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History of allergic rhinitis and risk of asthma; a systematic review and meta-analysis

Hamid Reza Tohidinik[a,b,c], Narmeen Mallah[c,d] and Bahi Takkouche[c,d]*

ABSTRACT

Background: Allergic rhinitis has been suspected to be a risk factor for asthma in several studies but this association is not firmly established. The objective of this study was to synthesize the evidence of the association between allergic rhinitis and the risk of asthma through a systematic review and meta-analysis.

Methods: We performed a search in Medline, Scopus, ISI Proceedings databases and other databases from inception until February 2019, followed by manual search to identify potentially relevant case-control and cohort studies that reported relative risk estimates and confidence intervals of the association between allergic rhinitis and asthma. Cross-sectional studies were excluded. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using fixed and random effects models and quality of studies was assessed through a modified version of the Newcastle-Ottawa scale.

Results: Twenty-nine eligible studies, 22 cohort and 7 case-control studies, with a total of 274489 subjects, were included in the meta-analysis. The results show that history of allergic rhinitis is significantly associated with the occurrence of asthma (OR = 3.82; 95% CI: 2.92–4.99). European studies showed a stronger association (OR = 4.35; (95% CI: 3.12–6.06) than non-European studies (OR = 2.75; 95% CI: 2.16–3.50), and case-control studies showed a stronger association (OR = 4.71; 95% CI: 3.58–6.17) than cohort studies (OR = 3.42; 95% CI: 2.60–4.50).

Conclusions: This meta-analysis shows that allergic rhinitis is strongly associated with asthma. Further prospective studies on the effect of treatment of allergic rhinitis on the development of asthma are needed. Relief of airway allergic manifestations may need dual control of allergic rhinitis and asthma.

Registration: PROSPERO database with registration number CRD42017055156.

Keywords: Allergic rhinitis, Asthma, Meta-analysis

[a]HIV/STI Surveillance Research Center, WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran
*Corresponding author. Department of Preventive Medicine. Faculty of Medicine University of Santiago de Compostela 15782 Santiago de Compostela, Spain. E-mail: bahi.takkouche@usc.es
Full list of author information is available at the end of the article

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INTRODUCTION

Asthma is an important health problem. Its prevalence is increasing worldwide, especially in low and middle income countries.[1] The Global Burden of Disease 2015 estimated that nearly 400 million people around the world suffer from this condition. Asthma is considered as the 11th highest cause of Years Lived with Disability (YLDs) worldwide.[2,3]

Allergic Rhinitis (AR) is a disease the prevalence of which is increasing in a similar fashion to that of asthma.[1] It affects 10–30% of the general population and is suspected to be a risk factor for onset of asthma in several epidemiologic studies.[4–7] However, most studies of this relation are of a cross-sectional nature, a design that could prove inadequate for causal inference. Furthermore, the remaining case-control and cohort studies evaluating this association show effect estimates the magnitude of which vary considerably from study to study, swaying between absence of statistically significant association,[8] and extremely strong relationships.[9] Yet in 2012, the ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines stated that sophisticated statistical methods should be implemented in order to have a more objective view of the link between AR and asthma.[10]

To provide a global assessment and a quantitative summary of the association between AR and asthma, we performed a systematic review and meta-analysis of cohort and case-control studies.

METHODS

Search strategy

We searched MEDLINE via Pubmed, Scopus, the Conference Proceedings Citation Index-Science (CPCI–S) database, the Open Access Theses and Dissertations (OATD), and the 5 regional bibliographic databases of the World Health Organization (WHO) (African Index Medicus, Latin American and Caribbean Health Science Literature Database, Index Medicus for the Eastern Mediterranean Region, Index Medicus for South-East Asia Region, Western Pacific Region Index Medicus), from inception of each database to the end of February 2019, without any language limitation. The search strategy was as follows: (((((("Rhinitis, Allergic, Seasonal"[Mesh]) OR ("Rhinitis, Allergic"[Mesh]) OR "allergic rhinitis" OR rhinitis)))) AND (("Asthma"[Mesh]) OR asthma) AND ((((("Case-Control Studies"[Mesh]) OR "Cohort Studies"[Mesh]) OR case-control) OR cohort) for Medline and equivalent wording in other databases. Due to the nature of exposure, rhinitis, our meta-analysis had to be based on observational studies only, in spite of their limitations. No experimental studies can be carried out on this topic. To find any additional published study, the reference lists of all retrieved articles and related review articles were searched manually. All searches were performed by two independent reviewers (HRT and NM) and disagreements about inclusion of some studies were resolved by consensus and, when needed, by consulting with a third party (BT). The review protocol was registered in PROSPERO with registration number CRD42017055156.

Inclusion criteria

Case-control and cohort studies were included if: 1) the main or secondary outcome was asthma, 2) the exposure of interest or one of the covariates was allergic rhinitis, 3) they reported a measure of association between allergic rhinitis and asthma such as Risk Ratio, Rate Ratio, Odds Ratio and their variance, standard error or 95% confidence intervals (CI), or provided enough raw data to calculate them. Whenever necessary, we contacted the authors to provide more information for the calculation of the effect measure or to clarify some methodologic aspects of the study.[11–14] Studies without comparison group (allergic rhinitis-free in cohort studies and asthma-free in case-control studies) and those that did not report measures of effect nor provide enough information for calculating them were excluded.[13] If a study did not adjust for any factor, this study was not excluded but instead, we used its crude estimate.[8,15] In case of duplication of a publication, we included the most complete one. When we were unable to assess whether two publications were from the same study, we contacted their authors to consult about this issue.[7,16–21]

Author (Year)	Country	Source of data	N° of cases of asthma/ cohort size	N° of allergic rhinitis patients	Age at start of cohort	Follow-up duration	RR (95%CI)	Adjusting or matching variables
Segura-Navas et al. (2018)[40]	Spain	Cohort of schoolchildren in Castellón, Spain	44/1280	106	13–15 years	10 years	4.05 (1.71–9.60)	Age, sex, family history asthma, family history of allergic rhinitis, history of respiratory diseases, breastfeeding, living place, passive smoking, mother's age at time of birth, and pet at home
Moshe et al. (2015)[41]	Israel	All-male Israel Defense Forces (IDF)[a]	1984/128591	4891	18–21 years	3 years	1.86 (1.57–2.21)	Sex
Tormanen et al. (2018)[42]	Finland	Cohort of infant hospitalized for bronchiolitis	18/138	39	less than 6 months	11–13 years	4.06 (1.35–12.25)	Age, maternal asthma, maternal allergy, parental asthma, paternal allergy, maternal and paternal smoking
Carr et al. (2019)[43]	USA	Tucson Children's Respiratory Study (TCRS)	117/521	87	6 years	26 years	3.7 (2.2–6.1)	age, sex, ethnicity, maternal asthma, maternal education, maternal smoking at enrolment, and history of 4 + colds per year
Arnedo et al. (2007)[44]	Spain	Cohort of schoolchildren in Castellón	108/1698	107	6–7years	8 years	3.21 (l.45–7.09)	Age, sex, family history of asthma, family history of allergic rhinitis, history of bronchitis, mother's age, other respiratory diseases, passive smoking, pet at home, social class.

(continued)

Author (Year)	Country	Source of data	N° of cases of asthma/ cohort size	N° of allergic rhinitis patients	Age at start of cohort	Follow-up duration	RR (95%CI)	Adjusting or matching variables
Verlato et al. (2016)[27]	Italy	Italian Study on Asthma in young Adults (ISAYA) and Italian Study on the Incidence of Asthma (ISIA)	145/5241	517	20–54 years	9 years	4.00 (3.68–4.35)	Age, sex, occupation, asthma-like symptoms, chronic bronchitis, smoking
Yeh et al. (2016)[12]	Taiwan	National Health Insurance Research Database	187/7599	2130	35–65 years	11 years	1.84 (1.38–2.45)	Age, sex, co-morbidities
Pallasaho et al. (2011)[28]	Finland	FinEsS study, Helsinki	157/6062	1387	20–69 years	11 years	2.00 (1.40–2.87)	Age, sex, family history of asthma, smoking
Rochat et al. (2010)[29]	Germany	German Multicentre Allergy Study (MAS) birth cohort.	50/1314	178	0	13 years	6.46 (2.93–14.23)	Age, sex, study center, parental atopy, parental education, maternal smoking during pregnancy, siblingship
Ekerljung et al. (2008)[31]	Sweden	Random sample of general population from Stockholm	159/4479	Not given	20–69 years	10 years	2.21 (1.41–3.48)	Age, sex, family history of asthma, smoking
Shaaban et al. (2008)[7]	14 European countries	European Community Respiratory Health Survey (ECRHS)	140/6461	1217	20–44 years	9 years	3.53 (2.11–5.91)	Age, sex, country, body mass index, IgE, FEV1, family history of asthma, history of respiratory infection, smoking

Rzehak et al. (2008)[30]	Germany	Bitterfeld study	142/3199	124	5–13 years	12 years	4.34 (2.73–6.9)	Age, sex, parental asthma
Morais-Almeida et al. (2007)[32]	Portugal	Hospital database	70/308	156	6 month-6 year old	8 years	15.76 (6.1–40.8)	Parental asthma, history of atopic eczema, history of food allergy, attendance of kindergarten, IgE, age of onset of symptoms, allergen sensitization
Burgess et al. (2007)[37]	Australia	Tasmanian Asthma Study	299/8583	1061	7 years	37 years	3.16 (2.46–4.05).	Age, history of allergy, impaired lung function, socioeconomic status
Porsbjerg et al. (2006)[8]	Denmark	Civil Registry	45/291	38	7–17 years	12 years	1.7 (0.70–3.90)	None
Thomsen et al. (2005)[16]	Denmark	Danish Twin Registry	838/19349	1667	12–41 years	8 years	3.90 (3.31–4.61)	Sex
Polosa et al. (2005)[38]	Italy	University Allergy Clinic database	161/436	332	18–40 years	10 years	7.81 (3.05–20.04)	Sex, family history of allergy, pet ownership, sensitization to allergens, parental smoking at home
Ronmark et al. (2002)[34]	Sweden	Obstructive Lung Disease in Northern Sweden (OLIN) studies	51/3247	156	7–8 years	2 years	5.91 (2.76–12.65)	Sex, family history of asthma, respiratory infections, breast feeding, mother's smoking, pets, dampness
Linneberg et al. (2002)[11]	Denmark	Copenhagen Allergy Study	48/1112	Not given	15–69 years	8 years	9.3 (4.38–19.74)	Age, sex

(continued)

Author (Year)	Country	Source of data	N° of cases of asthma/ cohort size	N° of allergic rhinitis patients	Age at start of cohort	Follow-up duration	RR (95%CI)	Adjusting or matching variables
Huovinen et al. (1999)[39]	Finland	Finnish Twin Cohort Study	261/11540	656	18–45 years	15 years	3.14 (1.61–6.12)	Age, sex, dizygotic/ monozygotic
Strachan et al. (1996)[36]	England, Scotland and Wales	British 1958 cohort study	2488/18559	1855	0	33 years	1.42 (1.33–1.51)	Age, sex, maternal age, birth order, social class, smoking, gestation, albuminuria, bleeding in pregnancy, history of pneumonia, whooping cough, tonsillectomy, eczema, abdominal pain, vomiting, and migraine.
Settipane et al. (1994)[15]	USA	Brown University cohort study	97/1836	162	18 years	23 years	2.92 (1.55–5.48)	None

Table 1. (Continued) Main characteristics of cohort studies included in the meta-analysis of association between allergic rhinitis and asthma. *a. Retrospective cohort study, RR; relative risk, CI; Confidence Interval*

Data extraction

Data were extracted using a predefined form with the following information: first author, year of publication, country, study design, source of data, type of population, number of participants, mean age of participants, measure of association, and adjustment, restriction or matching factors. The data were extracted following the same procedure as that used for the bibliographic searches. The extraction was carried out independently by 2 authors and discrepancies were resolved by consensus.

Quality assessment

We assessed the quality of the studies using a modified version of the Newcastle-Ottawa scale that we adapted to the needs of this meta-analysis. We used a common quality assessment form for both case-control and cohort studies to be able to use their score in a comprehensive fashion. We first performed an analysis based on the global score and then subsequent analyses based on each criterion. The following 5 criteria were considered on a yes/no basis: 1) whether the target population was clearly defined or just based on convenience sampling, 2) whether asthma diagnosis is based on clinical features and spirometry (flow rate) and/or reversal after treatment or was only based on clinical examination, 3) whether rhinitis diagnosis is based on clinical and lab examination or was based on questionnaire only, 4) whether or not asthma symptoms clearly occurred after rhinitis onset, and 5) whether or not results were adjusted for age, sex and family history of asthma. Each item was scored as 0 or 1. Quality assessment was independently conducted by two investigators (HRT and NM) and disagreements were solved by a third investigator (BT).

Statistical methods

Risk Ratios and Rate Ratios in cohort studies and Odds Ratios in case control studies were considered as measures of effect in this meta-analysis. Odds Ratios from case-control studies were assumed to be unbiased estimates of the Rate Ratios.[22] Heterogeneity among studies was evaluated via the Ri statistic (the proportion of total variance due to between-studies variance)[23] as well as the DerSimonian & Laird Q test, in which a p-value$<$0.1 was considered as statistically significant. For pooling the effect size estimates, the inverse of variance was considered as the weight for each study. We computed both fixed effects and random effects estimates, but as heterogeneity was frequent in subgroup analyses, we presented random effects data only. For each study we used the estimate that was adjusted for the largest number of variables.

We performed subgroup analysis according to the design of studies, region, age group, quality score, and items of quality assessment. Cumulative meta-analysis was conducted to identify any trend in estimates across time. The Begg's rank correlation test and the Egger regression test were used to statistically assess publication bias. We also visually assessed publication bias using a funnel plot and performed the Trim-and-Fill procedure to estimate the number of potential missing studies in our meta-analysis and their effect on the outcome.[24] HEpiMA software[25] and STATA 12 (Stata Corp, College Station, TX, USA) were used for statistical analysis.

RESULTS

We found a total of 29 eligible studies, including 22 cohort studies and 7 case-control studies with a total of 274,489 subjects.[6-9,11,12,15,16,26-45]

Twenty one studies were conducted in European countries and 8 in non-European countries between 1994 and 2019. Except for 2 articles published in Spanish[44] and German,[9] the rest were written in English. One article comprised 2 independent case-control studies carried out in different countries. We, therefore, considered these 2 studies separately.[45] Among the studies that could have been potentially included in our meta-analysis, we excluded 3 articles[17-19] because of overlap of data with a more comprehensive study.[7] Furthermore, we found 3 articles from the same author,[16,20,21] 2 of which were excluded after consulting with the author.[20,21] We also excluded 1 conference abstract,[46] as after contacting the authors, we were informed that the corresponding study was published later as a full paper in another language.[9] One study was excluded as we could

Author (Year)	Country	Source of data	Cases/controls	N° of allergic rhinitis patients	Age Mean ± SD	OR (95%CI)	Adjusting or matching variables
Jacob et al. (2016)[6]	Germany	German pediatricians database	34305/34305	24463	6–17 years	5.38 (5.17–5.59)	Age, sex, co-morbidities
Coelho et al. (2016)[26]	Brazil	Students registered in Family Health Strategy (FHS) program	172/379	326	6–14 years	3.35 (2.24–5.01)	Pets, passive smoking, consumption of cooked vegetables, consumption of fish, history of eczema, family history of allergy, skin tests for immediate hypersensitivity (STIH)
Tomic Spiric et al. (2007)[9]	Serbia	Hospital database	134/134	Not given	Cases: 38.96 ± 12.37 years Controls: 39.37 ± 12.38 years	30.74 (7.62–123.98)	Age, sex, living place, outpatient/ inpatient status, history of childhood lower respiratory infection, Sinusitis
Guerra et al. (2002)[35]	USA	Tucson Epidemiologic Study of Obstructive Lung Diseases	173/2177	1086	Cases: 50.81 ± 19.3 years Controls: 52.96 ± 21.2 years	3.21 (2.19–4.71)	Age, sex, atopic status, smoking status, presence of COPD
Toren et al. (2002)[33]	Sweden	MAP-study	235/2044	104	Cases:39.6 ± 0.82 years Controls: 36.9 ± 0.1 years	4.8 (3.4–6.7)	Age, atopy, year of diagnosis
Szentpetery et al. (A) (2017)[45]	Puerto Rico	Population-based case control	312/297	67	Age range: 6–14 years; Cases: 10.06 ± 2.6 years	3.9 (1.9–7.6)	Age, sex, household income, parental asthma, early life second hand

Szentpetery et al. (B) (2017)[45]	Sweden	The Children, Allergy, Milieu, Stockholm, Epidemiological Survey [BAMSE] Study	121/2169	32	Controls: 10.51 ± 2.7 years	Cases: 12.92 ± 0.77 Controls: 12.97 ± 0.83	7.8 (3.5–17.6)	Age, sex, parental asthma, early life second hand smoking, obesity smoking, obesity, diet, lifetime exposure to gun violence.

Table 2. Main characteristics of case-control studies included in the meta-analysis of association between allergic rhinitis and asthma. *OR; Odds Ratio, CI; Confidence Interval, SD; Standard Deviation*

not trace its authors to collect the necessary information to calculate effect measures.[13] Data from 2 studies were obtained through contact with the authors.[11,12] We did not find any relevant study published in a book or dissertation. The main characteristics of the remaining 29 studies included in this meta-analysis are summarized in Tables 1 and 2. The flow diagram presenting the screening process and the reasons for exclusion is presented in Fig. 1[47]

Association of allergic rhinitis and asthma

After pooling the data using the random effect model, we observed that history of allergic rhinitis is strongly associated with asthma (pooled Odds Ratio = 3.82; 95% CI: 2.92–4.99). Subgroup analysis showed that this association was weaker for non European studies (OR = 2.75; 95% CI: 2.16–3.50) than for European studies (OR = 4.35; 95% CI: 3.12–6.06). Although the association was significant in both designs, case-control studies showed a stronger association (OR = 4.71; 95% CI: 3.58–6.17) than cohort studies (OR = 3.42; 95% CI: 2.60–4.50). The association was similar in studies with low and high quality scores (OR = 3.86; 95% CI: 2.49–6.00 versus 3.61; 95% CI: 2.97–4.39, respectively), while studies on children showed a stronger relation (OR = 4.10; 95% CI: 2.56–6.56) than those conducted on adults (OR = 3.37; 95% CI: 2.64–4.30). The detailed information as well as results of other subgroup analyses are presented in Table 3. In all analyses (overall and subgroups) there was evidence of heterogeneity between studies (Table 3, Fig. 2). Based on the proportion of total variance due to between-study variance, this heterogeneity was low for studies with full adjustment and moderate for the following subgroups: case-control studies, good quality studies, non-European studies and studies with adequate diagnosis of asthma and rhinitis, while this heterogeneity was high for the rest of subgroups.

Publication bias

The funnel plot of effect size of the studies was slightly skewed to the right (Fig. 3), and the Begg's test (p-value = 0.023) provided some evidence for the presence of small-study effects. However, the Egger's test showed no evidence of publication

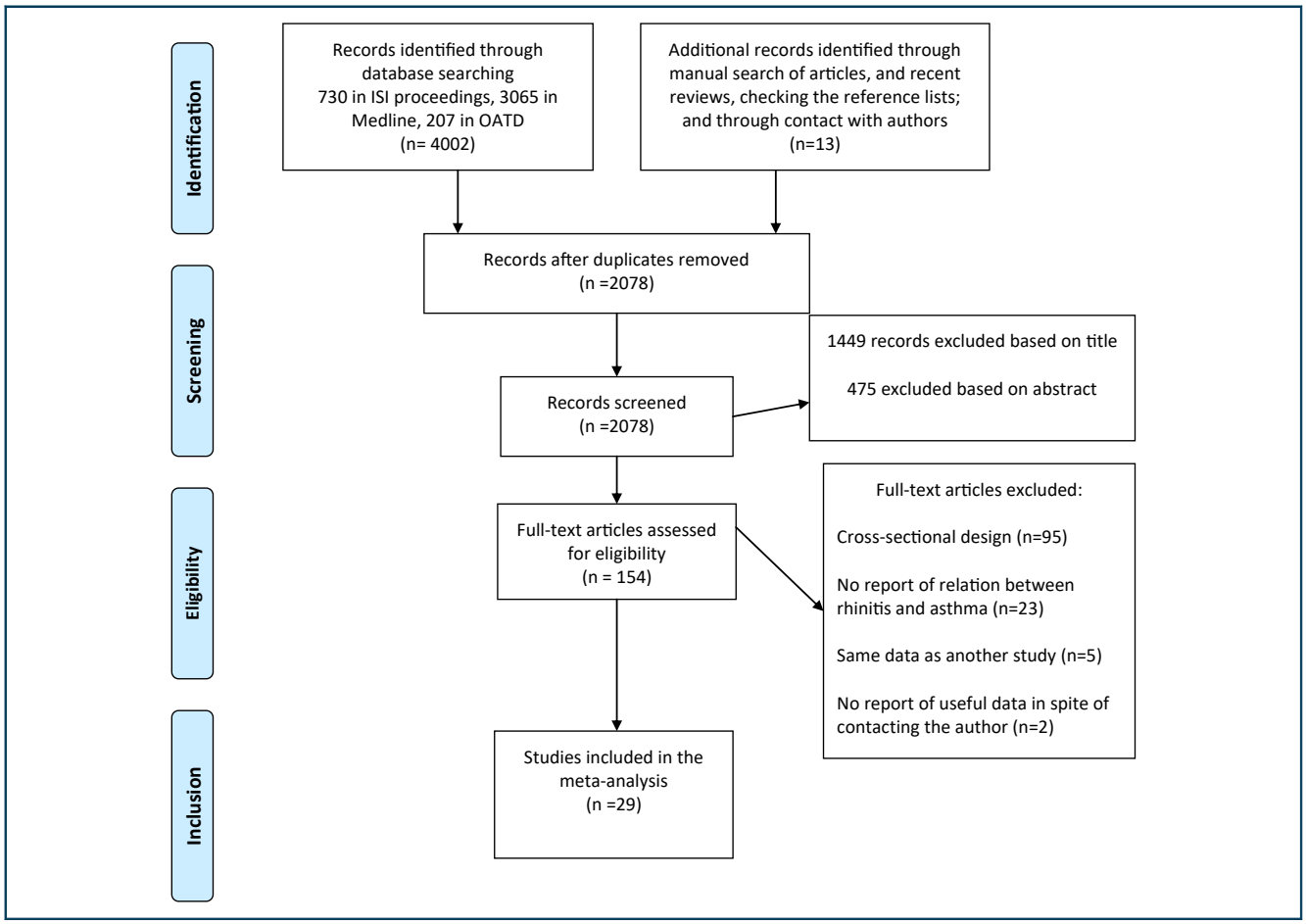

Fig. 1 Flow diagram of study selection in systematic review and meta-analysis of history of allergic rhinitis and risk of asthma

bias (p-value = 0.66). The Trim-and-Fill procedure did not impute any study when we applied the random effects model, while one study was imputed when the fixed effects model was used. The pooled OR after inclusion of this study was 3.67 (95% CI: 3.56–3.78), very close to the original pooled OR of 3.82 (95% CI: 2.92–4.99).

To evaluate the possibility of publication bias in case–control studies, the design most susceptible to be rejected by journals when results lack statistical signification, we recalculated our pooled estimates under the following extreme assumptions: 1) published studies listed in Table 2 are only half of the case-control studies on allergic rhinitis and risk of asthma ever conducted, 2) all studies of the unpublished half found null associations (ie, OR = 1) between allergic rhinitis and asthma, and 3) on average, the unpublished studies included as many cases and controls as the published ones. Under these assumptions, the observed pooled OR was 2.89 (95% CI: 2.19–3.81) that was still large enough to support the findings of our study.

We performed another simulation to evaluate the robustness of our results to the publication bias. We calculated how many unpublished negative (OR = 1) case-control studies with as many cases and controls as the average number of the published studies were necessary to reverse our conclusions. Our simulation showed that 187 negative studies were needed to obtain a pooled OR of 1.10 (95% CI: 1.06–1.14) and 945 studies to obtain an OR of 1.01 (95% CI: 1.003–1.018).

Cumulative meta-analysis

Cumulative meta-analysis by year of publication showed that the first stable and statistically

Groups	Number of studies	OR (95% CI)	Ri[a]	p- value of Q test
All studies	29	3.82 (2.92–4.99)	0.98	<0.001
Design				
Cohort studies	22	3.42 (2.60–4.50)	0.96	<0.001
Case-control studies	7	4.71 (3.58–6.17)	0.70	0.003
Region				
European	21	4.35 (3.12–6.06)	0.98	<0.001
Non European	8	2.75 (2.16–3.50)	0.73	<0.001
Age group				
Children	15	4.10 (2.56–6.56)	0.99	<0.001
Adults	14	3.37 (2.64–4.30)	0.89	<0.001
Quality Score				
<3	11	3.86 (2.49–6.00)	0.99	<0.001
≥3	18	3.61 (2.97–4.39)	0.51	0.006
Items of quality assessment:				
Proper definition of target population				
Yes	23	3.42 (2.62–4.48)	0.96	<0.001
No	6	6.26 (3.18–12.30)	0.97	<0.001
Proper diagnosis of asthma				
Yes	9	3.67 (2.52–5.34)	0.81	<0.001
No	20	3.82 (2.92–4.99)	0.98	<0.001
Proper diagnosis of Allergic Rhinitis				
Yes	12	5.06 (3.58–7.15)	0.64	0.001
No	17	3.18 (2.26–4.46)	0.99	<0.001
Clear temporal trend between rhinitis and occurrence of asthma				
Yes	24	3.55 (2.74–4.61)	0.96	<0.001
No	5	4.89 (3.26–7.35)	0.68	0.015
Adjustment				
Full adjustment	12	3.82 (2.92–4.98)	0.43	0.057
Incomplete adjustment	17	3.94 (2.77–5.61)	0.99	<0.001

Table 3. Random effects Pooled Odds Ratios (ORs) and 95% confidence intervals (CIs) of allergic rhinitis and asthma in different subgroups. *a. Proportion of total variance due to between-study variance*

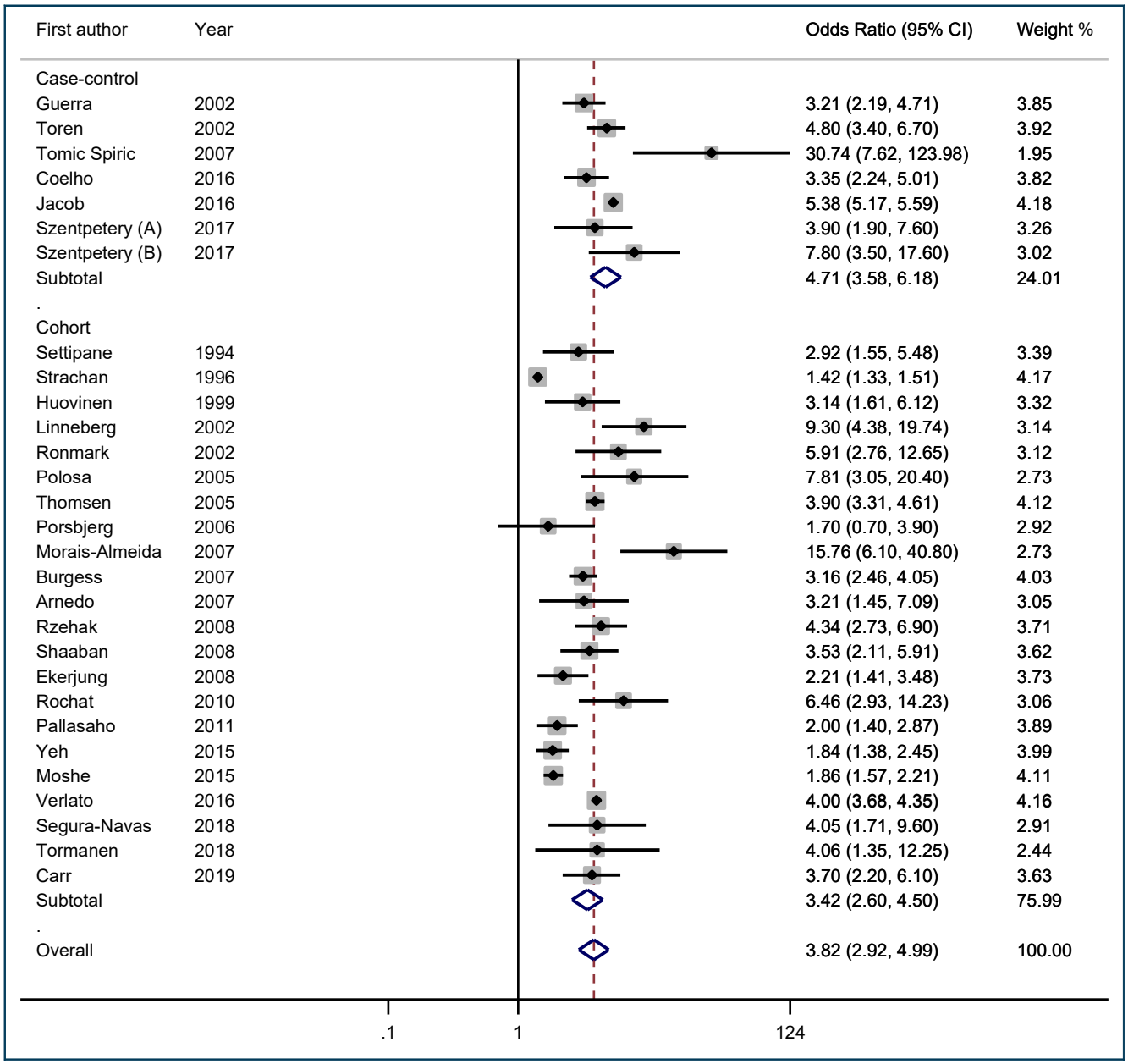

Fig. 2 Forest plot of the association between history of allergic rhinitis and risk of asthma (random effects)

significant effect was observed after including the study by Huovinen et al. published in 1999 (pooled OR = 2.19; 95% CI: 1.19–4.04).[39] The pooled OR increased up to a value of 3.46 (95% CI: 1.62–7.39) after adding the study of Linneberg et al., in 2002,[11] but subsequent studies did not change the strength of association in a meaningful fashion and just increased the precision of the pooled estimate (Fig. 4).

DISCUSSION

Our meta-analysis showed that allergic rhinitis is associated with the occurrence of asthma. This association was observed in all subgroups, albeit with different magnitudes. A plausible explanation of this association is provided by the "atopic march" hypothesis that considers atopic disorders as a series of consecutive clinical manifestations

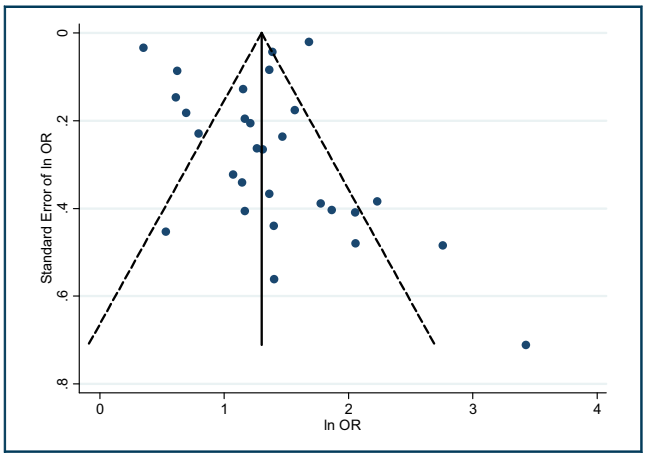

Fig. 3 Funnel plot of association between history of allergic rhinitis and risk of asthma

which start with atopic dermatitis, follow with allergic rhinitis, and end up with asthma as sensitizations in upper and lower airways, respectively.[48] A similar view is represented by the "one airway, one disease" concept, in which AR and asthma are believed to be but one unique disease.[49]

In a study in human subjects, Braunstahl et al. revealed that the provocation of nasal mucosa with allergens results in an increase in lower airways eosinophilia in patients with AR.[50] In addition, the increase in the risk of asthma after exposure to AR is supported by some experimental animal studies. Li et al. showed that exposure of nasal mucosa to allergens increases the concentration of factors that are related to asthma such as eosinophils, interleukin-5 and CD34 cells in peripheral blood and bone marrow in mice.[51]

Another explanation of the relation of allergic rhinitis and asthma could be represented by the existence of a common cause for these two diseases, which affects upper and lower airways in different periods and could play a role of confounder in this association. Some studies showed that polymorphisms in the filaggrin gene, such as R501X and 2282del4, are related to both AR and asthma.[52,53] Also, inhalant allergens, such as pollen, pets, house dust mites, and moulds could be predictors of AR and asthma. Nevertheless, the existence of a strong confounder that could explain the total of the association observed is unlikely. Even if this unidentified factor (either a polymorphism or an environmental factor) could multiply by 5 the risk of asthma among subjects exposed to it (Relative Risk confounder–disease = 5) and, at the same time, this factor is 5 times more prevalent among people suffering from AR than among the rest of the population (Relative Risk confounder–exposure = 5), the adjusted Relative Risk of the relation rhinitis-asthma would still be 2.30 (assuming one-third of people are exposed to this unknown factor).[54] The existence of a factor so strongly associated with rhinitis on one side, and with asthma on the other side, is highly improbable.

This meta-analysis showed a large amount of heterogeneity that persisted after stratification in subgroups. We therefore focused our interpretation on the random effects estimates as recommended.[55,56] Meta-analysis experts claim that there is no amount of heterogeneity that is unacceptable provided the eligibility criteria are sound and the data are correct,[55] and that heterogeneity in meta-analysis, due to the differences in methods and populations, should be viewed as the "expectation, rather than the exception".[57]

Publication bias is unlikely to happen in this meta-analysis because the association remained strong even after extremely conservative assumptions about the potentially related but unpublished studies. In addition, although the Begg's test showed some evidence of publication bias, Egger's test did not confirm it and the Trim-and-Fill procedure did not modify the results obtained previously. Furthermore, to prevent this bias, we conducted a thorough electronic and manual search, without any language restriction, in virtually every available database that could provide articles, dissertations, and conference abstracts.

Furthermore, the results observed do not depend on the intrinsic quality of the studies as the magnitude of the association is similar among studies deemed to be of high quality and studies with a lower quality score.

To the best of our knowledge, this study is the first meta-analysis on this topic. However, there are previous narrative reviews which have not

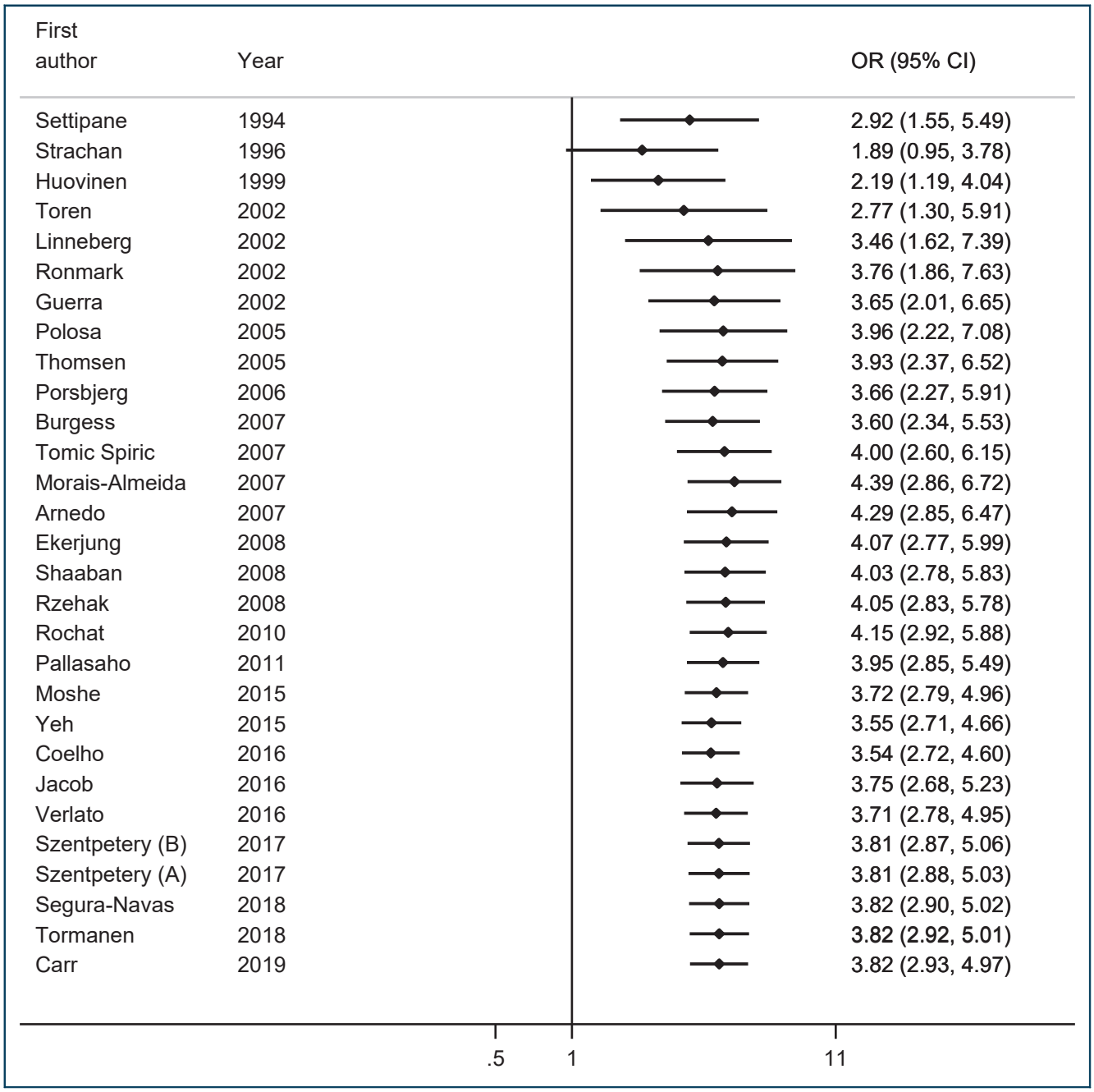

Fig. 4 Cumulative forest plot of the association between history of allergic rhinitis and risk of asthma

retrieved all related studies or which have included cross sectional studies, a type of studies which cannot provide reliable evidence for cause-effect relationship due to its inability to assess a temporal trend between the occurrence of AR and that of asthma. To avoid this bias, our meta-analysis excluded cross-sectional designs and used cohort and case-control studies only.

In conclusion, the magnitude of the associations, and the consistency of the results in different settings provide strong epidemiological evidence that people with allergic rhinitis have a higher odds of asthma occurrence than healthy people. Further prospective studies on the effect of treatment of allergic rhinitis on the development of asthma are needed. Relief of airway allergic

manifestations may need dual control of allergic rhinitis and asthma.

Potential competing interests
The authors report no competing interests.

Ethics statement
This article is a meta-analysis. It does not use any patients or personal data that could be submitted to the evaluation of an Ethics committee.

Contributions
Hamid Reza Tohidinik took the lead, made substantial contributions to conception, design and writing. Narmeen Mallah performed data extraction and contributed to the drafting of the article. Bahi Takkouche revised the study critically, contributed substantially to the interpretation of data and drafting of the article.

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All authors of this paper have read the manuscript, agree that the work is ready for submission to a journal, and accept responsibility for the manuscript's content. All authors certify that they do not have any conflict of interest.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2019.100069.

Author details
[a]HIV/STI Surveillance Research Center, WHO Collaborating Center for HIV Surveillance, Institute for Futures Studies in Health, Kerman University of Medical Sciences, Kerman, Iran. [b]Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran. [c]Department of Preventive Medicine, University of Santiago de Compostela, Santiago de Compostela, Spain. [d]Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBER-ESP), Madrid, Spain.

REFERENCES

1. Asher MI, Montefort S, Bjorksten B, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368(9537):733–743.
2. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380(9859):2163–2196.
3. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1545–1602.
4. Pawankar R, Canonica GW, Holgate S, Lockey R. *WAO White Book on Allergy: Update 2013*. World Allergy Organization; 2013.
5. Leynaert B, Bousquet J, Neukirch C, Liard R, Neukirch F. Perennial rhinitis: an independent risk factor for asthma in nonatopic subjects: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol*. 1999;104(2 Pt 1):301–304.
6. Jacob L, Keil T, Kostev K. Comorbid disorders associated with asthma in children in Germany - national analysis of pediatric primary care data. *Pediatr Allergy Immunol*. 2016;27(8):861–866.
7. Shaaban R, Zureik M, Soussan D, et al. Rhinitis and onset of asthma: a longitudinal population-based study. *Lancet*. 2008;372(9643):1049–1057.
8. Porsbjerg C, von Linstow ML, Ulrik CS, Nepper-Christensen S, Backer V. Risk factors for onset of asthma: a 12-year prospective follow-up study. *Chest*. 2006;129(2):309–316.
9. Tomic Spiric V, Jankovic S, Bogic M, Maksimovic N, Djuric V, Bolpacic J. Atopic asthma and related risk factors. *Allergologie*. 2007;30(2):41–49.
10. Bousquet J, Schunemann HJ, Samolinski B, et al. Allergic rhinitis and its Impact on asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol*. 2012;130(5):1049–1062.
11. Linneberg A, Henrik Nielsen N, Frolund L, Madsen F, Dirksen A, Jorgensen T. The link between allergic rhinitis and allergic asthma: a prospective population-based study. *The Copenhagen Allergy Study*. Allergy. 2002;57(11):1048–1052.
12. Yeh JJ, Wang YC, Hsu WH, Kao CH. Incident asthma and Mycoplasma pneumoniae: a nationwide cohort study. *J Allergy Clin Immunol*. 2016;137(4):1017–1023. e1011-1016.
13. Garcia-Larsen V, Potts JF, Del Giacco S, et al. Changes in symptoms of asthma and rhinitis by sensitization status over ten years in a cohort of young Chilean adults. *BMC Pulm Med*. 2016;16(1):116.
14. Izuhara Y, Matsumoto H, Nagasaki T, et al. Mouth breathing, another risk factor for asthma: the Nagahama Study. *Allergy*. 2016;71(7):1031–1036.
15. Settipane RJ, Hagy GW, Settipane GA. Long-term risk factors for developing asthma and allergic rhinitis: a 23-year follow-up study of college students. *Allergy Proc*. 1994;15(1):21–25.
16. Thomsen SF, Ulrik CS, Kyvik KO, et al. The incidence of asthma in young adults. *Chest*. 2005;127(6):1928–1934.
17. Anto JM, Sunyer J, Basagana X, et al. Risk factors of new-onset asthma in adults: a population-based international cohort study. *Allergy*. 2010;65(8):1021–1030.
18. de Marco R, Locatelli F, Cazzoletti L, Bugianio M, Carosso A, Marinoni A. Incidence of asthma and mortality in a cohort of young adults: a 7-year prospective study. *Respir Res*. 2005;6:95.

19. Toren K, Gislason T, Omenaas E, et al. A prospective study of asthma incidence and its predictors: the RHINE study. *Eur Respir J*. 2004;24(6):942–946.
20. Thomsen SF, Ulrik CS, Kyvik KO, et al. Risk factors for asthma in young adults: a co-twin control study. *Allergy*. 2006;61(2):229–233.
21. Thomsen SF, Duffy DL, Kyvik KO, Backer V. Genetic influence on the age at onset of asthma: a twin study. *J Allergy Clin Immunol*. 2010;126(3):626–630.
22. Rothman K, Greenland S, Lash T. *Modern Epidemiology*. third ed. Philadelphia: Lippincott, Williams and Wilkins; 2008:61.
23. Takkouche B, Cadarso-Suarez C, Spiegelman D. Evaluation of old and new tests of heterogeneity in epidemiologic meta-analysis. *Am J Epidemiol*. 1999;150(2):206–215.
24. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455–463.
25. Costa-Bouzas J, Takkouche B, Cadarso-Suarez C, Spiegelman D. HEpiMA: software for the identification of heterogeneity in meta-analysis. *Comput Methods Progr Biomed*. 2001;64(2):101–107.
26. Coelho MA, de Pinho L, Marques PQ, Silveira MF, Sole D. Prevalence and factors associated with asthma in students from Montes Claros, Minas Gerais, Brazil. *Ciência Saúde Coletiva*. 2016;21(4):1207–1216.
27. Verlato G, Nguyen G, Marchetti P, et al. Smoking and new-onset asthma in a prospective study on Italian adults. *Int Arch Allergy Immunol*. 2016;170(3):149–157.
28. Pallasaho P, Juusela M, Lindqvist A, Sovijarvi A, Lundback B, Ronmark E. Allergic rhinoconjunctivitis doubles the risk for incident asthma–results from a population study in Helsinki, Finland. *Respir Med*. 2011;105(10):1449–1456.
29. Rochat MK, Illi S, Ege MJ, et al. Allergic rhinitis as a predictor for wheezing onset in school-aged children. *J Allergy Clin Immunol*. 2010;126(6):1170–1175. e1172.
30. Rzehak P, Schoefer Y, Wichmann HE, Heinrich J. A prospective study on the association between hay fever among children and incidence of asthma in East Germany. *Eur J Epidemiol*. 2008;23(1):17–22.
31. Ekerljung L, Ronmark E, Larsson K, et al. No further increase of incidence of asthma: incidence, remission and relapse of adult asthma in Sweden. *Respir Med*. 2008;102(12):1730–1736.
32. Morais-Almeida M, Gaspar A, Pires G, Prates S, Rosado-Pinto J. Risk factors for asthma symptoms at school age: an 8-year prospective study. *Allergy Asthma Proc*. 2007;28(2):183–189.
33. Toren K, Olin AC, Hellgren J, Hermansson BA. Rhinitis increase the risk for adult-onset asthma–a Swedish population-based case-control study (MAP-study). *Respir Med*. 2002;96(8):635–641.
34. Ronmark E, Perzanowski M, Platts-Mills T, Lundback B. Incidence rates and risk factors for asthma among school children: a 2-year follow-up report from the obstructive lung disease in Northern Sweden (OLIN) studies. *Respir Med*. 2002;96(12):1006–1013.
35. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol*. 2002;109(3):419–425.
36. Strachan DP, Butland BK, Anderson HR. Incidence and prognosis of asthma and wheezing illness from early childhood to age 33 in a national British cohort. *BMJ*. 1996;312(7040):1195–1199.
37. Burgess JA, Walters EH, Byrnes GB, et al. Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: a longitudinal study. *J Allergy Clin Immunol*. 2007;120(4):863–869.
38. Polosa R, Al-Delaimy WK, Russo C, Piccillo G, Sarva M. Greater risk of incident asthma cases in adults with allergic rhinitis and effect of allergen immunotherapy: a retrospective cohort study. *Respir Res*. 2005;6:153.
39. Huovinen E, Kaprio J, Laitinen LA, Koskenvuo M. Incidence and prevalence of asthma among adult Finnish men and women of the Finnish Twin Cohort from 1975 to 1990, and their relation to hay fever and chronic bronchitis. *Chest*. 1999;115(4):928–936.
40. Segura-Navas L, Arnedo-Pena A, Tosca-Segura R, et al. Incidence of asthma in young adults from Castellon, Spain: a prospective cohort study. *Allergol Immunopathol (Madr)*. 2018;46(2):112–118.
41. Moshe S, Slodownik D, Yagev Y, et al. Atopy as a risk factor for the development of asthma in young recruits. *J Asthma*. 2015;52(5):453–457.
42. Tormanen S, Lauhkonen E, Riikonen R, et al. Risk factors for asthma after infant bronchiolitis. *Allergy*. 2018;73(4):916–922.
43. Carr TF, Stern DA, Halonen M, Wright AL, Martinez FD. Non-atopic rhinitis at age 6 is associated with subsequent development of asthma. *Clin Exp Allergy*. 2019;49(1):35–43.
44. Arnedo A, Bellido JB, Pac MR, et al. [Incidence of asthma and risk factors in a cohort of schoolchildren aged from 6-7 years old to 14-15 years old in Castellon (Spain) following the International Study of Asthma and Allergies in Childhood (ISAAC)]. *Med Clínica*. 2007;129(5):165–170.
45. Szentpetery SS, Gruzieva O, Forno E, et al. Combined effects of multiple risk factors on asthma in school-aged children. *Respir Med*. 2017;133:16–21.
46. Tomic Spiric V, Bogic M, Peric-Popadic A, et al. Allergic rhinitis as a risk factor of atopic asthma. *Allergy*. 2008;63, 71-71.
47. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7), e1000097.
48. Spergel JM. Atopic march: link to upper airways. *Curr Opin Allergy Clin Immunol*. 2005;5(1):17–21.
49. Grossman J. One airway, one disease. *Chest*. 1997;111(2 Suppl):11s–16s.
50. Braunstahl GJ, Overbeek SE, Kleinjan A, Prins JB, Hoogsteden HC, Fokkens WJ. Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. *J Allergy Clin Immunol*. 2001;107(3):469–476.
51. Li J, Saito H, Crawford L, Inman MD, Cyr MM, Denburg JA. Haemopoietic mechanisms in murine allergic upper and lower airway inflammation. *Immunology*. 2005;114(3):386–396.
52. van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ*. 2009;339:b2433.

53. Ziyab AH, Karmaus W, Zhang H, et al. Association of filaggrin variants with asthma and rhinitis: is eczema or allergic sensitization status an effect modifier? *Int Arch Allergy Immunol*. 2014;164(4):308–318.

54. Greenland S. Basic methods for Sensitivity analysis of biases. *Int J Epidemiol*. 1996;25(6):1107–1116.

55. Higgins JP. Commentary: heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol*. 2008;37(5):1158–1160.

56. Council NR. *Combining Information: Statistical Issues and Opportunities for Research*. Washington, DC: National Academy Press; 1992:52.

57. Berlin JA. Invited commentary: benefits of heterogeneity in meta-analysis of data from epidemiologic studies. *Am J Epidemiol*. 1995;142(4):383–387.