari 2012	1.7%	2.98 [1.89, 4.68]
Hailu 2003	1.6%	33.56 [18.76, 60.03]
Hong 2012 (0-3yr)	1.9%	1.45 [1.12, 1.88]
Hong 2012 (10-13yr)	1.9%	1.36 [1.11, 1.67]
Hong 2012 (4-6yr)	1.9%	1.09 [0.86, 1.36]
Hong 2012 (7-9yr)	1.9%	1.20 [1.00, 1.44]
Janahi 2006	1.9%	4.88 [3.77, 6.32]
Lamnisos 2013 (13-14yr)	1.4%	14.69 [7.24, 29.83]
Lamnisos 2013 (7-8yr)	1.4%	6.73 [3.41, 13.28]
Liao 2005	1.8%	6.55 [4.75, 9.04]
Liao 2009	1.8%	6.38 [4.50, 9.04]
Mallol 2012 (AF; 13-14yr)	2.0%	5.68 [5.24, 6.15]
Mallol 2012 (AF; 6-7yr)	1.8%	11.12 [8.15, 15.19]
Mallol 2012 (AS; 13-14yr)	1.9%	7.31 [6.49, 8.25]
Mallol 2012 (AS; 6-7yr)	1.9%	7.42 [6.61, 8.34]
Mallol 2012 (EM; 13-14yr)	1.9%	7.96 [6.91, 9.17]
Mallol 2012 (EM; 6-7yr)	1.9%	11.93 [10.03, 14.18]
Mallol 2012 (IN; 13-14yr)	1.9%	16.24 [13.73, 19.20]
Mallol 2012 (IN; 6-7yr)	1.9%	19.92 [16.33, 24.30]
Mallol 2012 (N/E-E;13-14)	1.9%	8.56 [7.56, 9.70]
Mallol 2012 (N/E-EU; 6-7)	1.9%	11.44 [9.76, 13.41]
Mallol 2012 (NA; 13-14yr)	1.9%	73.37 [60.25, 89.35]
Mallol 2012 (NA; 6-7yr)	1.8%	8.43 [6.25, 11.37]
Mallol 2012 (OC; 6-7yr)	1.9%	5.53 [4.86, 6.29]
Mallol 2012 (OC; 13-14yr)	1.9%	5.04 [4.50, 5.65]
Mallol 2012 (SA; 13-14yr)	2.0%	6.14 [5.78, 6.51]
Mallol 2012 (SA; 6-7yr)	2.0%	6.63 [6.19, 7.11]
Mallol 2012 (W-EU; 13-14)	2.0%	5.75 [5.32, 6.21]
Mallol 2012 (W-EU; 6-7)	2.0%	10.40 [9.41, 11.49]
Manning 1997	1.7%	3.18 [2.05, 4.95]
Marinho 2007	1.5%	1.77 [0.98, 3.21]
Martin Fernández 2004	1.7%	2.62 [1.69, 4.05]
Musharrafieh 2009	1.9%	4.17 [3.26, 5.33]
Nwaru 2013	1.7%	6.48 [4.33, 9.68]
Rahimi Rad 2007	1.8%	14.03 [9.84, 20.00]
Rahimi Rad 2008	1.0%	9.14 [3.10, 26.96]
Remes 1998	1.9%	2.32 [1.98, 2.72]
Robertson 1998 (13-14yr)	1.9%	4.75 [4.10, 5.52]
Robertson 1998 (6-7yr)	1.9%	4.65 [3.92, 5.51]
Wördemann 2006	1.4%	5.08 [2.42, 10.65]
Yao 2011	1.2%	16.91 [6.83, 41.88]
Ziyab 2014	1.5%	7.70 [4.16, 14.23]
Škvorc 2014	1.7%	9.20 [6.09, 13.91]
Total (95% CI)	**100.0%**	**6.20 [5.30, 7.27]**

Total events

Heterogeneity: Tau² = 0.33; Chi² = 2811.31, df = 56 (P < 0.00001); I² = 98%

Test for overall effect: Z = 22.59 (P < 0.00001)

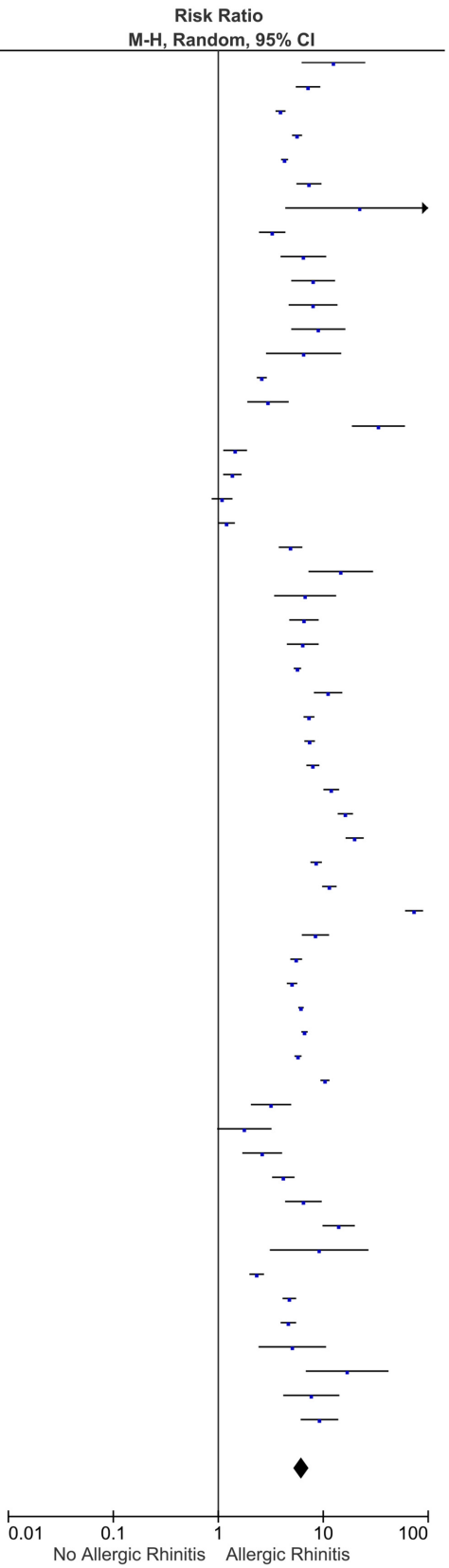

Fig 5. Forest plot of risk ratios for allergic rhinitis.

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groups of children with asthma, eczema or allergic rhinitis, there seems to be a fourth distinct group of children with all three disorders, that may show distinct characteristics regarding severity, causes, treatment or prognosis.

We suggest to add another chapter to the already impressive ISAAC study, focusing on this potentially distinct fourth group of children with all three manifestations. Is this group distinctive due to severity of symptoms? Does this group have a different genotype? Does this group need a different pharmacological approach? Does this group have a different prognosis? Which factors influence this group?

This meta-analysis has some limitations. First, one reviewer selected the studies based on title and abstract. Despite a random check of 50% of the retrieved articles showing concordance, we assumed that no relevant articles were missed. However, the full-text selection was done by two independent reviewers. In our review there was no limitation for any language and (where possible) authors were contacted for missing data.

When conducting a large multicenter international cross-sectional study, there is always a risk of potential limitations. Clear examples include language problems, cultural differences, environmental aspects, different healthcare systems, etc. Either an overestimation or an underestimation might be found. Another concern is the possible overestimation of the prevalence of the three atopic diseases. Although the questionnaires asked about symptoms, the symptoms could well be attributable to other diseases; this concern is shared by others [28, 46, 48, 51]. Furthermore, Cane et al.[52] showed that the conceptual understanding of 'wheeze' differs between reporting parents and epidemiology definitions. Finally, different research groups used different definitions for the atopic disorders; this could have influenced our results.

The high level of heterogeneity that we found suggests that the included studies differ significantly from each other. However, this can be explained by the large number of participants in each study. Because the studies have such large populations, the CIs will be very small. Even small differences will result in statistical heterogeneity, but not in clinical heterogeneity.

This meta analyses supports the hypothesis that these three atopic disorders are clearly related. A biological plausible pathway for these relationships can be found in the atopic march theory. However, the obtained data in this meta-analysis does not allow to quantify the effect of this atopic march theory. This is due to two limitations. The first limitation relates to the cross sectional methods used. We have no follow-up data available for an individual child. The second one is that we limited our data inclusion to symptoms within the previous year (year prevalence). Using year-prevalences instead of life-time prevalences could result in an underestimation of the prevalences. Atopic dermatitis often goes into a clinical remission, but the atopic phenotype persists. The same applies to asthma. For example, when establishing the prevalence at the age of e.g. 12 years, the child may answer no, but in fact might still have an atopic phenotype.

Conclusions

We studied the prevalence and interrelationships between asthma, allergic rhinitis and eczema in children using data obtained from ISAAC questionnaires. The interrelationships were studied using risk ratios, adjusted for potential confounders. Our meta-analysis has shown that the prevalence of children with a co-occurrence of asthma, eczema and allergic rhinitis was low, but significantly higher than could be expected by chance. The prevalence of having all three atopic disorders was remarkably consistent in all continents. This study supports the hypothesis that there might be a forth distinct group of children with all three disorders, in contrast to the traditional classification of children with asthma or allergic rhinitis or atopic eczema.

Researchers and clinicians might need to consider this forth group as a separate group of children with their own characteristics.

Supporting Information

S1 Appendix. Search strings used for literature search.
(DOCX)

S2 Appendix. PRISMA 2009 Checklist.
(DOC)

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Author Contributions

Conceived and designed the experiments: DP HM PB AB. Performed the experiments: DP JW EA HM NR AB. Analyzed the data: DP AB. Contributed reagents/materials/analysis tools: DP AB. Wrote the paper: DP JW NR EA PB AB. Article selection: DP JW EA NR.

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S1 Appendix

Search string ONE contained the following specific terms:

For EMBASE:

(asthma/exp OR wheezing/de OR (asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper NEXT/1 (responsiv* OR sensitiv*))):ab,ti) AND (eczema/de OR 'atopic dermatitis'/de OR (eczem* OR (atopic NEAR/3 dermatit*)):ab,ti) AND (rhinitis/exp OR conjunctivitis/exp OR (rhinitis* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen NEAR/3 Allerg*) OR Pollinos* OR ((hay) NEXT/1 (fever*)) OR hayfever):ab,ti) AND (Epidemiology/exp OR 'epidemiological data'/exp OR epidemiology:lnk OR (prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case NEAR/3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR (odds NEXT/1 ratio*) OR etiol* OR aetiol* OR (natural NEXT/1 histor*) OR predict* OR prognos* OR outcome* OR course*):ab,ti) AND (child/exp OR newborn/exp OR adolescent/exp OR adolescence/exp OR 'child behavior'/de OR 'child parent relation'/de OR (adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti)

For Medline via OvidSP

(exp asthma/ OR (asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper ADJ (responsiv* OR sensitiv*))).ab,ti.) AND (exp Dermatitis, Atopic/ OR exp Eczema/ OR Eczem*.ab,ti. OR (atopic ADJ3 dermatit*).ab,ti.) AND (exp Rhinitis/ OR exp Conjunctivitis/ OR (rhinit* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen ADJ3 Allerg*) OR Pollinos* OR hayfever* OR hay fever*).ab,ti.) AND (exp Epidemiologic Studies/ OR exp Epidemiologic Factors/ OR epidemiology.xs. OR (prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case ADJ3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR odds ratio* OR etiol* OR aetiol* OR natural histor* OR predict* OR prognos* OR outcome* OR course*).ab,ti.) AND (exp child/ OR exp infant/ OR (infan* OR newborn* OR new born* OR baby OR babies OR neonat* OR perinat* OR postnat* OR child* OR kid? OR toddler* OR teen* OR boy? OR girl? OR minor? OR underag* OR (under ADJ2 ag?) OR juvenil* OR youth? OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatric* OR peadiatric* OR school* OR preschool* OR highschool* OR suckling*).ab,ti. OR ((adoles*.ab,ti. OR adolescent/) NOT exp adult/))

PubMed publisher

(asthma[mh] OR (asthma*[tiab] OR wheez*[tiab] OR hyperresponsiv*[tiab] OR hypersensit*[tiab] OR hyper responsiv*[tiab] OR hyper sensitiv*[tiab])) AND (Dermatitis, Atopic[mh] OR Eczema[mh] OR Eczem*[tiab] OR (atopic AND dermatit*[tiab])) AND (Rhinitis[mh] OR Conjunctivitis[mh] OR (rhinit*[tiab] OR rhinoconjunctivit*[tiab] OR conjunctivit*[tiab] OR (Pollen AND Allerg*[tiab]) OR Pollinos*[tiab] OR hayfever*[tiab] OR hay fever*[tiab])) AND (Epidemiologic Studies[mh] OR Epidemiologic Factors[mh] OR epidemiology[sh] OR (prevalenc*[tiab] OR inciden*[tiab] OR trend*[tiab] OR associat*[tiab] OR comorbid*[tiab] OR relat*[tiab] OR correlat*[tiab] OR (case AND (control*[tiab] OR comparison OR referent)) OR epidemiolog*[tiab] OR cohort*[tiab] OR risk*[tiab] OR caus*[tiab] OR odds ratio*[tiab] OR etiol*[tiab] OR aetiol*[tiab] OR natural histor*[tiab] OR predict*[tiab] OR prognos*[tiab] OR outcome*[tiab] OR course*[tiab])) AND (child[mh] OR infant[mh] OR (infan*[tiab] OR newborn*[tiab] OR new born*[tiab] OR baby OR babies OR neonat*[tiab] OR perinat*[tiab] OR postnat*[tiab] OR child*[tiab] OR kid* OR toddler*[tiab] OR teen*[tiab] OR boy* OR girl* OR minor* OR underag*[tiab] OR under ag* OR juvenil*[tiab] OR youth* OR kindergar*[tiab] OR puber*[tiab] OR pubescen*[tiab] OR prepubescen*[tiab] OR prepuberty*[tiab] OR pediatric*[tiab] OR peadiatric*[tiab] OR school*[tiab] OR preschool*[tiab] OR highschool*[tiab] OR suckling*[tiab]) OR ((adoles*[tiab] OR adolescent[mh]) NOT adult[mh])) AND publisher[sb]

For Cochrane

((asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper NEXT/1 (responsiv* OR sensitiv*))):ab,ti) AND ((eczem* OR (atopic NEAR/3 dermatit*)):ab,ti) AND ((rhinitis* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen NEAR/3 Allerg*) OR Pollinos* OR ((hay) NEXT/1 (fever*)) OR hayfever):ab,ti) AND ((prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case NEAR/3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR (odds NEXT/1 ratio*) OR etiol* OR aetiol* OR (natural NEXT/1 histor*) OR predict* OR prognos* OR outcome* OR course*):ab,ti) AND ((adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti)

Google scholar

asthma eczema rhinitis prevalence|incidence|epidemiology|cohort|risk|etiology|prognosis|outcome adolescents|infants|children|newborns "family|general|primary physician|practice|doctor|care"

Search string TWO contained the following specific terms:

For EMBASE:

((asthma/exp OR wheezing/de OR (asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper NEXT/1 (responsiv* OR sensitiv*))):ab,ti) OR (eczema/de OR 'atopic dermatitis'/de OR (eczem* OR (atopic NEAR/3 dermatit*)):ab,ti) OR (rhinitis/exp OR conjunctivitis/exp OR (rhinitis* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen NEAR/3 Allerg*) OR Pollinos* OR ((hay) NEXT/1 (fever*)) OR hayfever):ab,ti)) AND (Epidemiology/exp OR 'epidemiological data'/exp OR epidemiology:lnk OR (prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case NEAR/3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR (odds NEXT/1 ratio*) OR etiol* OR aetiol* OR (natural NEXT/1 histor*) OR predict* OR prognos* OR outcome* OR course*):ab,ti) AND (child/exp OR newborn/exp OR adolescent/exp OR adolescence/exp OR 'child behavior'/de OR 'child parent relation'/de OR (adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti) AND (Isaac OR 'Asthma and Allergies in Childhood' OR 'Asthma and Allergy in Childhood'):de,ab,ti

For Medline via OvidSP

((exp asthma/ OR (asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper ADJ (responsiv* OR sensitiv*))).ab,ti.) OR (exp Dermatitis, Atopic/ OR exp Eczema/ OR Eczem*.ab,ti. OR (atopic ADJ3 dermatit*).ab,ti.) OR (exp Rhinitis/ OR exp Conjunctivitis/ OR (rhinit* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen ADJ3 Allerg*) OR Pollinos* OR hayfever* OR hay fever*).ab,ti.)) AND (exp Epidemiologic Studies/ OR exp Epidemiologic Factors/ OR epidemiology.xs. OR (prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case ADJ3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR odds ratio* OR etiol* OR aetiol* OR natural histor* OR predict* OR prognos* OR outcome* OR course*).ab,ti.) AND (exp child/ OR exp infant/ OR (infan* OR newborn* OR new born* OR baby OR babies OR neonat* OR perinat* OR postnat* OR child* OR kid? OR toddler* OR teen* OR boy? OR girl? OR minor? OR underag* OR (under ADJ2 ag?) OR juvenil* OR youth? OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepuberty* OR pediatric* OR peadiatric* OR school* OR preschool* OR highschool* OR suckling*).ab,ti. OR ((adoles*.ab,ti. OR adolescent/) NOT exp adult/)) AND (Isaac OR "Asthma and Allergies in Childhood" OR "Asthma and Allergy in Childhood").ab,ti.

Pubmed publisher

((asthma[mh] OR (asthma*[tiab] OR wheez*[tiab] OR hyperresponsiv*[tiab] OR hypersensit*[tiab] OR (hyper responsiv*[tiab] OR hypersensitiv*[tiab])) OR (Dermatitis, Atopic[mh] OR Eczema[mh] OR Eczem*[tiab] OR (atopic AND dermatit*[tiab])) OR (Rhinitis[mh] OR Conjunctivitis[mh] OR (rhinit*[tiab] OR rhinoconjunctivit*[tiab] OR conjunctivit*[tiab] OR (Pollen AND Allerg*[tiab]) OR Pollinos*[tiab] OR hayfever*[tiab] OR hay fever*[tiab]))) AND (Epidemiologic Studies[mh] OR Epidemiologic Factors[mh] OR epidemiology[sh] OR (prevalenc*[tiab] OR inciden*[tiab] OR trend*[tiab] OR associat*[tiab] OR comorbid*[tiab] OR relat*[tiab] OR correlat*[tiab] OR (case AND (control*[tiab] OR comparison OR referent)) OR epidemiolog*[tiab] OR cohort*[tiab] OR risk*[tiab] OR caus*[tiab] OR odds ratio*[tiab] OR etiol*[tiab] OR aetiol*[tiab] OR natural histor*[tiab] OR predict*[tiab] OR prognos*[tiab] OR outcome*[tiab] OR course*[tiab])) AND (child[mh] OR infant[mh] OR (infan*[tiab] OR newborn*[tiab] OR new born*[tiab] OR baby OR babies OR neonat*[tiab] OR perinat*[tiab] OR postnat*[tiab] OR child*[tiab] OR kid* OR toddler*[tiab] OR teen*[tiab] OR boy* OR girl* OR minor* OR underag*[tiab] OR (under ag*) OR juvenil*[tiab] OR youth* OR kindergar*[tiab] OR puber*[tiab] OR pubescen*[tiab] OR prepubescen*[tiab] OR prepuberty*[tiab] OR pediatric*[tiab] OR peadiatric*[tiab] OR school*[tiab] OR preschool*[tiab] OR highschool*[tiab] OR suckling*[tiab]) OR ((adoles*[tiab] OR adolescent[mh]) NOT adult[mh])) AND (Isaac OR "Asthma and Allergies in Childhood" OR "Asthma and Allergy in Childhood") AND publisher[sb]

For Cochrane

(((asthma* OR wheez* OR hyperresponsiv* OR hypersensit* OR (hyper NEXT/1 (responsiv* OR sensitiv*))):ab,ti) OR ((eczem* OR (atopic NEAR/3 dermatit*)):ab,ti) OR ((rhinitis* OR rhinoconjunctivit* OR conjunctivit* OR (Pollen NEAR/3 Allerg*) OR Pollinos* OR ((hay) NEXT/1 (fever*)) OR hayfever):ab,ti)) AND ((prevalenc* OR inciden* OR trend* OR associat* OR comorbid* OR relat* OR correlat* OR (case NEAR/3 (control* OR comparison OR referent)) OR epidemiolog* OR cohort* OR risk* OR caus* OR (odds NEXT/1 ratio*) OR etiol* OR aetiol* OR (natural NEXT/1 histor*) OR predict* OR prognos* OR outcome* OR course*):ab,ti) AND ((adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 ag*) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool*):ab,ti) AND (Isaac OR 'Asthma and Allergies in Childhood' OR 'Asthma and Allergy in Childhood'):ab,ti

Google scholar

asthma|wheezing|hyperresponsive|hypersensitivity|eczema|"atopic dermatitis"|rhinitis|conjunctivitis|"Pollen Allergy|allergies"|Pollinos|"hay fever"|hayfever prevalence|incidence|comorbidity|comorbidities|epidemiology|epidemiological infants|children Isaac

S2 Appendix: PRISMA 2009 Checklist: Pols et al.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	-
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5 + S1
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5 + S1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6 + table 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8-9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8-9

S2 Appendix: PRISMA 2009 Checklist: Pols et al.

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8-9
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10 + fig1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10 + table1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Forest plot 1-3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11 Forest plot 1-3 Fig 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-11 Forest plot 1-3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	No funding

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097