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Allergic rhinitis and asthma assessment of risk factors in pediatric patients: A systematic review

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ABSTRACT

Allergic rhinitis (AR) is the most prevalent allergic disease in children and can be associated with asthma (A); this association can have significant effect on child's quality of life. The objective of this work was to systematically review existing literature on the risk factors of AR and A in children to better understand the link between these two diseases. We performed a literature search over the last 25 years in PubMed and Medline. Inclusion criteria comprised English language papers containing original human data with greater than 30 subjects and papers that statistically analyze the relationship between AR and A and the risk factor(s), in children population. A statistically significant correlation was found between children with AR and A and ambient Polycyclic Aromatic Hydrocarbons exposure, live in an industrialized city with elevated traffic, dampness and moulds exposure, electric cooking, male gender, single nucleotide polymorphisms in PTNP22 gene and CTLA-4 gene, fast food and margarine products consumption, use of paracetamol in last year, history of tuberculosis, parental atopy, high total serum IgE, antibiotics in uterus and infections in uterus exposure, history of formula feeding and caesarian section. A strong and complex link between AR and A was accounted: A represents a major risk factor for the onset of AR, that correlates with more severe asthmatic symptoms. Even the onset of A in a child with AR worsen it. The interaction of genetic and environmental risk factors and the consequent epigenetic, microbiota and immunological changes, were found to led to the development of AR and A in children, with both atopic and non-atopic pathways. Close monitoring of evidenced risk factors may help with an early recognize and treat A in patients with AR.

1. Introduction

Allergic rhinitis is a chronic disease characterized by inflammatory changes in the nasal mucosa, caused by exposure to inhaled allergens [1]. It is the most prevalent allergic disease in children and can have significant effects on quality of life [2]. One of the main disorders that can be associated with it is asthma. The 2019 Update of Global Initiative for Asthma (GINA), Global Strategy for Asthma Management and Prevention, gave a definition of asthma as a heterogeneous disease, usually characterized by chronic airway inflammation, defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation [3].

The link between rhinitis and asthma has been highlighted in a World Health Organization report, Allergic rhinitis and its impact on asthma (ARIA), approximately 30% of patients with rhinitis develop asthma and up to 80% of patients with perennial asthma have rhinitis [4–6].

Alongside the objective of establishing a new classification of allergic rhinitis, resulting with the introduction of the distinction between perennial and seasonal rhinitis, one of the main goal of ARIA was in fact to promote the concept of multi-morbidity in asthma and allergic rhinitis [4–6].

Cingi et al. in the European Academy of Allergy and Clinical Immunology Task Force Report explained that the term multi-morbidity is to be encouraged over co-morbidity in allergic diseases. Multimorbidity is the presence of one or more additional disorders (or diseases) co-occurring with a primary disease or disorder; or the effect of such additional disorders or diseases, when the primary organ is not known [7].

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The multi-morbidity of allergic disease/atopy has been identified in most epidemiological studies as two or more of: allergic rhinitis, asthma and eczema [8,9].

ARIA report and subsequent studies tried to better understand risk factors and protective factors in patients with allergic multi-morbidity and to establish the utility of allergen avoidance and other prevention methods in allergic disease, with lack of success, concerning children a series of recommendation were made, but with low or very low evidence [5,10,11].

Currently is emerging the treatment of allergic rhinitis as a strategy for preventing asthma, but is recognized that there is limited knowledge about the risk factors responsible for the progression of allergic rhinitis to asthma [12].

The aim of this systematic review is to better identify the risk factors in children with both allergic rhinitis (AR) and asthma (A), with the main purpose to move closer what is clinically relevant: early recognize and treat A in patients with AR.

2. Materials and methods

2.1. Study design

This systematic review explores the literature from the last 25 years. An extensive series of studies concerning the risk factors in pediatric patients with AR and A was conducted using two databases: Medline and PubMed. Both databases were searched from 1st January 1994 to 1st July 2019.

The research methodology was adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist [13]. The search incorporated use of Medical Subject Headings (MeSH) and key text words.

Several search strings were used combining MeSH terms and key words afferent to three main groups using “OR” within the group and by using “AND” to combine the three groups, in Medline and PubMed: (i) Terms identifying target Population (ii) Terms identifying Allergic Rhinitis (iii) Terms identifying Asthma (Table 1).

The results of the searches were then filtered to include English language papers containing original human data, including randomized controlled trials, prospective cohort studies with or without comparison groups, case-control studies, and case series that had data on 30 or more participants (in order to avoid potential for bias of smaller series).

From analysis, were then excluded articles: published prior to 1994, without abstract, not written in English, did not statistically analyzing the relationship between the risk factor(s) and AR and A, not regarding children population (Fig. 1).

Results of all electronic searches were imported into Endnote X9 (Thomas Reuters, New York, NY). Two reviewers independently review titles and abstracts for initial inclusion in this systematic review, considering just the abstracts concerning risk factors; any discrepancies in the selection of articles was then discussed, in order to avoid the elimination of any abstract based on only one reviewer's judgment.

Reviewers were not blinded to publication authors, journal titles and institutions of origin.Full-length publications were obtained following initial selection of abstracts (abstracts without full publications were excluded as well as articles with not available full-text).

Articles were assessed and synthesized for Author, Year, Country, Type of study, Study size, Age range, how was characterized AR and A, Potential risk factor(s) considered and how each of these was characterized, Statistical association with AR and A and finally the eventual additional conclusion specifically about AR and A link (Table 2) [14–40].

A quantitative meta-analysis was not performed due to the different study designs of the selected articles and the heterogeneity of data.

For the purpose of the point by point discussion on each risk factor, a later research of systematic review, meta-analysis and other evidences was made.

Table 1
Three groups of MeSH terms and key words used in search strings.

(i) Target Population	(ii) Allergic Rhinitis	(ii) Asthma
Infant	Rhinitis, Allergic, Seasonal	Asthma
Child	Rhinitis, Allergic, Perennial	Respiratory diseases
Adolescent	Rhinitis, Allergic	
	Hay fever	

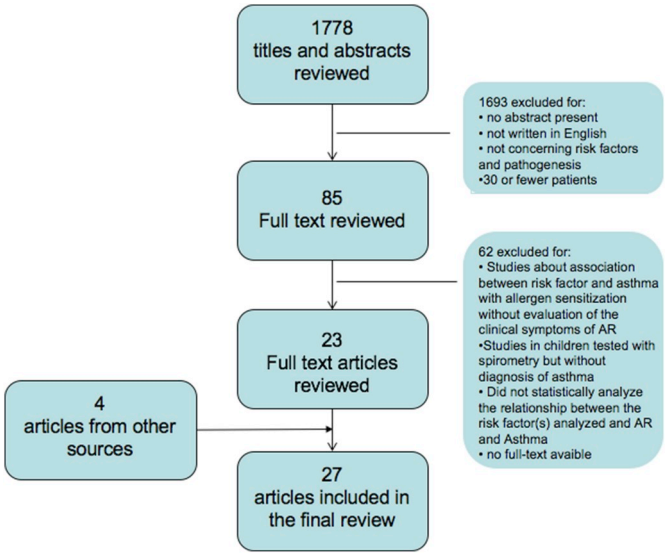


Fig. 1. Search algorithm.

3. Results

A final selection of 27 included studies was obtained (Table 2). Across these studies populations from all continents were studied; from a total of 43 countries. 17 European countries (Albania, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, Italy, Latvia, Netherlands, Norway, Poland, Spain, Sweden, Turkey and United Kingdom), 11 Latin American countries (Argentina, Brazil, Bolivia, Chile, Colombia, Ecuador, Mexico, Panama, Peru, Venezuela and Uruguay), 6 Oceania's countries (New Zealand, Samoa, Fiji, Tokelau, French Polynesia and New Caledonia), 4 Asian countries (China, India, Korea and Taiwan), 2 Middle-East countries (Georgia and Palestine), 2 Central-North American countries (Mexico, USA) and 1 African country (South Africa) were included in this systematic review [14–40].

Final studies included were prospective cohort studies, case control only studies and, the major part, cross sectional studies.

In order to characterize AR and A, International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was the most common strategy adopted.

In Table 3, are summarized all the potential risks factor taken in account from the studies included in this review.

The risks factors analyzed by the different authors were clustered in 9 categories (Tables 4–11):

- external environment (living in a farm area vs a rural area, in an urban area vs in a rural area, Polycyclic Aromatic Hydrocarbons PAH exposure, live in an industrialized city);
- home environment (passive smoking, exposure to dampness and moulds, Polyvinylchloride PVC flooring, electric cooking, interaction with older siblings, wood or coal heating, father bedding, socioeconomic status and hygiene intervention);
- individual non-modifiable factors (gender, elevated Exhaled Nitric

Table 2
Summary of included studies about Risk factors in children with Asthma (A) and Allergic Rhinitis (AR) [14–40].

	Author	Year	Country	Type of Study	Study size	Age range	Characterizing AR and A	Risk Factor(s)	Characterizing Risk factor	Statistical Association with AR and A	Additional comment about link between AR and A
1	Fuss et al.	2019	Poland	Case-Control (both AR + A, farm vs rural)	35	8 to 16	ARIA and GINA	Living in a farm area	diff. in CD4+/CD25 + and CD4+/ CD25 + Foxp3+ cell expression	No	
2	Krzych-Fałta et al.	2018	Poland	Cross sectional study	18617	6-7 and 13-14	ECRHS II and ISSAC questionnaires	Familiar allergy history Being born from cesarean section Number of siblings	Questionnaire	Positive Positive Negative with AR	
3	Yavuz et al.	2018	Germany	Retrospective cohort study (grass pollen AR + A)	293	7 to 13	Questionnaire	Parental asthma Prematurity History of Formula Feeding	Questionnaire	Positive Positive Positive	Close monitoring of patients with these RF may help with an earlier diagnosis of asthma and prompt initiation of therapy in children with grass pollen AR.
4	Cepeda et al.	2017	Latin America	Cross sectional study (AR + A vs AR)	143967	6-7 and 13-14	ISAAC	elevate fast food intake and low fruits and vegetables intake diets	Questionnaire	Positive	
5	Song et al.	2016	China	Case-control (AR + A vs healthy)	327	1 to 16	ARIA	SNPs in PTPN22, CTLA-4 gene	Genotyped PCR	Positive	
6	Kim et al.	2016	Korea	Cross sectional study	3040	4 to 15	Questionnaire	high-fat and low-carbohydrate diets	Questionnaire	Positive with AR	
7	Dogru et al.	2016	Turkey	Prospective cohort study	509	1 to 18	ISAAC, ARIA and GINA	polysensitization familial atopy exposure to smoke	Prick test, Serum IgE Questionnaire Questionnaire	Positive Positive with AR Positive with AR	the majority of children with AR had asthma comorbidity
8	Sybilski et al.	2015	Poland	Cross sectional study	18617	6-7 and 13-14	ISAAC	obesity	BMI	Positive with A, Negative with AR	
9	Hew et al.	2015	USA	Case-Control	256	10 to 21	Questionnaire, Serum IgE, NHLBI criteria	Ambient PAH exposure (air pollution)	Model of exposure, exposing blood sample, cytometry, DNA and Methylation studies	Positive	Associations with ambient PAH exposure and immune parameters were more pronounced in subjects with atopic vs. non-atopic diseases (i.e. A + AR)
10	Baumann et al.	2015	Peru	Cross sectional study (group AR + A vs healthy)	1441	13 to 15	Questionnaire, Prick test, Serum IgE, spirometry, exhaled nitric oxide	socioeconomic status exposure to cigarette smoke 25OH vitamin D levels elevated exhaled nitric oxide allergic sensitization to common household aeroallergens parental rhinitis overweight high total serum IgE Urban/rural setting	Questionnaire, blood sample, BMI	No No No Positive (>with AR) Positive (>with AR) Positive (>with AR) Positive (>with AR) Positive (>with AR) No	When considering subject-specific factors, the difference in prevalence between the urban and rural settings became non-important
11	Farrokhi et al.	2014	Iran	Cross sectional study	2395	2 Age groups: 6–7 and 13-14	ISAAC	bread and rice consumption Fast food consumption	Questionnaire	Positive with AR (in 6-7y) Positive with A	.

(*continued on next page*)

Table 2 (*continued*)

	Author	Year	Country	Type of Study	Study size	Age range	Characterizing AR and A	Risk Factor(s)	Characterizing Risk factor	Statistical Association with AR and A	Additional comment about link between AR and A
12	Weinmayr et al.	2013	20 countries	Cross sectional study	46051	8 to12	ISAAC	Exposure to dampness and moulds	Questionnaire	Positive	the non-atopic process is important in the onset of A and AR (same results in affluent e non-affluent countries)
13	von Kobyletzki et al.	2012	Sweden	Prospective cohort study	3124	1 to 7	ISAAC	Eczema in infancy		Positive	children with early onset of eczema, moderate to severe eczema, and persistence of eczema had the highest odds of developing asthma and rhinitis.
								parental history of allergic disease		Positive	
								Period of breast feeding <6 months		Positive with A	
								polyvinylchloride flooring		Positive with AR	
14	Flohr et al.	2012	20 countries	Cross sectional study	23901	8 to12	ISAAC	History of TB	Questionnaire	Positive	
								Bacillus Chalmette-Guerin vaccination		No	
15	Yao et al.	2011	Taiwan	Cross sectional study	5351	4 to18	ISAAC	Male gender	Questionnaire	Positive	.
								obesity	BMI	Positive with A	
16	Keil et al.	2010	Germany	Prospective cohort study	467	up to 13	ARIA	Sensitization to aero-allergens	Prick test, Serum IgE	Positive with AR	Asthma more associated in particular with children with severe persistent AR
								Having 2 Parents with allergy	Questionnaire	Positive with AR	
17	Gonzalez-Diaz et al.	2010	Mexico	Cross sectional study	23191	2 Age groups: 6–7 and 13-14	ISAAC	Other allergic condition (Asthma and/or eczema RF for AR)	Questionnaire	Positive (both age groups)	Asthma identified as a risk factor for AR
								Paracetamol consumption in last yr	Questionnaire	Positive (both age groups)	
								Passive smoking at home	Questionnaire	Positive (both age groups)	
								Interaction with older siblings	Questionnaire	Negative (6-7y group)	
								Use of antibiotics in 1st year of life	Questionnaire	No	
18	Musaad et al.	2009	USA	Case-Control (AR + A vs AR)	584	5 to 18	Questionnaire, Prick test, spirometry	Central obesity	BMI, waist circumference, waist/height ratio, conicity index	Positive with A	Positive, Prevalence of moderate-to-severe A is higher in centrally obese children with AR
19	Foliaki et al.	2008	8 Pacific Countries	Cross sectional study	17683	2 Age groups: 6–7 and 13-14	ISAAC	regular margarine consumption	Questionnaire	Positive	
								regular meat consumption		Positive with AR	
								paracetamol use		Positive	
								electric cooking		Positive	
								maternal smoking		Positive	
								having older siblings		Negative with A	
20	De Batlle et al.	2008	Mexico	Cross sectional study	1476	6-7 y	ISAAC	Mediterranean diet in the last 12 m	Questionnaire, Mediterranean diet score	Negative	
								Mediterranean diet in pregnancy		No	
21	Dunder et al.	2007	Finland	Prospective cohort study	928	1 to 18	Questionnaire	Hygiene intervention	*	No	
22	Obihara et al.	2005	South Africa	Cross sectional study	861	6 to 14	ISAAC	Prolonged breastfeeding	Questionnaire	Negative**	

(*continued on next page*)

Table 2 (*continued*)

	Author	Year	Country	Type of Study	Study size	Age range	Characterizing AR and A	Risk Factor(s)	Characterizing Risk factor	Statistical Association with AR and A	Additional comment about link between AR and A
23	Magnusson et al.	2005	Denmark	Cross sectional study	7844	14 to 18	Questionnaire	Prenatal maternal smoking	Questionnaire	No	
24	Fasce et al.	2005	Italy	Cross sectional study	269	8 to 12	Questionnaire, Prick test, GINA	Early cat ownership	Questionnaire	Negative with AR, No for A	
25	McKeever et al.	2002	UK	Cross sectional study	24690	to 11	General Practice Research Database	Exposure to antibiotics in utero Exposure to infections in utero Perinatal mother depression Complication in pregnancy	General Practice Research Database	Positive (dose related) Positive Positive (>with A) Positive with A	
26	Henriksen et al.	2001	Norway	Cross sectional study (AR + A vs AR)	8571	13 to 19	Questionnaire, spirometry, ISAAC	Keeping cat Keeping dog Keeping horse	Questionnaire	Negative No No	In asthmatics, concomitance of allergic rhinitis was associated with higher total allergy scores and increased DRR and ENO, indicating more severe disease.
27	Duhme et al.	1998	Germany	Cross sectional study	13754	2 Age groups: 5–8 and 12-15	ISAAC	Truck traffic Active smoking or home exposure Live in industrialized city West Germany moulds or wet spots in bedroom Wood or coal heating feather bedding	Questionnaire	Positive Positive (in 12–15y) Positive Positive with A (in 5-8y) Negative Negative	

Summary of included studies about Risk factors in children with Asthma (A) and Allergic Rhinitis (AR); * = Hygiene intervention was done with several steps for one year and it resulted in a successful prevention of respiratory tract and enteric infections (Uhari et al.). After 12 years the follow-up was done evaluating A and AR; ** = not in children with allergic predisposition.

Table 3
All risks factor for AR and A in the systematic review.

Positive association	Negative association (protective)	No Statistical association
Ambient PAH exposure	Interaction with older siblings	Farm or Rural setting
Industrialized city with elevated truck traffic	Wood or coal heating	Urban or Rural setting
Passive smoke (with AR)	Feather bedding	Socioeconomic status
Exposure to dampness and moulds	Obesity (with AR) 1 study	Hygiene intervention
PVC flooring (with AR)	High vegetables and fruits intake	Use of antibiotics in 1st year
Electric cooking	Keeping cat	Bacillus Calmette-Guerin vaccination
Male gender	Prolonged breastfeeding > 6 months (not in children with allergic predisposition)	Keeping dog
Elevated exhaled nitric oxide (prevalent with A)		Keeping horse
SNPs in PTPN22 e CTLA-4 gene		Prenatal maternal smoking
Obesity (with A) 3 studies, Overweight (with AR) 1 study		Mediterranean diet during pregnancy
Fast food consumption		
High fat low carb diet (AR)		
Bread and rice consumption (AR)		
Meat consumption (AR)		
Margarine consumption		
Use of Paracetamol in last y		
History of TB		
Parental atopy		
Other allergic condition (Asthma, Eczema)		
High total serum IgE		
Polisensitization to aero-allergens (prevalent AR)		
Exposure to antibiotics in uterus (dose-related)		
Exposure to infections in uterus		
Perinatal mother depression (>in A)		
Complication in pregnancy (A)		
Caesarian delivery		

Table 4
External environment risk factors for AR and A.

Positive association	*No statistical association*
Ambient PAH exposure	Farm or Rural setting
Industrialized city with elevated truck traffic	Urban or Rural setting

Oxide ENO, single nucleotide polymorphisms SNPs in specific genes);
- obesity;
- diet (fast food, high fat low carb, bread and rice, meat, margarine, low vegetables and fruits);
- medications assumption and infection history (Paracetamol, Antibiotics, Tuberculosis TB and other infections, Bacillus Calmette-Guerin BCG vaccination);
- atopy (parental atopy, other allergic conditions, high total serum IgE, polisensitization to aero-allergens);
- pet ownership (cat, dog, horse);
- pregnancy and mother-related risk factors (exposure to antibiotics and infections in uterus, perinatal mother depression, complication in pregnancy, caesarian delivery, prolonged breastfeeding > 6 months, prenatal maternal smoking, Mediterranean diet during pregnancy).

A statistically significant correlation was noted between: children with AR and A and ambient PAH exposure; living in an industrialized city with elevated traffic; exposure to dampness and moulds; electric cooking; male gender; SNPs in Protein tyrosine phosphatase non-receptor 22 (PTPN22) gene and the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) gene; fast food and margarine products consumption: use of paracetamol in last year; history of TB; parental atopy, high total serum IgE; exposure to antibiotics and infections in uterus; caesarian delivery; children with just AR and passive smoking; PVC flooring; overweight, high fat low carb diet, bread and rice consumption, elevated meat consumption and other allergic condition as asthma and eczema; children with just A and complication in pregnancy, perinatal mother depression, obesity, elevated ENO (Tables 2 and 3).

From this review emerged also as protecting factors of AR and A, with a negative significant statistical correlation: interaction with older

Table 5
External environment risk factors for AR and A.

Positive association	*Negative association (protective)*	*No Statistical association*
Passive smoke (with AR)	Interaction with older siblings	Socioeconomic status
Exposure to dampness and moulds	Wood or coal heating	Hygiene intervention
PVC flooring (with AR)	Feather bedding	
Electric cooking		

Table 6
Individual non-modifiable risk factors for AR and A.

Positive association	*Negative association (protective)*	*No Statistical association*
Male gender		25OH vitamin D levels
Elevated exhaled nitric oxide (prevalent with A)		
SNPs in PTPN22 e CTLA-4 gene		

Table 7
Weight and diet risk factors for AR and A.

Positive association	*Negative association (protective)*
Obesity (with A) 3 studies, Overweight (with AR) 1 study	Obesity (with AR) 1 study
Fast food consumption	High vegetables and fruits intake
High fat low carb diet (AR)	
Bread and rice consumption (AR)	
Meat consumption (AR)	
Margarine consumption	

Table 8
Medications assumption and infections as risk factors for AR and A.

Positive association	*No Statistical association*
Use of Paracetamol in last y	Use of antibiotics in 1st year
History of TB	Bacillus Calmette-Guerin vaccination

Table 9
Atopy and AR and A.

Positive association
Parental atopy
Other allergic condition (Asthma, Eczema)
High total serum IgE
Polisensitization to aero-allergens (prevalent AR)

Table 10
Pet ownership as risk factors for AR and A.

Negative association (protective)	*No Statistical association*
Keeping cat	Keeping dog
	Keeping horse

Table 11
Pregnancy and mother-related risk factors for AR and A.

(i) Target Population	(ii) Allergic Rhinitis	(ii) Asthma
Infant	Rhinitis, Allergic, Seasonal	Asthma
Child	Rhinitis, Allergic, Perennial	Respiratory diseases
Adolescent	Rhinitis, Allergic	
	Hay fever	

siblings, wood or coal heating, feather bedding, high vegetables and fruit intake, keeping a cat and prolonged breastfeeding after six months of life.

It wasn't found any statistical correlation between children with AR and A and their living setting (farm rural or urban) or with being less early expose to infection, as well as having a dog or a horse or in case of prenatal maternal smoking [14–40].

4. Discussion

4.1. External environment

4.1.1. Farm area vs rural area

In farm children, the prevalence of asthma and atopy is substantially lower [41]. Chronic environmental farm exposure to low-dose bacterial endotoxin or farm dust has been associated with higher regulatory T-cell numbers, and protects mice from developing house dust mite (HDM)-induced asthma which can result in lower prevalence of atopy in farm children [42].

Fuss et al. [14] 2019 study is the first showing the immunological profile of regulatory cells in allergic asthmatic children living in two environments, in particular they analyzed differences in CD4+/CD25+ T-regulatory cells and forkhead box transcription factor 3 (FOXP3, recognized key locus involved in atopy) expression in asthmatic children allergic to house dust mites (HDM) within and between two groups: one living in a rural area and one in a farm area. They didn't found a statistically significative difference between the two groups. Their hypothesis is that only pre-exposure to LPS protects against asthma through the epithelial production of A20 (an ubiquitin-modifying enzyme that attenuates NK- jB activation and release of GM-CSF), but currently the precise mechanistic sequence of events remained elusive.

4.1.2. Urban vs rural setting

Baumann et al. [23] observed that AR was prevalent in both settings, with the urbanized setting of Lima being characterized by a higher prevalence of AR than the rural setting of Tumbes, however, this difference became not-significant when they accounted for the important risk factors subject specific as elevated exhaled nitric oxide, allergic sensitization to common household aeroallergens, parental rhinitis, being overweight and high total serum IgE.

4.1.3. Ambiental Polycyclic Aromatic Hydrocarbons (PAH) exposure

Hew et al. [22] studied immunity of children with AR and/or A in Ambient with PAH exposure (Fresno, California). The results showed that increased PAH exposure in air pollution is associated with impaired systemic immunity and epigenetic modifications in FOXP3, with a higher impact in atopic children.

Industrialized city in West Germany vs East Germany and truck traffic exposure (higher in the first one).

Duhme et al. [40] reported that atopic disease symptoms in 5–8 years old were generally higher in West Germany city, whereas only a few prevalence differences were observed in 12–15 years old. In both age groups the reported lifetime prevalence of A, hay fever and eczema were lower in East Germany city. Exposure such as truck traffic in a residential street was positively associated with symptoms. The findings provide additional evidence for a role of several characteristics and exposures as potential determinants of A and allergies in children. (Table 4).

4.2. Home environment

4.2.1. Smoke exposure

Dogru et al. [20] reported that there was a significant association with exposure to smoke and AR.

Foliaki et al. [32] considered passive smoking, with two or more people smoking in the house, a risk for wheezing, but not for A.

Gonzalez-Diaz et al. [30] showed that in both 6- to 7-year-old and 13- to 14-year-old children, AR was associated with passive smoking at home, intended as current maternal smoking or the presence of at least one smoker in the home.

Baumann et al. [23] did not show any significant association between children with both AR and A and exposure to cigarette smoke.

Duhme et al. [40] reported that environmental tobacco smoke showed weak or no associations with atopic disease symptoms in 5–8 yr olds, but it was positively and statistically significantly associated with asthma symptoms in 12–15 yr olds in Est Germany. However, in this group there was a strong component of active smokers and this was one of the strongest factors associated with respiratory atopic disease symptoms in 12–15 yr olds.

Nowadays, it is well known that constituents of tobacco smoke can cause loss of cilia, hypertrophy of the mucus gland in the upper

airways, inflammation, epithelial changes, fibrosis and secretory congestion; moreover, the gas exchange surface area can be lost [43]. Consistent with the highlighted correlation found between home tobacco exposure and smoking itself and AR, tobacco smoking has also been described as a modifier of allergy markers (i.e., total IgE level, skin prick test results and eosinophilia) [44].

4.2.2. Exposure to dampness and moulds

Baumann et al. [23] observed, as many others, that there were correlations between AR and exposure to common household aeroallergens.

Weinmayr et al. [25] showed that exposure to dampness and moulds is correlated with AR and A. Duhme et al. [40] noticed that moulds and wet spots in bedroom correlate especially with A in 5-8y old.

Caillaud et al. [45] reviewed literature between 2006 and 2017 about the associations between exposure to moulds, alone or in combination with dampness and A and AR. Longitudinal epidemiological data in children were analyzed separately from those of adults. There was an evidence of a causal relationship for a development and exacerbation in children, and sufficient evidence of an association with AR.

4.2.3. Socioeconomic status

Baumann et al. [23] did not show a correlation between socioeconomic status (SES) and AR and A.

The prevalence of allergic disease is usually reported lower in persons with low SES, but allergy has a higher impair in Quality of Life (QoL) in those with low SES [46].

Also ARIA statement highlighted the health and social inequalities incurred by the disease and the importance to provide an active and healthy life to AR and A suffers, whatever their socio-economic status [6].

4.2.4. Polyvinylchloride flooring

Von Kobyletzki et al. [26] showed and increased incidence of AR was increased in condition of PVC flooring. PVC is one important source for phthalates in indoor dust, and exposure to such phthalates was found to be associated with AR. Studies in rodents indicate that phthalates can function as adjuvants, increasing the potency of allergens [47].

4.2.5. Electric cooking

Foliaki et al. [32] noticed that electric cooking is a risk factors for symptoms of A, rhinoconjunctivitis and eczema. This finding was explained by the Authors considering electric cooking as a marker of 'affluence' or degree of 'Westernisation' in the Pacific countries of the study.

4.2.6. Interaction with older siblings

Foliaki et al. [32] and Gonzalez-Diaz et al. [30] analyzed that the interactions with older siblings was a protective factor for development of AR and A.

Consistently Krzych-Fałta et al. [15] demonstrated that the higher the number of siblings, the lower the risk of AR.

The mechanism driving this association is unknown, but an interesting hypothesis has been made by Wolsk et al. [48]: siblings carry out a transferable early immune modulatory effect mediating a Type 1/Type 17-related immune-stimulatory effect in the airways of asymptomatic neonates, also after adjustment for pathogenic bacteria and viruses, and this can represent an utero immune priming effect of the fetal immune system caused by previous pregnancies or it could relate to the presence of unidentified microbes.

The discovery of Tregs revolutionized the primary concepts of immune regulation previously interpreted just within a binary Th1/Th2 paradigm. Tregs like Type 17 play a central role in the maintenance of the establishment of controlled immune responses, and the inhibition of allergen-specific effector cells [49].

4.2.7. Wood or coal heating and feather bedding

Indoor exposures such as wood or coal heating and feather bedding were negatively associated with symptoms of AR and A in Duhme et al. study [40]. This association was explained with an increased risk in early childhood of upper and lower respiratory tract infections when exposed to wood burning stoves at home, which, in accordance with the hygiene hypothesis, postulated by Strachan in 1989, could play a protective role in the development of atopic diseases [50].

4.2.8. Hygiene intervention and hygiene hypothesis discussion

In contrast, Dunder et al. [34] observed that the prevention of common respiratory tract and enteric infections with an extensive hygiene intervention during early childhood does not change later allergic morbidity. Currently there is a considerable body of evidence which warrants scepticism about the hygiene hypothesis, it is possible that a general version of the hygiene hypothesis is still valid, but is the etiologic mechanisms involved that is currently unclear [51]. A recent review tried to re-interpreter the hypothesis in the current age of the microbiome; assessment of environmental microorganisms in upper airways microbiome suggested an additional protective effect of microbial diversity on asthma beyond atopy. What is not clear yet is if this microbial diversity stands for a higher probability to encounter protective clusters of microorganisms or if is a sign of a balanced environmental exposure. More critical assessment of the various effects of microbial exposure on different disease phenotypes is needed [52].

4.3. Individual non-modifiable factors

4.3.1. Male gender

Yao et al. [28] in their study with more than 5000 children, showed statistically significant effect modification by gender for AR and A.

The male-to-female prevalence ratios of A increased with age from <1 at 4–5 years, peaked at 10–11 years (2.24), then reversed to 0.57 at 16–18 years (inverted U-shaped curve). AR prevalence showed nearly equal distributions in all age group except a significant male predominance between 6 and 11 years; in this age group was also found a higher prevalence of allergic sensitization and higher serum total IgE levels.

4.3.2. 25OH vitamin D levels

Baumann et al. [23] observed that there were no differences in 25OH vitamin D levels between children with AR and A and in healthy ones.

4.3.3. Elevated exhaled nitric oxide (ENO)

Baumann et al. [23] found a strong association between airway inflammation and AR, and children with higher ENO (cut-off values $\geq$ 20 ppb). This could reflect permanent inflammation of the nasal cavity and the paranasal sinus mucosa in AR.

4.3.4. SNPs in PTPN22 e CTLA-4 gene

Song et al. [18] showed a significant association between single nucleotide polymorphisms (SNPs) in Protein tyrosine phosphatase non-receptor 22 (PTPN22) gene and the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) gene and AR with asthma in Chinese Han children, which might be susceptibility factors for AR and asthma.

Shared genetic origin of A, AR and eczema was widely analyzed in Ferreira et al. genome-wide association study [53]. 132 nearby genes in allergic disease pathophysiology were identified. Disease-specific effects were detected for only six variants, confirming that most represent shared risk factors. Shared risk variants influence lymphocyte-mediated immunity, as suggested by tissue-specific heritability and biological process enrichment analyses. Multy-morbidity of A, AR and eczema can

be explained by the sharing of many genetic risk variants that dysregulate the expression of immune-related genes [53].

4.4. Obesity and diet

4.4.1. Obesity

Sybliski et al. [21] showed that there was no correlation between BMI and sensitization to aeroallergens but only a trend towards atopy in children; higher BMI was negatively associated with the prevalence of AR in overweight and obese man. In 13-14-year-olds, only obesity increased the prevalence of A.

Baumann et al. [23] noticed that being overweight was an important risk factors for AR.

Yao et al. [28] showed that obesity is associated with a greater prevalence of A in children.

Musaad et al. [31] analyzed central obesity and showed that it was associated with A, A severity, lower lung function, and reduced atopy in asthmatic subjects; these conditions are more associated to AR when compared with standard BMI measures.

There is growing evidence that obesity may be associated with the development of non-atopic asthma, whilst further study of the relationship between obesity and overweight and allergic disease are needed.

4.4.2. Diet

De Battle et al. [33] analyzed that adherence of Mexican children to a Mediterranean dietary pattern was inversely associated with A and AR.

Cepeda et al. [17] noticed that fast-food was positively associated with a higher prevalence of wheeze and allergic symptoms in adolescents.

Farrokhi et al. [24] showed an association between the fast food consumption and A.

Cepeda et al. [17] noticed that a higher intake of fruits and vegetables was associated with a lower prevalence of allergic symptoms in Latin American children.

Kim et al. [19] analyzed that AR was related to high-fat and low-carbohydrate diets.

Farrokhi et al. [24] showed that AR and A in children were correlated to bread and rice consumption.

Regular meat and margarine consumption are risk factors for symptoms of A, rhinoconjunctivitis and eczema in the Pacific. However, most of these associations were weak, and account for only a small proportion of cases [32].

Although the underlying mechanisms and causal relationships remain elusive, literature provides reliable evidence regarding the associations between nutritional factors and AR by considering numerous factors in large and representative populations. Improved dietary habits in children might help reduce the epidemic of allergic symptoms.

4.5. Medications assumption and tuberculosis

4.5.1. Paracetamol use

Gonzales-Diaz et al. [30] and Foliaki et al. [32] included in their studies paracetamol (acetaminophen) consumption during the first year of life and in the last year in children 6–7 years old, for treatment of infection-related fever. In both, it was found correlating with AR, A, rhinoconjunctivitis and eczema.

Because of the cross-sectional nature of these two studies, there is the possibility of confounding. It is not known if this drug has a causal effect or whether patients were treated with acetaminophen for their allergy symptoms, which may resemble symptoms of infection.

A probable etiologic mechanism for asthma is a depletion of glutathione in the lungs, decreasing the ability to mitigate oxidative stress produced by reactive oxygen species and leading then to inflammatory triggering with inflammatory cell stimulation, release of leukotriens, edema and bronchoconstriction [54] The epidemiological evidence supports the hypothesis of a similar mechanism in AR [30,32]. Prospective studies are needed to better evaluate the causal relationship.

4.5.2. Antibiotics in first year of life

Gonzalez-Diaz et al. [30] found no relationship between rhinitis and the use of antibiotics in the 1st year of life.

4.5.3. History of tuberculosis (TB) and Bacillus Calmette-Guerin (BCG) vaccination

Flohr et al. [27] found a uniform positive association between TB and all allergic disease outcomes, moreover it showed also that BCG vaccination during the first year of life was also not associated with any of the allergy outcomes. Further longitudinal studies are required (Table 8).

4.6. Atopy and multi-morbidity of allergic disease

4.6.1. Familiarity

Baumann et al. [23], and Von Kobyletzki et al. [26] agreed that parental history of allergic disease is an important risk factor for AR and atopy. Consistently, Keil et al. [29] correlated having 2 parents with allergy as a risk factor significantly associated with AR.

Krzych-Fałta et al. [15] confirm these findings, highlighting a two-fold higher risk of inheriting atopy from the mother and father in the case of AR, and from both maternal and paternal grandparents in the case of A.

Dogru et al. [20] categorized patients in two groups: AR and A comorbidity group and AR-only group. They found that familiar atopy, defined as allergic diseases seen in first-degree relatives (parents and siblings), was no significantly different between these two groups.

In Yavuz et al. [16] parental asthma was associated with asthma in school-age children with grass pollen-induced AR.

These findings suggest that familiar atopy is a risk factor just for AR, whilst familiarity for asthma is an important risk factor not only for A, but also in the developing of A in patients with AR.

4.6.2. Sensitization to aero-allergens and IgE levels

Baumann et al. [23] noticed that polisentitization to common household aeroallergen and high total serum IgE correlated with AR.

Also Kell et al. [29] recognized sensitization to aero-allergens as a risk factor significantly associated with AR.

Dogru et al. [20] showed that children with AR and A were likely to have a higher IgE levels, HDM sensitivity, sensitivity to cockroaches, and polysensitization, despite children with just AR.

Whilst Dogru et al. sensitization evaluation was made with skin prick tests, Siroux et al. [55] measured IgE reactivity to 64 micro-arrayed aeroallergen molecules. They demonstrated different patterns of sensitization in children with A and AR, just A, just AR and healthy controls; no or few sensitizations were found in the A-AR- group, predominant sensitization to indoor allergens in A + AR-, predominant pollen allergens in A-AR+ and frequent IgE-sensitization to both pollen and indoor allergens in A + AR+.

Higher levels of total and specific IgE were detected in children with A and AR but further studies are required to enlighten the precise role of IgE in the underlying pathogenetic mechanism of this findings.

4.6.3. Multymorbility of allergic disease

Concerning the link between AR and A, it was explored in a lot of papers included in this review.

Dogru et al. [20] noticed that the majority of children with AR had A comorbidity and showed that children with asthma were likely to have a higher duration of AR;

Keil et al. [29] found that A was more associated in particular with children with severe persistent AR.

On the other hand, Musaad et al. [31] reported that prevalence of

moderate-to-severe A is higher in children with AR. Consistently, Henriksen et al. [39] highlighted that in asthmatics, concomitance of AR was associated with higher total allergy scores and increased Dose-Response-Ratio (DRR) and elevated levels of ENO, indicating more severe disease.

In the complexity of the link between the two diseases, that is still to be fully understood, appears evident that not only A worsen AR, but is possible to state that vice versa AR is correlated with a more severe A.

Hew et al. [22] and Weinmayr et al. [25] focused on evidencing the important role of non-atopic process in the onset of A and AR in children.

In particular, children PAH exposure may alter methylation patterns of genes involved in immune regulation in T cells, which leads to adverse immune effects with the development of AR and A [22].

Weinmayr et al. [25] found a consistent association of dampness with AR and A and with just A. The significantly stronger association between dampness and wheeze in centers from less affluent countries provides further argument for the link being possible also through non-atopic mechanisms such as non-allergic inflammatory processes. HDM exposure and sensitization may contribute, but the link in children of the study seemed to be related principally to non-atopic mechanisms.Pinart et al. [56] remarked this concept, evidencing that the presence of IgE sensitization, independently associated with excess comorbidity of eczema, rhinitis, and asthma, accounted only for 38% of comorbidity, suggesting that IgE sensitization can no longer be considered the dominant causal mechanism of comorbidity for these diseases.

In northern Mexico Gonzalez-Diaz et al. [30] determined that in both 6- to 7-year-old and 13- to 14-year-old children other allergic condition were the main risk factors associated AR. Within these asthma symptoms were associated as a risk factor not only to AR but also with rhinoconjuntivitis in both age group.

In Von Kobyletzki et al. [26] prospective study, early onset of eczema during first year of life, especially if moderate to severe and persistent, was correlated to the development of A and AR during the next 5 years of follow-up. They identified eczema as one of the strongest independent risk factor for A and AR.

Gonzalez-Diaz et al. [30] results were consistent with this finding, dermatitis symptoms and diagnosis of eczema were found to be important risk factors of AR and A, in both the child cohort examined (6–7 years old and 13–14 years old).

4.7. Pet ownership

4.7.1. Keeping cat

Early cat ownership was significantly associated with a lower risk of cat sensitization compared with never cat ownership. Cat ownership in early childhood can play an important role in preventing sensitization to cat and in lowering the frequency of AR. early cat ownership seems to be protective against AR but not against A. The effect of early exposure to cats on nasal symptoms might be related to a deposition of greater amounts of allergen (and, eventually, of pet-derived endotoxins) on the upper airway mucosa, possibly leading to antigen tolerance. This phenomenon has been thought to have a key role during “mucosal” immunotherapy against grass pollen, in which high allergen loading results in stimulation of antigen-presenting cells and local production of “suppressive” cytokines such as transforming growth factor or interleukin 10 from T-regulatory cells [37].

4.7.2. Keeping dog and keeping horse

Henriksen at al [39]. showed that current exposure to pet allergens did not lead to increase in Dose-Response-Ratio (DRR) or elevated levels of Exhaled-Nitric-Oxide (ENO); however, in non-smoking, steroid-naive asthmatics a tendency towards increased levels of ENO among those both sensitized and exposed to the actual pet was seen.

4.8. Pregnancy and mother-related factors

4.8.1. Mother and pregnancy morbidity

McKeever et al. [38] studied the importance of prenatal exposures on the development of allergic disease. Perinatal maternal depression was associated with an increased risk of having a diagnosis of AR, eczema and, in particularly, A. Complication during pregnancy were found to increase the risk of development of allergic diseases in children, as well as exposure to infections in utero.

Antibiotics in utero was associated with an increased risk of A and eczema in a dose-related manner.

The risk of developing AR and A depended also on the mode of delivery; in Krzych-Fałta et al. [15] it was higher for a Cesarean section than vaginal delivery.

The probable explanation is that in caesarian delivery is missed the colonization by physiological bacteria, which are transferred from the mother to the child during a vaginal delivery and affects the intestinal balance of the newborn child. These disturbances in bacterial colonization, especially in the gastrointestinal tract, are involved in the development of the immune system and increase the risk of developing allergic conditions [57].

4.8.2. Mediterranean diet during pregnancy

De Battle et al. [33] assessed if the adherence to a Mediterranean dietary pattern for mothers during pregnancy was associated with children with AR and A. No associations were found using a mothers' pregnancy Mediterranean diet score, except for current sneezing.

4.8.3. Prenatal maternal smoking

Magnusson et al. [36] analyzed that late gestational smoke exposure was associated with wheezing but not with A, while null or even protective estimates were indicated for hay fever and atopic eczema.

Other reports have indicated a causal relationship between exposure to tobacco smoke during pregnancy and early infancy and allergic diseases, especially asthma. The proposed mechanism is that tobacco smoke reduces 1-antitrypsin, a lung protease that blocks normal inactivation of allergenic house-dust mite proteases in the airways. This results in an increased risk of sensitization to these allergens [58].

4.9. Prolonged breastfeeding

Obihara et al. [35] observed that in children without a maternal or paternal allergic history, there was a significant linear inverse association between the breastfeeding duration and allergic disease in general, and AR in particular, with the maternal history having the stronger influence. There was a significant interaction factor between maternal allergic history and breastfeeding duration for allergic disease in general and A in particular.

Consistently, history of formula feeding was associated with A in children with AR [16].

5. Conclusion

The lack of success in the prevention of allergy disorders lies on their complexity, which involves many genetic, epigenetic, and environmental interactions, this review gives an indication on this important and complex interconnection between AR and A in children and provides a useful synthesis of what are currently considerable risk factors for their multi-morbidity.

The genetic and familiar predisposition plays a role in the development of AR and A, as well as some strong environmental factors, that range from the mother habits, to many different early life exposures in both home and outside environment. The interaction of these factors led to epigenetic, microbiota and consequent immunological changes. Both atopic and non-atopic pathways are involved, with a possible prevalence of the second.

Close monitoring of evidenced risk factors for both A and AR and especially those that more probably are associated with the development of A in AR children, may help with an earlier diagnosis of A and prompt initiation of therapy in children with AR.

The main limit of our analysis was not evaluating more literature database; indeed, further studies are needed, future research should be forward the pathogenic mechanism of these factor and their precise impact on the development of A in children with AR and, consequently, studying the link between A and AR.

There is a need to identify the involved interconnected pathogenesis and target populations widening the understanding of shared genetics origin, epigenetic, microbiota and consequent immunological changes, in order to get to the best interventions.

Declaration of competing interest

None declared.

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