

Allergies in Children: What's New? —A Cross-Sectional Descriptive Study

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Abstract

Background: The prevalence of respiratory allergies is increasing worldwide, with important consequences especially for little children. **Objective:** The aim of this study was to assess the prevalence of respiratory allergies, such as rhinitis and asthma, and to point out the risk factors and their relationship with allergic diseases in a specific area of Northern Italy. **Methods:** 110 children, male and female, from our outpatient service for allergic children, between 3 and 17 years old, were examined. After a skin prick test and a nasal cytology, the written questionnaire of the International Study of Asthma and Allergies in Childhood was filled by parents together with their children. **Results:** 110 children were examined. 74% of children had rhinitis and 71% asthma. 88 patients were allergic, grass pollen and house dust mite was the most frequent allergens. A family history of atopy, family background, geographic area, active and passive smoking and home pets were associated to allergies. Older children (6 - 15 years old) had more often rhinitis associated with asthma and conjunctivitis as compared to younger. 21 Children were also affected by non allergic rhinitis. **Conclusions:** Respiratory allergies are widespread and associated to a low quality of life among little children. Sensitization to Ragweed is increasing with important consequences. Rhinitis precedes the onset of asthmatic symptoms. Moreover non allergic rhinitis is increasing and frequently underdiagnosed.

Keywords

Allergies, Environment, Asthma, Rhinitis

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1. Introduction

More than 150 million European Union citizens suffer from chronic allergic diseases and they will be 250 million in the next ten years; moreover allergic diseases are increasing especially among young children [1]-[3].

Allergic diseases are the first leading cause of loss of productivity, low quality of life, and reduction of school performance followed by cardiovascular diseases. They must be considered a major global public health issue and a real epidemic in the European Union [1] [4] [5].

Despite this data they are underdiagnosed, in fact 45% of patients have never received a diagnosis [4] [6].

Allergic rhinitis has a prevalence of 0.8% to 14.9% in the 6 - 7 years old group and of 1.4% to 39.7% in the 13 - 14 years old, till 20% - 30% among teenagers and young adults.

These data are underestimated because especially young children do not present sufficiently severe symptoms to require medical attention, in fact they often have rhinorrhea, coughing and sneezing; 19% - 38% of patients have also asthma associated with rhinitis which may lead to a worsening of their clinical condition [6].

The aim of this study was to investigate the prevalence and the risk factor of allergic diseases, such as rhinitis and asthma, in a specific area of Northern Italy, Varese and surroundings (an area of 1.199 km²), with particular characteristics possibly affecting the spread of these diseases (presence of urban, mountain, and lake areas; rainfall: more than 1500 mm of annual average, wetness: 75.2% of annual average). It could be considered a little model of the different conditions that can be found everywhere.

Although primarily descriptive this study allows us to have an analysis of the epidemiological situation in the pediatric population.

2. Methods

This was a cross-sectional, descriptive study. 110 children, 70 males and 40 females, aged 3 to 17 (15% aged 3 - 5, 8 males and 8 females, 47% aged 6 - 10, 36 males and 16 females, 32% aged 11 - 15, 22 males and 13 females, and 6% aged 15 - 17, 4 males and 3 females) from our outpatient service for allergic children, were examined from November 2013 to March 2014. Children with asthma, rhinitis or dermatitis, who came for the first time or were already followed by our service, were eligible to participate.

First each child underwent an ear, nose, throat, lung examination, a skin prick test and a nasal cytology. We tested a panel of allergens: grasses, birch, nut tree, olive tree, ragweed, lichwort, dog, cat, house dust mite (*Dermatophagoides pteronyssinus*, DPP, and *Dermatophagoides farinae*, DPF), mould (*alternaria*) and foods (cow lactalbumin, cow casein, egg white and yolk, peanuts), according to the European society guidelines [7] and to Gelardi recommendation for the nasal cytology [8].

Then each child with his/her parents was asked to fill a questionnaire. The questionnaire used in this study was primarily adapted from the reliable, written questionnaire of the International Study of Asthma and Allergies in Childhood (ISAAC), the largest worldwide epidemiological collaborative research project ever undertaken [9]. Questions (84) included socioeconomic status, parental atopy, presence of cigarette smokers and furred pets at home, therapy. Additional questions were about the presence of wheezing, rhinorrhea, coughing, and sneezing.

3. Results

Of children evaluated 88 showed positive skin prick tests (60 males, 28 females), 22 negative (12 females, 10 males) and they were affected by asthma or rhinitis as shown in **Figure 1**. Of children between 3 and 5, 4% presented only rhinitis; among children from 6 to 10, 9% had asthma, 8% rhinitis, 9% rhinitis associated with asthma and/or rhinoconjunctivitis; 10% of patients from 11 to 15 presented rhinoconjunctivitis and asthma. According to the nasal cytology, 21 non allergic children were affected by non allergic rhinitis (20 non-allergic rhinitis with eosinophils, NARES, 1 non-allergic rhinitis with eosinophils and mast cells, NARESMA).

Of allergic patients 56% was polyallergic both to perennial and seasonal allergens, 9% was polysensitized but only to perennial allergens, 15% was sensitized to only one allergen (10% grasses, 6% DPP, 2% mould). 16 children were allergic to grasses and to another allergen (13% DPP, 3% animals, 1% food). The most common sensitizing allergens are shown in **Figure 2**. According to the age, 98% of allergic children was more than 6 years old, only 2 children were aged 3 - 5, most of them were polyallergic: 26 children aged 6 - 10, 17 aged 11 - 15 and 5 older than 15 years. Positivity to specific allergens according to age is shown in **Figure 3(a)**. In 13

children a variation of allergens over time was seen: positivity to allergens increased through the years, especially to grasses and DPP. Positivity to ragweed is more common when the child grows up (Figure 3(b)).

We also evaluated the treatments followed by the children as shown in Figure 4. Each child received treatments with Montelukast or Fluticasone dipropionate and 13 children were under SLIT (Sublingual Immunotherapy), 2 for grasses and 11 for DPP.

4. Risk Factors

Family History and Socioeconomic Status

Of patients evaluated 68% reported a family history of diagnosed allergy (17% both parents, 26% mother only, 25% father only). Allergies were more common among children whose parents had high school education: 47% mother, 40% father.

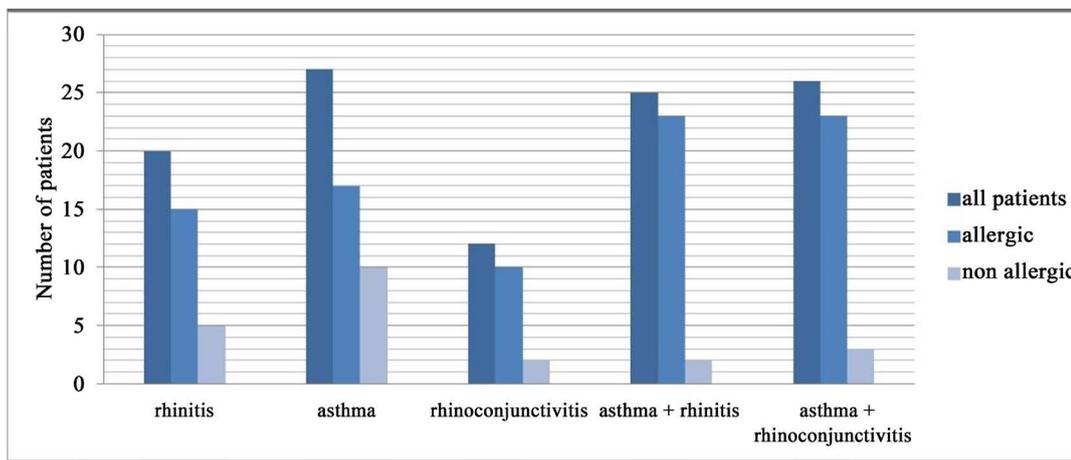


Figure 1. Prevalence of respiratory diseases: Among allergic children there was a prevalence of asthma associated with rhinitis (26%) or rhinoconjunctivitis (26%). Among non-allergic children 5 had only rhinitis, 10 asthma and 2 rhinoconjunctivitis, 5 asthma with rhinitis or rhinoconjunctivitis.

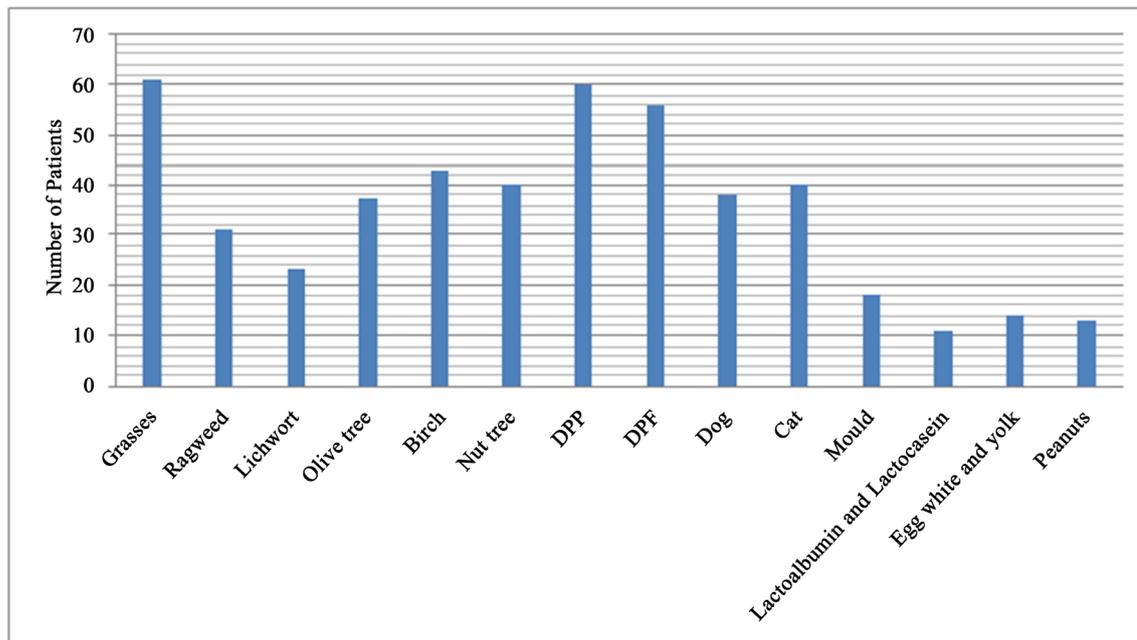
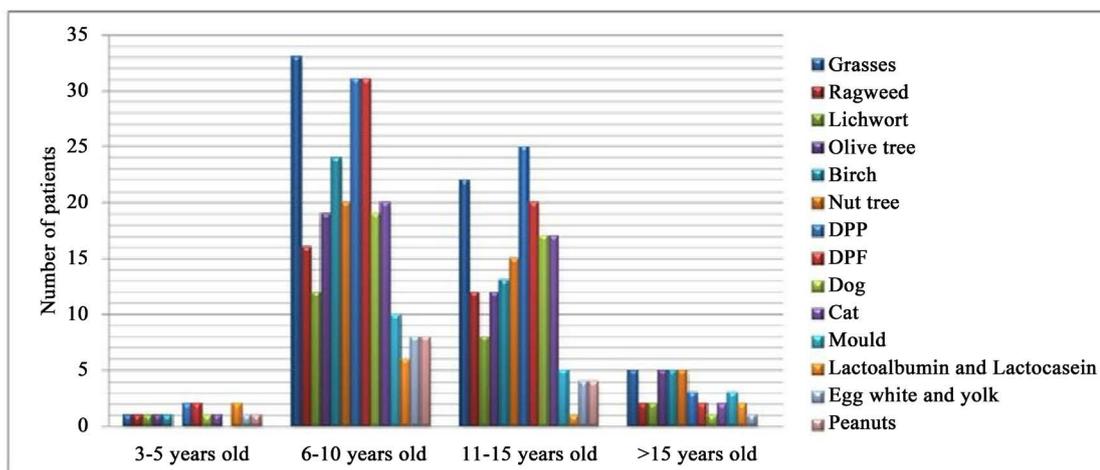
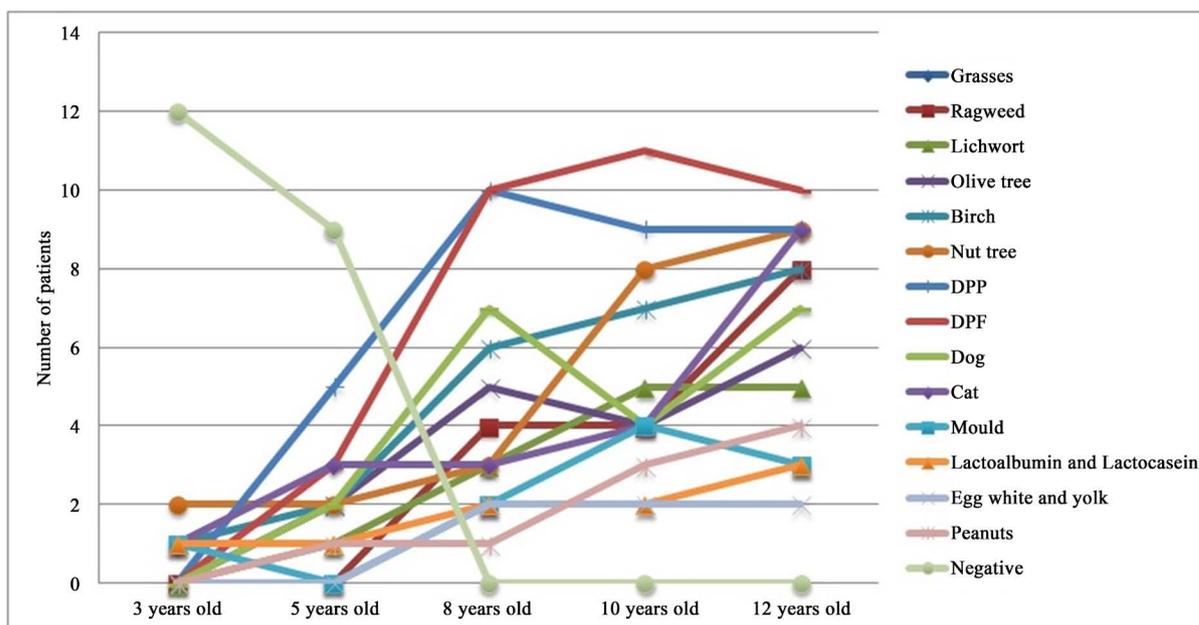


Figure 2. Prevalence of sensitization to different allergens: The most common sensitizing allergens in children were grasses 69%, DPP 68%, DPF 64%, Birch 49%, Cat 45%.



(a)



(b)

Figure 3. (a) Prevalence of sensitization to different allergens according to the age of patients; (b) variation of the positivity to allergens in 13 patients followed through the years: each child underwent skin prick test at 3, 5, 8, 10, 12 years old.

Geographic Area

The children living areas were examined. Varese and surroundings were divided into: urban, lake and mountain (>1000 m) areas: 61 patients lived in urban areas (53 allergic, 8 non allergic), 33 in lake areas (23 allergic, 10 non allergic), 5 in mountain areas (4 allergic, 1 non allergic). Among allergic children 60% lives in urban areas and only 5% in the mountains; among non allergic children 45% lives near a lake, 36% in urban areas.

Presence of Animals at Home, Smoking Exposure, Antibiotics Use

Of children evaluated 57 have animals at home, (47 allergic, 10 non allergic), 47 have no animals, (35 allergic, 12 non allergic). Of allergic patients 53% has pets, while 55% of non allergic children has no pets. The presence of pets in the first year of life was examined: allergic children hadn't more often pets at home as compared to non allergic children (51% of allergic children, 36% of non allergic).

Among allergic patients, 86% used antibiotics in the first years of life, 73% of non allergic.

Of all children 44%, allergic and non allergic (32% only one, 12% both) and 44% of allergic children (33% only one, 11% both) have smoking parents.

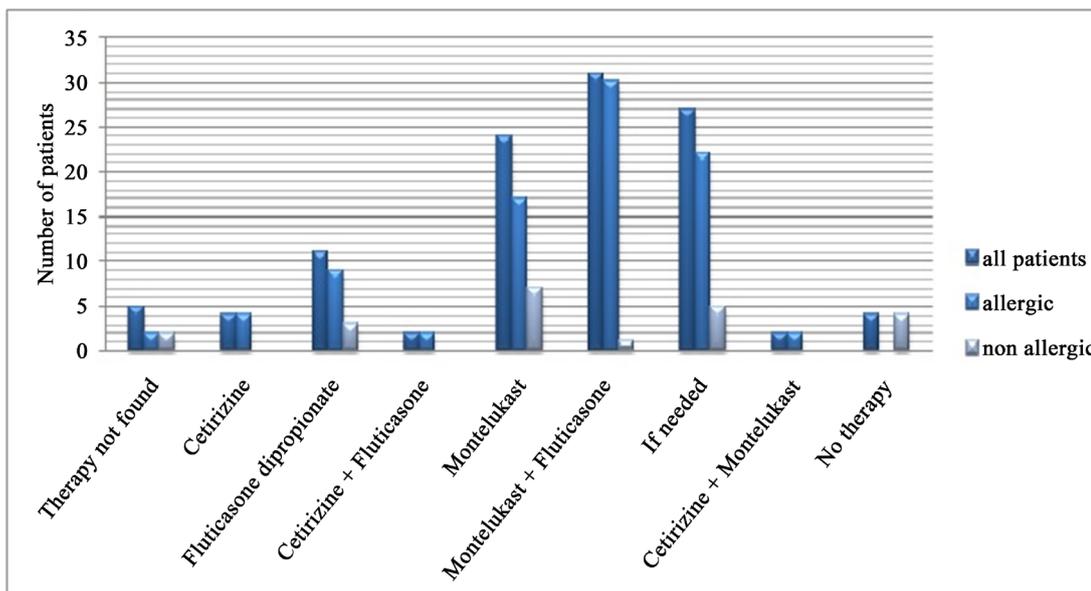


Figure 4. Patients' treatments of the patients studied 74 received treatment with montelukast and fluticasone dipropionate (85% allergic, 15% non allergic), 27 patients used treatments only when symptoms appeared, (81% allergic, 16% non allergic), 4 didn't follow any treatment, all non allergic; of allergic children 34% received a current treatment with Montelukast and Fluticasone, 32% of non allergic children only with montelukast.

Symptoms and Diseases

Of all children 89% reported to have sneezing, running and blocked nose in the past 12 months, both allergic and non allergic (91% allergic, 82% non allergic). However in 38% of allergic children symptoms didn't affect day-to-day routine; on the contrary in 36% of non allergic children "a little" was the answer. Children reported also the loss of school days for asthma and rhinitis, 23% 1 to 5 days, 11% 6 to 10, 7% more than 10. Both allergic and non allergic children reported that colds and flu are the first condition that make wheezing worse, followed by pollen and dust for allergic patients and weather for non allergic (**Table 1**).

5. Discussion

The study design allowed us to investigate the epidemiological situation of children affected by asthma and rhinitis and to point out the issues on which to focus the attention.

Despite the sample group analyzed is recruited from a single specialty clinic, it was heterogeneous as to age, diagnosis and living areas; this allowed us to examine the different spread of allergies and allergens and to compare our results with other centres.

Polyallergic children, affected by respiratory diseases and who underwent different treatments, were examined. This type of child is common in pediatric clinical practice. The majority of children was male and allergic, in fact boys are more likely to develop allergies than girls [4].

Children were more often polyallergic and the most common sensitizing allergens were grass pollen and DPP along with other Italian studies, as D.P. Peroni's [6]. Moreover allergies increased with the increasing of children age; 3 - 5 years old children were more often monosensitized or had negative skin prick test than older children and at this age skin prick test were positive to DPP and food; on the contrary when children grew up, sensitization to grass pollen and tree (birch, olive tree, nut tree) appeared.

In the last years Ragweed is spreading invasively in many countries, also in Northern Italy. In the north-west region of Italy, where Varese is situated, ragweed started to colonise the area in the 1930s and nowadays is widely widespread. It takes some years of exposure to high pollen concentration to develop an allergy [10] and therefore previous studies showed that the age of onset of ragweed allergy is adult age, around 35, and only 10% of the subjects is younger than 20 [11]. Despite this, in our study the prevalence of Ragweed sensitization is higher with an important prevalence, in fact 35% of children is positive; probably because of the increased diffusion of Ragweed and because of its allergenic potency, children will be exposed to this allergen at early ages

Table 1. Prevalence of symptoms and interference with children daily life.

	All patients (110)		Allergic (88)		Non allergic (22)	
	n	%	n	%	n	%
Sneezing, runny or blocked nose in the last 12 months	98	89	80	91	18	82
Symptoms interference with daily activities						
Not at all	38	35	33	38	5	23
A little	40	36	32	36	8	36
A moderate amount	13	12	11	13	2	9
A lot	4	4	2	2	2	9
No answer	15	14	10	11	5	23
Use of medication for rhinitis	51	46	42	48	9	41
Loss of school days for respiratory diseases						
None	55	50	48	55	7	32
1 to 5	25	23	20	23	5	23
6 to 10	12	11	10	11	2	9
More than 10	8	7	4	5	4	18
No answer	10	9	6	7	4	5
Presence of wheezing and asthma in the last 12 months	77	70	63	74	12	55
What makes child wheezing worse						
Weather	24	22	20	23	4	18
Pollen	34	31	33	38	1	5
Emotion	10	9	10	11	0	0
Fume	6	5	5	6	1	5
Dust	30	27	30	34	0	0
Pets	9	8	8	9	1	5
Wool clothing	3	3	3	3	0	0
Colds or flu	47	43	37	42	10	45
Cigarette smoke	7	6	6	7	1	5
Food or drinks	3	3	3	3	0	0
Soap, sprays, detergents	5	5	4	5	1	5
Other things/nothing	9	8	6	7	3	14

and so they are going to develop sensitization earlier and more and more children will show this allergy. It might be important to monitor the situation, because the exposure to Ragweed has serious consequences.

Allergy is more common in children whose parents had high school education, as shown also in other studies where this result was interpreted as an easier access to physicians [12].

Although the number of our patients is low for this type of study, it looks like that environmental factors have an influence on respiratory diseases. According to other studies, most of allergic children lived in an urban area. The ISAAC study has shown an increase of asthma and allergy in urban areas because children are exposed to higher levels of outdoor and indoor allergens and pollutants [12]-[16]. On the other hand, most of non allergic children (45%) lived near lakes, an increase of rhinitis in these patients may be associated to the wetter environment.

Also in our study a family history of allergic disorders and the presence of pets at home are associated with the development of allergies. Pets kept at home are more common in allergic children than in non allergic. Even if cats are more often a risk factor for atopy, Anne L. Wright at all. found that atopic rhinitis was associated more with the presence at home of dogs rather than cats; in our study we obtain the same results, possibly because more families kept dogs as opposed to cats. Furthermore, in our study we observed these data because of a higher presence of dogs at home. On the contrary, in the first year of life the situation was different: allergic children weren't exposed to pets, this fact was already observed by Strachan, Von Mutius and Vercelli: early contact with multiple animal species is a protective factor for atopy because there is a modulation of the human immune system [17]-[19].

Although in another study, always adopting the ISAAC questionnaire, it was found an association between antibiotic use in the first year of life and the presence of rhinitis and wheezing in the next years [20], we didn't find this correlation; as it is said in other studies it is difficult to make this correlation because there are too

many biases [20]-[22].

Of children studied 44% was exposed to parental smoking, this datum is alarming because environmental tobacco smoke exposure makes rhinitis and especially asthma symptoms worse [23]-[26].

Our data show that sneezing, rhinorrhea and blocked nose are more common than the real diagnosis of rhinitis. This was observed in another epidemiological study where nasal symptoms were reported in 16.8% of children while diagnosis of allergic rhinitis was present only in the 4% of the study population. This confirms the fact that allergic rhinitis are underestimated because physicians think more often of a viral cause [6].

We found also an early onset of allergic rhinitis, and after the development of other allergic manifestations. In fact patients between 11 and 15 years old have more often rhinoconjunctivitis and asthma. Rhinitis may be considered a risk factor for the development of asthma, this is important to offer an appropriate treatment to the patient [5]. Moreover rhinitis is frequently associated with rhinoconjunctivitis as it was also shown in phase three of the ISAAC study, where it was reported that rhinoconjunctivitis is increasing in European children especially among children aged 13 - 14 [19].

We also made the diagnosis of non allergic rhinitis in 21 children. Non allergic rhinitis are increasing worldwide, NAR:AR is 1:4, but they are usually underdiagnosed [27].

Most of children received a current treatment, especially allergic patients and subjects with asthma, probably because of the strict follow up undergone in these children. Allergic children are usually treated with Fluticasone and Montelukast, non allergic patients only with Montelukast. On the other hand 25% of children used treatments only when there were symptoms. 23% of patients reported a 1 to 5 school days loss for allergic symptoms, these data support what stated in the European Federation of Allergy and Airways Diseases Patients' Association (EFA) book and by the European Academy of Allergy and Clinical Immunology (EAACI) [1] [4].

6. Conclusion

Our study confirms that allergies are constantly increasing; family history of atopy, pet and smoke exposure, and urban area are risk factors for them. An important raising of positivity to Ragweed was also found. As children are exposed to this allergen since early ages, these data are going to increase in the next years. It is important to pay attention to this fact because it could have important consequences. Rhinitis is more often associated with rhinoconjunctivitis and asthma, especially when the child grows up, and this makes children quality of life worse. Moreover non allergic rhinitis is widespread but underdiagnosed, and so they must be taken into account. All these situations should be considered in order to offer appropriate diagnosis, correct treatments and to give children a better life quality.

References

- [1] A European Declaration on Allergen Immunotherapy. The European Academy of Allergy and Clinical Immunology (EAACI) 2011. <http://www.eaaci.org/372-resources/immunotherapy-declaration.html>
- [2] Ring, J. (2012) Davos Declaration: Allergy as a Global Problem. *Allergy*, **67**, 141-143. <http://dx.doi.org/10.1111/j.1398-9995.2011.02770.x>
- [3] Bousquet, J., Schünemann, H.J., Samolinski, B., *et al.* (2012) Allergic Rhinitis and Its Impact on Asthma (ARIA): Achievements in 10 Years and Future Needs. *Journal of Allergy and Clinical Immunology*, **130**, 1049-1062. <http://dx.doi.org/10.1016/j.jaci.2012.07.053>
- [4] Valovirta, E. (2011) EFA Book on Respiratory Allergies: Raise Awareness, Relieve the Burden. <http://www.efanet.org>
- [5] Keil, T., Bockelbronn, A., Reich, A., *et al.* (2010) The Natural History of Allergic Rhinitis in Childhood. *Pediatric Allergy and Immunology*, **21**, 962-969. <http://dx.doi.org/10.1111/j.1399-3038.2010.01046.x>
- [6] Peroni, D.G., Piacentini, G.L., Alfonsi, L., *et al.* (2003) Rhinitis in Pre-School Children: Prevalence, Association with Allergic Diseases and Risk Factors. *Clinical & Experimental Allergy*, **33**, 1349-1354. <http://dx.doi.org/10.1046/j.1365-2222.2003.01766.x>
- [7] Bousquet, J., Heinzerling, L., Bachert, C., *et al.* (2012) Practical Guide to Skin Prick Tests in Allergy to Aeroallergens. *Allergy*, **67**, 18-24. <http://dx.doi.org/10.1111/j.1398-9995.2011.02728.x>
- [8] Gelardi, M., Fiorella, M.L., Leo, G. and Incorvaia, C. (2007) Cytology in the Diagnosis of Rhinosinusitis. *Pediatric Allergy and Immunology*, **18**, 50-52. <http://dx.doi.org/10.1111/j.1399-3038.2007.00634.x>
- [9] The International Study of Asthma and Allergies in Childhood, 2012. <http://isaac.auckland.ac.nz/>

- [10] Tosi, A., Wüthrich, B., Bonini, M. and Pietragalla-Köhler, B. (2011) Time Lag between Ambrosia Sensitisation and Ambrosia Allergy: A 20-Year Study (1989-2008) in Legnano, Northern Italy. *Swiss Medical Weekly*, 9 October 2011, 141:w13253.
- [11] Asero, R. (2012) Ragweed Allergy in Northern Italy: Are Patterns of Sensitization Changing? *European Annals of Allergy and Clinical Immunology*, **44**, 157-159.
- [12] Morais-Almeida, M., Santos, N., Pereira, A.M., Branco-Ferreira, M., Nunes, C., Bousquet, J. and Fonseca, J.A. (2013) Prevalence and Classification of Rhinitis in Preschool Children in Portugal: A Nationwide Study. *Allergy*, **68**, 1278-1288. <http://dx.doi.org/10.1111/all.12221>
- [13] Wright, A.L., Holberg, C.J., Martinez, F.D., Halonen, M., Morgan, W. and Taussig, L.M. (1994) Epidemiology of Physician-Diagnosed Allergic Rhinitis in Childhood. *Pediatrics*, **94**, 895-901.
- [14] Fuertes, E., Butland, B.K., Ross Anderson, H., Carlsten, C., Strachan, D.P. and Brauer, M., ISAAC Phase Three Study Group (2014) Childhood Intermittent and Persistent Rhinitis Prevalence and Climate and Vegetation: A Global Ecologic Analysis. *Annals of Allergy, Asthma & Immunology*, **113**, 386-392.e9. <http://dx.doi.org/10.1016/j.anaai.2014.06.021>
- [15] Stafoggia, M., Cesaroni, G., Galassi, C., Badaloni, C. and Forastiere, F. (2014) Long-Term Health Effects of Air Pollution: Results of the European Project ESCAPE. *Recenti Progressi in Medicina*, **105**, 450-453.
- [16] Di Menno di Bucchianico, A., Cattani, G., Gaeta, A., Caricchia, A.M., Troiano, F., Sozzi, R., *et al.* (2014) Air Pollution in an Urban Area nearby the Rome-Ciampino City Airport. *Epidemiologia & Prevenzione*, **38**, 244-253.
- [17] Genuneit, J. (2012) Exposure to Farming Environments in Childhood and Asthma and Wheeze in Rural Populations: A Systematic Review with Meta-Analysis. *Pediatric Allergy and Immunology*, **23**, 509-518. <http://dx.doi.org/10.1111/j.1399-3038.2012.01312.x>
- [18] Von Mutius, E. and Vercelli, D. (2010) Farm Living: Effects on Childhood Asthma and Allergy. *Nature Reviews Immunology*, **10**, 861-868. <http://dx.doi.org/10.1038/nri2871>
- [19] Genuneit, J., Strachan, D.P., Büchele, G., Weber, J., Loss, G., Sozanska, B., *et al.* (2013) The Combined Effects of Family Size and Farm Exposure on Childhood Hay Fever and Atopy. *Pediatric Allergy and Immunology*, **24**, 293-298. <http://dx.doi.org/10.1111/pai.12053>
- [20] Foliaki, S., Pearce, N., Björkstén, B., Mallol, J., Montefort, S., von Mutius, E. and the International Study of Asthma and Allergies in Childhood Phase III Study Group (2009) Antibiotics Use in Infancy and Symptoms of Asthma, Rhinoconjunctivitis, and Eczema in Children 6 and 7 Years Old: International Study of Asthma and Allergies in Childhood Phase III. *Journal of Allergy and Clinical Immunology*, **124**, 982-989. <http://dx.doi.org/10.1016/j.jaci.2009.08.017>
- [21] Gagliardi, L., Rusconi, F., Galassi, C. and Forastiere, F. (2011) Re.: "Antibiotic Exposure by 6 Months and Asthma and Allergy at 6 Years: Findings in a Cohort of 1,401 US Children". *American Journal of Epidemiology*, **173**, 1343. <http://dx.doi.org/10.1093/aje/kwr082>
- [22] Rusconi, F., Gagliardi, L., Galassi, C., Forastiere, F., Brunetti, L., La Grutta, S., Piffer, S. and Talassi, F., SIDRIA-2 Collaborative Group (2011) Paracetamol and Antibiotics in Childhood and Subsequent Development of Wheezing/Asthma: Association or Causation? *International Journal of Epidemiology*, **40**, 662-667. <http://dx.doi.org/10.1093/ije/dyq263>
- [23] Agabiti, N., Mallone, S., Forastiere, F., Corbo, G.M., Ferro, S., Renzoni, E., *et al.* (1999) The Impact of Parental Smoking on Asthma and Wheezing. SIDRIA Collaborative Group. Studi Italiani sui Disturbi Respiratori nell'Infanzia e l'Ambiente. *Epidemiology*, **10**, 692-698. <http://dx.doi.org/10.1097/00001648-199911000-00008>
- [24] Virkkula, P., Liukkonen, K., Suomalainen, A.K., Aronen, E.T., Kirjavainen, T. and Pitkaranta, A. (2011) Parental Smoking Nasal Resistance and Rhinitis in Children. *Acta Paediatrica*, **100**, 1234-1238. <http://dx.doi.org/10.1111/j.1651-2227.2011.02240.x>
- [25] Landau, L.I. (2001) Parental Smoking: Asthma and Wheezing Illnesses in Infants and Children. *Paediatric Respiratory Reviews*, **2**, 202-206. <http://dx.doi.org/10.1053/prv.2001.0141>
- [26] Silvestri, M., Franchi, S., Pistorio, A., Petecchia, L. and Rusconi, F. (2015) Smoke Exposure, Wheezing, and Asthma Development: A Systematic Review and Meta-Analysis in Unselected Birth Cohorts. *Pediatric Pulmonology*, **50**, 353-362. <http://dx.doi.org/10.1002/ppul.23037>
- [27] Mølgaard, E., Thomsen, S.F., Lund, T., Pedersen, L., Nolte, H. and Backer, V. (2007) Differences between Allergic and Nonallergic Rhinitis in a Large Sample of Adolescents and Adults. *Allergy*, **62**, 1033-1037. <http://dx.doi.org/10.1111/j.1398-9995.2007.01355.x>