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Review

Allergic Rhinitis Systematic Review Shows the Trends in Prevalence in Children and Adolescents in Greece since 1990

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Abstract: Allergic rhinitis is the most common immune disorder worldwide, affecting approximately 10–40% of the general population. It is characterized by an inflammatory response of the nasal mucosa following exposure to non-infectious, inhaled, and airborne allergens that are defined based on the period of exposure to the allergen as annual, seasonal, or episodic. A variety of factors are found to relate to the prevalence of allergic rhinitis, i.e., sex, race, age, seasonality, personal and family-positive atopic history, as well as exposure to environmental and epigenetic factors. In addition to the local inflammation in the nasal mucosa, systemic inflammation is activated in the entire respiratory system, such as rhinoconjunctivitis, asthma, sinusitis, and otitis media with effusion. The aim of this study was to evaluate the trends in the prevalence of allergic rhinitis in the Greek pediatric and adolescent population since 1990. Research was performed in electronic databases (PubMed, ScienceDirect, and Cochrane Library) using appropriate MeSH terms for related studies from 1990 to 2023. We found 12 studies, 11 prospective and 1 cross-sectional, conducted in the cities of Athens, Thessaloniki, Patras and Evros prefecture, with sample sizes varying from 517 to 3076 subjects aged 6–17 years old. The prevalence of allergic rhinitis showed geographic and temporal variability, ranging between 2.1 and 32.5% in children and 25.3 and 30.8% in adolescents, with increasing trends. Factors such as gender (male), age (8–10 years), environmental exposures (moisture, mites, and fungi), positive atopic profile, and family history (asthma and eczema) were related to the manifestation of the disease. The need for systematic research in the Greek child and adolescent population is vital to recognize, prognosis, and control allergic rhinitis manifestations.

Keywords: child; adolescent; rhinitis; allergic; prevalence; Greece; Greek

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1. Introduction

Allergic rhinitis (AR) is an inflammatory response of the nasal mucosa after exposure to non-infectious, inhaled, and airborne allergens via IgE-mediated hypersensitivity reactions. It is the most common immune disorder worldwide, affecting approximately 15–40% of the global population, as well as the daily routine of almost 400 million people [1,2]. It has been found that the prevalence of AR is related to sex, race, age, seasonality, personal and family-positive atopic history, as well as exposure to environmental and epigenetic factors [2,3].

Clinical manifestations of AR are divided into general and specific. Specific manifestations are divided into nasal, i.e., anterior and posterior rhinorrhea, stuffy nose, itching of the nose, and nasal congestion and non-nasal, i.e., redness and itching of the eyes, lacrimation, itching of the palate, and cough [2]. General manifestations include fatigue,

sleep disturbances, poor concentration, irritability, and declined work and school performance [1,4]. AR is classified based on the period of exposure to the allergen as annual, seasonal, or episodic, based on the clinical manifestations and their frequency of incidence as intermittent or persistent, and based on the severity as mild, moderate, or severe [2,5].

The pathophysiological mechanism of AR includes two different patterns according to time sequence. When AR patients are exposed to allergens, allergic reactions develop in an early and a late phase. Early reaction is characterized by sneezing and rhinorrhea and develops in 30 min and disappears. Late reaction is characterized by nasal obstruction, develops approximately 6 h after exposure, and subsides slowly. The primary exposure of the nasal mucosa to an allergen is followed, within 20 min, by the activation of T and B lymphocytes, synthesis of the allergen-specific immunoglobulin IgE, and generation of homologous memory cells. During the early phase, after re-exposure to the above allergen, this allergen-specific IgE binds to high-affinity IgE receptors present on mast cells, leading to mast cell activation, degranulation, and release of mediators that promote rhinorrhea, pruritus or nasal itching, within minutes, lasting 2–4 h. The late phase, which follows within 4–6 h and lasts 18–24 h, includes the concentration of T lymphocytes, basophils, and eosinophils in the nasal mucosa and the release of mediators that prolong symptoms and lead to nasal congestion [1,4].

In addition to the local inflammation in the nasal mucosa, systemic inflammation may also be activated in the entire respiratory system. Diseases such as rhinoconjunctivitis, asthma, sinusitis, and otitis media with effusion are also reported by patients who suffer from AR [2]. In addition, common biological and etiological factors related to the incidence of AR, asthma, allergic conjunctivitis, atopic dermatitis or eczema, and food allergies are found in allergic patients, who account for more than 40% of the European and US population [3,6]. The above factors also explain the "allergic march", which includes the consecutive occurrence of atopic diseases such as food allergy, eczema, asthma, and AR in the same person. However, there are many infants with eczema who never develop asthma or rhinitis, and both latter conditions can evolve without prior eczema or food allergy [7].

It is well known that 40% of children suffering from AR show symptoms by the age of 6 years; 80% of the clinical manifestations of the disease appear at the end of adolescence, while their peak occurs between the second and fourth decade of life and follow a decreasing course over time [1]. Early diagnosis, which is confirmed by taking medical history, clinical examination, and laboratory testing, is vital for a better prognosis [5]. Furthermore, in a recent study from Sweden, the cost of managing AR was estimated at about EUR 950 per affected person per year, upscaling the disease to an important public health problem that needs immediate solution at the level of the European Union, by implementing targeted health programs [8].

The aim of this work was to investigate the trends in prevalence and the risk factors of AR in children and adolescents in Greece during the period 1990–2023. To the best of our knowledge, this is the first study in Greece that aims to systematically review the Greek literature of the last 30 years concerning AR.

2. Materials and Methods

2.1. Search Process

Systematic literature research was carried out in three different databases, MEDLINE, Science Direct, and Cochrane Library, from January 1990 to June 2023. Initially, 69 articles were found, all written in the English language, after using the relevant Medical Subject Headings (MeSH) terms "child", "adolescent", "rhinitis", "allergic", "prevalence", Greece", "Greek" in the title, abstract, or keywords of the article. The initial search yielded 40 studies in PubMed, 28 in ScienceDirect, and 1 in Cochrane Library. Of them, 25 were excluded as duplicates. Of the remaining 44 articles, 36 were excluded due to non-compliance with the selection criteria. Finally, 8 studies were included in the present review (Figure S1). This review has been conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines [9] and has been registered in PROSPERO (ID 472632).

2.2. Eligibility

Only epidemiological, observational studies published in English or Greek language and referring to the Greek pediatric and adolescent population regarding AR were included in the present review. The studies were grouped according to their retrospective, cross-sectional, and cohort (prospective) design. AR was defined by the collected data from (1) self-report questionnaires of the adolescents and children's parents regarding symptoms of atopic diseases (AR, asthma, and eczema), (2) children's laboratory analyses (spirometry, measurement of exhaled nitric oxide, a bronchial hyperreactivity test with a methacholine challenge test and fatigue test, as well as a nasal histamine challenge test), (3) clinical examination of participants (body folds for atopic dermatitis), and (4) skin prick tests (SPT) from seven (pollen from grass, trees, and olives, Dermatophagoides Farinae and Pteronyssinus, Alternaria tenuis, and cat epithelia) up to eleven common airborne allergens (pollen from flowers, trees, bushes, grains, grass and olives, Parietaria officinalis, Dermatophagoides Farinae and Pteronyssinus, and cat and dog epithelia).

2.3. Selection Process

All potentially relevant full texts identified in the three electronic databases were screened by two authors (AD and DP) independently of one another, and three additional authors (CK, GA, and KD) confirmed the data obtained. Discrepancies were resolved by discussion. No attempts were made to contact the study's authors to identify missing and confusing data.

2.4. Data Items

Studies' findings were collected as prevalence and incidence rates (i.e., frequencies), stratified by age group and gender whenever available. Children and adolescents' specific characteristics were recorded when provided by the studies. These characteristics included the year and sample size of the study, the region, gender (boy/girl), age (in years), environmental exposures (i.e., to moisture, mites, fungi), and atopic personal and family history (i.e., asthma, eczema).

2.5. Quality Assessment and Risk of Bias

Study quality was independently assessed by two authors (CK and GA) who used the levels of evidence suggested by the Centre for Evidence-Based Medicine (Oxford, UK). In particular, Level I included validating cohort studies with good reference tests that were applied blindly or objectively to all patients, Level II included exploratory cohort studies with good reference tests, Level III included studies with non-consecutive patients or with the reference test not applied to all patients, Level IV included case–control studies, poor or non-independent reference tests that were not applied to all patients but still interpreted independently of the index test, and Level V included expert opinion without an explicit critical appraisal, or based on physiology, bench research, or first principles.

3. Results

Sample sizes of the retrieved epidemiological studies ranged from 517 subjects aged 6–17 years old [10] to 3076 subjects aged 8–9 years old [11]. Participants lived in the city of Patras [11,12], the wider region of Evros prefecture [13], as well as the capital cities of Thessaloniki [14–16] and Athens [10,15–17]. Eleven of the epidemiological studies were cross-sectional [11–17], and one was prospective [10]. All studies were conducted between 1 January 1990 and 31 May 2023.

Six surveys were carried out in Patra from 1991 to 2018, during the winter months of January and February, and included children retrieved from 44 public primary schools. These surveys investigated the prevalence of AR, allergic conjunctivitis, eczema, asthma, and its trend during the winter and published their results in two different studies [11,12]. The collected data included self-report questionnaires by the patients' parents [11] and their respiratory test results, i.e., spirometry exhaled nitric oxide [12]. The questionnaire was

standardized and weighted in the Greek population. It was different from the International Study on Asthma and Allergies in Children (ISSAC) questionnaire [18], as the primary allergic rhinitis survey took place in 1991 before the ISAAC questionnaire was introduced. The prevalence of AR or allergic conjunctivitis was found to increase between 1991 and 2008 and then decrease in subsequent years [11,12]. Furthermore, the prevalence of AR was estimated in boys at 2.0%, 4.5%, and 4.8%, and in girls at 2.2%, 2.6%, and 4.4% for the years 1991, 1998, and 2003, respectively. Males were found to have a greater contribution to the increasing trend of AR prevalence than girls in the above interval and a 26% greater risk of developing AR than girls of the same age group, with an RR of 1.26 (95%Cl: 1.00–1.58) [11].

From 2000 to 2002, two cross-sectional studies were carried out in Thessaloniki in children concerning the estimation of the prevalence of AR [14–16]. One study that was part of the ISAAC-phase II multicenter study was conducted from October 2000 to December 2001 and included children from 31 primary schools. Data included patient parents' responses to the ISAAC questionnaire [18] regarding symptoms of asthma, AR, and eczema, as well as the SPT results to seven common airborne allergens (i.e., pollen from grass, trees, and olives, Dermatophagoides Farinae and Pteronyssinus, Alternaria tenuis, and cat epithelia). Boys had a 25% higher probability of developing AR than girls with an OR of 1.25 (95%Cl: 0.91–1.71) [15,16]. From 2001 to 2002, primary school students from the Municipality of Polichni underwent SPT to 11 allergens (i.e., pollen from flowers, trees, bushes, grains, grass, and olives, Parietaria officinalis, Dermatophagoides Farinae and Pteronyssinus, and cat and dog epithelia), a bronchial hyperreactivity test with a methacholine and fatigue test, and a nasal histamine challenge test. Moreover, participants' parents completed a Ferris-type self-report questionnaire [19] regarding the existence of a positive history of symptoms from the upper and lower respiratory tract concerning allergic or inflammatory diseases. Almost seven out of ten patients (68.2%) were boys with sensitization to at least one allergen, while one out of three parents knew that their child had AR [14].

In 2016, in the prefecture of Evros, another cross-sectional epidemiological study was carried out and included students from primary and secondary public schools [13]. In total, 117 boys and 114 girls were found with AR. The inclusion criteria of that study were a positive response to self-report questionnaires concerning atopic symptoms and a positive result in SPT to specified allergens, i.e., house dust mites (Dermatophagoides), grass pollen, trees (olive, cypress, and fir) and grasses, animal epithelia (cat and dog) and fungi (Alternaria and Cladosporium spp). The prevalence of AR was estimated at 32.5% and 30.8% in subjects aged 6–11 and 12–17 years of age, respectively. Among the results of this study, it was found that three out of ten subjects were teenagers (28.7%), the majority of the participants (59.7%) showed multi-sensitization to aeroallergens, 87/231 (37.6%) patients had a positive family history for atopy, and one out of three parents did not know that their child had AR [13].

In addition, two cross-sectional [15–17] and one prospective [10] study investigated the prevalence of AR in children and adolescents in Athens for the period 2000–2020. Students from 43 primary schools participated in the study of Papadopoulou et al. [15,16], which was part of the ISAAC-phase II multicenter study. ISAAC questionnaire responses [18] regarding symptoms and signs of asthma, AR, and eczema, as well as the results of the clinical examination of skin folds for atopy and SPTs to seven aeroallergens, were collected. Boys had a 6% higher probability of developing the disease than girls (OR = 1.06; 95%Cl: 0.70–1.47). Furthermore, in the iFAAM study [10] that was conducted from 2014 to 2017, 15.3% of the participants had a positive history of atopy before completing their second year of life, while 6.8% of them showed symptoms of AR in that period. The above study was a component and final assessment of a follow-up of 12,049 newborns from nine European cities who took part between 2005 and 2010 in the EuroPrevall prospective study [10]. Ultimately, 921 boys and 1013 girls, adolescents attending secondary schools, participated in the February to March 2020 survey as part of the multicenter Global Asthma Network (GAN) phase I study by Antonogeorgos et al. [17]. The data came from the completed GAN

questionnaires of the adolescents and their parents regarding symptoms of atopic diseases in the last 12 months and behavioral data. In total, 491 subjects (49.5% boys) were found with AR in the last year. Moreover, six out of ten patients had a positive family history of atopy ($p = 0.038$) [17].

An attempt was made to evaluate temporal trends throughout the period covered by the retrieved studies. Linear trend analysis revealed an increasing trend in AR prevalence by 0.4% per year ($p = 0.007$). This trend was mainly guided by the increased prevalence rates observed in two studies, i.e., Katotomichelakis et al. [16] and Antonogeorgos et al. [20].

4. Discussion

This systematic review aimed at investigating the epidemiology of AR in children and adolescents in Greece. It revealed that prevalence rates range between 2.1% in 1991 and 32.5% in 2016 in children and between 25.3% in 2020 and 30.8% in 2016 in adolescents, with significant geographical and temporal variability [11,13,17]. An increasing trend in prevalence rates was revealed in our study; thus, it should be interpreted with caution because of information bias concerning specific time points and differences in the design of the different studies. Moreover, gender (boys), age (particularly between 8 and 10 years old), specific environmental exposures (i.e., moisture, mites, and fungi), and positive personal and family history of asthma or eczema were found to be related to the onset of the disease in children and adolescents [10,11,14,15,17]. The lack of data shows that the incidence of AR has been underestimated in many countries, including Greece, leading to disease exacerbation and extensive medication instead of early prevention and control of the disease.

AR is a common immunological disorder related to increased morbidity on a global scale and, therefore, a significant burden on the health system [20]. A worldwide increase in the incidence of atopy diseases during the last fifteen years was noted by the ISAAC multicenter epidemiological study that included children and adolescents from 91 and 155 centers in 38 and 91 countries, respectively. In particular, the prevalence of AR was estimated to vary between 8.5% and 14.6% in 6–7 and 13–14-year-old children, respectively, with marked variation by sex, race, and environmental exposures [21–24]. In addition, in recent population studies in Europe and the USA, the prevalence of the disease approached 40% in children and adolescents. Symptoms started even before their sixth year of age [25]. It should be highlighted that robust epidemiological data from cohort studies on AR are lacking, especially in Europe.

AR prevalence in Greece followed worldwide trends and was shown to increase during the past several years, in line with the increase in the prevalence of atopy. Furthermore, a geographical variation regarding AR prevalence was also revealed. In particular, AR in southern western Greece, i.e., Patras city, showed an increasing trend in children aged 8–10 years old between 1991 (2.1%) and 2008 (5.1%), followed by a decreasing trend until 2018 (3.0%) [11,12]. The absence of an overall biological hypothesis that can explain the trend in the prevalence rates of AR was highlighted in the study of Malliori et al. [12]. The authors proposed that various well-established risk factors, which operate separately or combined in space and time, may be responsible for the diversity of the epidemiological observations [15]. Increasing trends were observed in children aged 9–12 who lived in Northern Greece, i.e., Thessaloniki capital city, which increased from 8.2% to 12.6% between 2000 and 2022 [14–16]. Moreover, in primary and secondary school students in Central Greece, i.e., Athens capital city, AR prevalence had a five-time increase between 2000 and 2020 [10,15,17]. It is also notable that the AR prevalence observed in the Katotomichelakis et al. [16] and Antonogeorgos et al. [20] studies, although between the spread world limits, i.e., 1.8–40%, seems to be much higher than in other studies in Greece. Possible explanations could be that the aforementioned studies included a wider range of age groups, including adolescents. They took place during specific periods of the year, mainly in springtime, and they had differences in the questionnaires or other tools used to assess AR.

Taking into consideration the lack of a valid biological hypothesis that can explain those trends, there is a possibility that other factors could be responsible for the diversity of the available epidemiologic observations [12]. It might be related to differences in the macro- and micro-environmental characteristics of an area, such as climate or urban/rural region. It is hard to conduct studies examining the geographical variations of AR in the world because of the lack of systematic studies that have focused on this factor. However, the up-to-date knowledge suggested that there was a worldwide increase in the prevalence of AR among children and adolescents, according to the results of the latest studies. The ISAAC Phase III study found that the prevalence increased more than 1% annually in up to 33.3% of centers in Africa and Eastern Europe, 20% in Latin America, 13.3% in Asia–Pacific, 12.5% in India, and 2.9% in Western and Northern Europe. Furthermore, it was noticed that the highest prevalence was confirmed mainly in the centers from middle- and low-income countries, especially in Africa and Latin America. Diversities in income, healthcare access, and medication availability did not affect Greek children, as the National Health System was available for everyone who sought care. This increase was more obvious in adolescents compared to children, implying that environmental influence on the development of allergy may not be limited to early childhood [26,27]. Additionally, the most common allergens present in the Greek population were already mentioned in the studies included in our review, without any indications for differences as compared with the European mainland or the worldwide average.

Particularly, air pollution, climate change, and lifestyle were found to be related to the prevalence of AR [26]. These considerable variations between the centers could be attributed to language or cultural differences. In some regions, there is not a certain pollen season, and the diagnosis of hay fever is often misunderstood. Lack of availability and poor affordability of pharmacotherapy for AR from middle- and low-income countries results in an improper management of AR [27].

On the other hand, various studies have shown the protective role of dietary patterns, such as the Mediterranean diet, in the development of allergic diseases [28–31]. The Mediterranean diet is a traditional nutritional pattern in the Mediterranean basin countries, such as Greece. It is a plant-based diet, rich in antioxidants, unrefined carbohydrates, fibers, and monounsaturated and omega-3 polyunsaturated fatty acids. Antioxidants have a beneficial role in the inflammatory response as they appear to modulate immune reactions and chronic inflammatory processes, such as allergic diseases [30]. In a recent cross-sectional study, it was found that the consumption of rice and cereals equal to or more than three times weekly had a protective effect on physician-diagnosed AR with an OR of 0.53 (95%Cl: 0.32–0.87) and an even higher OR of 0.58 (95%Cl: 0.36–0.92) among 11,483 Turkish children aged 6–7 years old. However, children and adolescents with a modern urban lifestyle reduce their physical activity and increase their consumption of junk food. These unhealthy lifestyle behaviors are strongly associated with the presence of allergic diseases [28]. Other factors that may exhibit a protective role in the development of allergic diseases are microbial exposure in early life and climate. Microbiota during early life are crucial for the development of a healthy immune system and disease protection. Inappropriate or insufficient microbiota can have various harmful effects on immune health, contributing to the development of allergic diseases [32,33]. The climate crisis could have numerous negative impacts on health. Pathogen profiles are changing, and the transmission and spread of vector-borne diseases are increasing. The overall milder weather, in combination with air pollution and increased CO_2 levels, is changing the production and allergenicity of pollen [34].

In recent years, the significant effect of AR on the quality of life of an affected person and society has been recognized. Children and adolescents with AR often present with fatigue, irritability, reduced attention, concentration, memory, learning difficulties, and reduced school performance. AR clinical manifestations, along with reduced physical activity and sleep disturbances, promote cardiovascular diseases and obstructive sleep apnea while leading to social isolation and sometimes depression [35]. It often coexists

with other atopic diseases, such as asthma, allergic conjunctivitis, and eczema, in the same person. Allergic patients request twice as frequent medical visits and twice the pharmaceutical expenditure of non-sufferers. It was pointed out that the annual cost of managing the disease at the public health level was estimated in the USA for 2010 at about 17.5 billion dollars, while in a recent study, it was estimated at 1.3 billion euros for Sweden and between EUR 9.4 and EUR 9.9 billion for Germany, France, and the United Kingdom [25].

Primary healthcare providers play a substantial role in the management of AR. Both general practitioners and pharmacists offer health information and educational strategies for preventing and treating AR's manifestations at home [36–39]. However, there are many patients who choose to rely on self-diagnosis and select over-the-counter medication for their treatment prior to a health professional consultation. Oral or intranasal antihistamines, corticosteroids, and decongestants are not only available over-the-counter but also the most frequent pharmaceutical agents for self-monitoring of AR by patients. On the other hand, it is well known that access to self-care of AR is sometimes suboptimal, and consequently, these patients remain undertreated [36–39].

A comprehensive history and SPT are recommended to establish a certain medical diagnosis of AR. In addition, the treatment of the disease includes the avoidance of critical allergens and the appropriate medication in order to control the symptomatology, ensure the patient's quality of life, and prevent the progress of the sequelae of AR [40].

Limitations of Study

Our study has some limitations. According to each survey, the definition or diagnosis of AR was based on objective and subjective measurements, which may also explain the differences in the prevalence rates reported. In addition, the self-reported questionnaires varied and sometimes were not comparable. All the studies included but one [10] were cross-sectional surveys that could not address the causality of associations. Moreover, they were at moderate risk of bias (i.e., selection, recall), while the cohort survey was at low risk of bias (i.e., selection). The studied population included in the retrieved studies came from urban areas, and the studies were performed during autumn and winter; thus, a possible over/under-estimation of the prevalence of AR versus rural areas or spring–summer season should be noted.

5. Conclusions

AR is a major problem that has a role both on personal and social levels and undoubtedly affects people's quality of life. More methodical epidemiological studies are needed in children and adolescents with AR to further assess the prevalence and investigate the factors with a protective or aggravating effect, both at the individual and social level, and undoubtedly to achieve an improvement in the patient's quality of life.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/allergies3040014/s1, Figure S1: Flow chart of the selection process. Table S1: Characteristics of surveys reported.

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