

Is the Prevalence of Allergy Continuously Increasing?

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Health systems and investigators worldwide have been asking themselves for many years whether the prevalence of atopic illnesses has been increasing continuously. It is mandatory to consider studies using comparable methods to validate these results.

The Aberdeen study considered the presence of asthma diagnosis, wheezing, eczema, and rhinitis between the decades of 1960 and 1990, showing a significant increase in all of them, not attributable to a diagnosis fashion but to a truly change in prevalence, using the same methodology in two time points in 25 years [1]. In this population and throughout these years, the proportion of wheezing increased from 10% to almost double, diagnosis of asthma from 4% to 10%, rhinitis from 3% to almost four times, and eczema from 5% to more than double. All these variables increased particularly noticeable in boys.

Is the Prevalence of Asthma Continuously Increasing?

In Finnish young men, the incremental tendency of asthma diagnosis remained from 0.29% in 1966 to 1.79% in 1989. The possibility of confounding factors in the diagnosing is improbable, as the exemption of military service due to incapacitating asthma was correlated with the increase reported [2].

In another wider evaluation in the UK, from 1955 to 2004, several indicators of asthma such as primary care, prescriptions, hospitalizations, and mortality evidenced an increase until the 1990s, where the curve flattened and even decreased [3].

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The opposing evolution of these effects compared to the sale of inhaled corticosteroids (ICS) is one explanation, since the recognition of the inflammatory component of asthma began in the 1980s.

However, also in the UK, an evaluation of prevalence in schoolchildren between 1991 and 2002 showed a significant increase in wheezing in the past 12 months, in severe speech-limiting episodes and night waking, but non-significant increase in medical visit because of wheezing. Here again, this last finding could be explained by the significant increase in steroids prophylactic treatment reported in this population [4]. This explanation will be reconsidered ahead.

Another trend study also evidenced a significant increase from 1990 to 2003 in doctor-diagnosed asthma, more evident in females (7.3–14.6%) than in males (7.8–9.4%), in all age groups but larger in people aged 55 and older [5].

Is It the Same in Low- and Medium-Income Countries (LMIC) in the Planet?

Some years ago, Faniran et al. [6] compared the prevalence of asthma and atopy in children between an affluent versus a non-affluent country, having a smaller prevalence of wheeze and persistent cough in Nigeria when compared to Australia (10.2% and 5.1% compared to 21.9% and 9.6%, respectively).

Anyway, a recent report from Aït-Khaled et al. [7] evidenced a wide range of atopic disorders prevalent all over Africa, not only with the highest presence of current asthma in urban areas with higher standard of living (concordant with the hygiene hypothesis) but also with a representative prevalence in endemic parasite and tuberculosis zones (opposed to the hygiene hypothesis).

In Latin America, protective factors to avoid having asthma seem not to play a role, and the non-allergic factors like pollution are not conditioning a higher prevalence of respiratory symptoms. However, this prevalence is similar to industrialized countries [8]. In a recent survey of rural Asian children, 16.1% of wheezing prevalence in the past 12 months was found, not different from other developing regions of the planet [9].

The former reports, the International Study of Allergy and Asthma in Children (ISAAC), utilized the same methodology of evaluation, having strength enough to make conclusions and to compare different cultures and latitudes.

However, scarce tendency data are available from LMIC since the possibility of having these tools for evaluation has become recently available. An example is the ISAAC Phases I and III in comparison with Brazil, where nocturnal cough and wheezing slightly but significantly diminished [10]; however, the generalization of these results is improbable when considering previous references.

Taken all together, we could conclude that globally, the prevalence of asthma is high and still demonstrates a slight increasing tendency, even though there is a lessening of differences.

What Is the Scenario of the Rest of Atopic Diseases?

Other than analyzing asthma, a European study (SCARPOL) that was conducted four times between 1992 and 2001, revealed evidence of stabilizing asthma and hay fever, but with a predominant increase in atopic eczema in girls that was stable in boys [11].

The same tendency was found in the Aberdeen evaluation when considered up to 2004 [12]. There, the three atopic illnesses demonstrated a stable prevalence that was a pattern in the past 10 years, with a continuous increase present in girls that makes no sex difference at the end (Fig. 1). As in the former study, when evaluating eczema, females were more prevalent.

However, an Italian evaluation demonstrated an increasing trend from 1994 to 2002 in wheezing, allergic rhinoconjunctivitis and atopic eczema in both 6- to 7-year-old and 13- to 14-year-old populations, except for wheezing in the last group (Fig. 2) [13].

A global time trend analysis of prevalence in rhinoconjunctivitis symptoms evidenced yet again a smooth increase, being more evident in LMIC and in the older age group, suggesting that environmental influences in the development of allergy may not be limited to early childhood [14].

Related to these asseverations, a recent evaluation in the tendency of aeroallergen sensitization for 25 years (from 1976–1977 to 1999–2001) evidenced a significant increase in the prevalence of sensitivity as well as in the mean age of allergic patients [15].

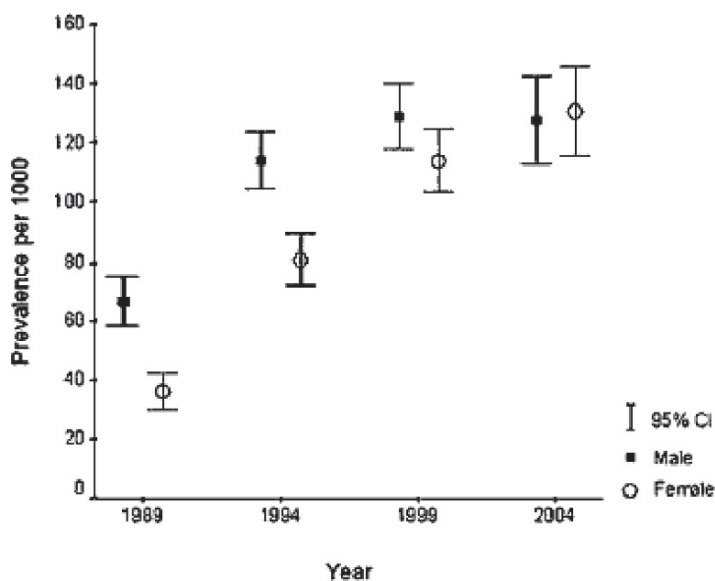


Fig. 1 Sex-specific prevalence rate for asthma reported by year of survey. (From [12], with permission.)

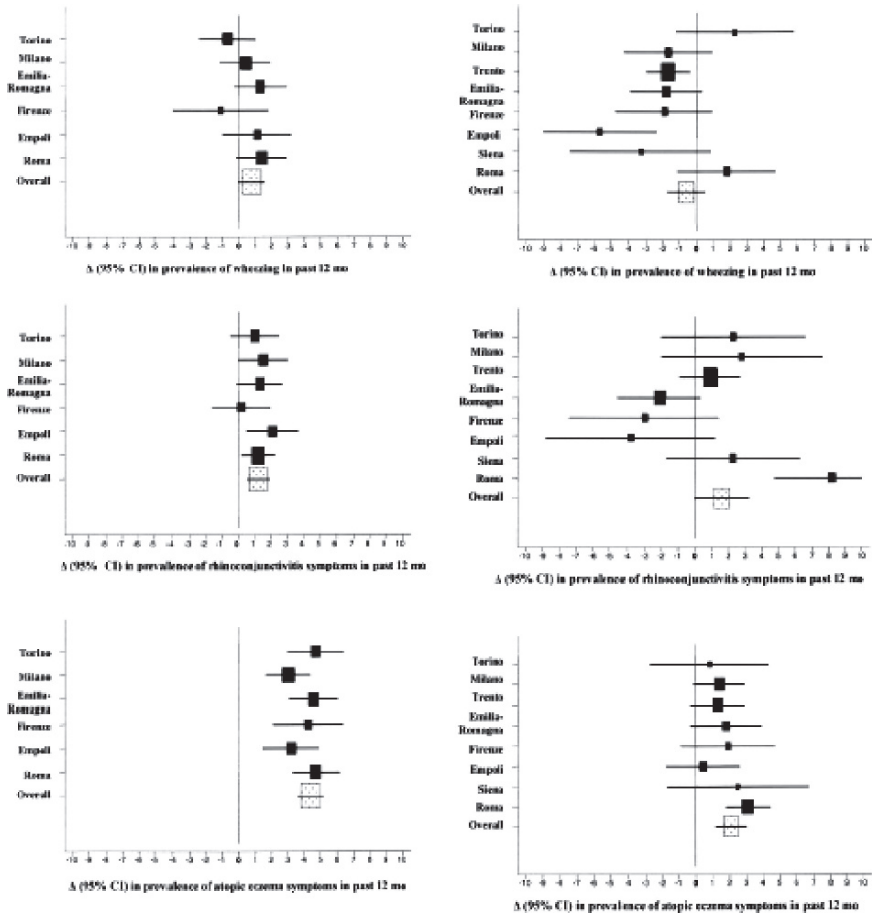


Fig. 2 Changes (*delta*) and 95% confidence interval in prevalence of wheezing, atopic rhinoconjunctivitis, and atopic eczema in the past 12 months, reported by parents of children 6–7 years of age (*left*) and by adolescents 13–14 years of age (*right*) in six areas of Italy. (From [13], with permission.)

Again, ISAAC is the option to have a global vision. A recent publication of a worldwide comparison of two phases in 6- to 7-year-old and 13- to 14-year-old populations, using the same methodology both times with a mean of 7 years of difference, allowed to evidence several projections of concern [16]: (a) In 6- to 7-year-old, an incremental tendency in asthma, rhinoconjunctivitis, and eczema was observed in Asia-Pacific, India, North America, Eastern Mediterranean, and Western Europe. (b) In 13- to 14-year-old, this augmentation was evidenced in Africa, Asia-Pacific, India, Latin America, and Northern and Eastern Europe. (c) In asthma at 6- to 7-year-old, more centers reported increase of prevalence, while in the 13- to 14-year-old group, almost equal centers reported up and down tendency. Those having larger prevalence in the first phase tend to have a decrease in the third phase and vice versa. (d) For allergic rhinoconjunctivitis, most centers at both ages

reported an incremental variation between phases. (e) For atopic eczema, the 6- to 7-year-old participants showed increased tendency in average, while in the 13- to 14-year-old samples, such tendency was not that evident. (f) Taking all disorders together, the younger group had an increase from 0.8% to 1%, and the older one from 1.1% to 1.2%.

We can then preliminarily conclude that globally, there is still a growing prevalence of atopic disorders, predominantly in developing regions of the planet.

Let us analyze the risk factors that could help to explain these phenomena:

Sex

In childhood, male sex has been considered to be a risk factor for having atopic diseases and asthma. Some years ago, this predominance was partially explained by an increased sensitivity to inhalant allergens [17]. However, we mentioned earlier that the increasing prevalence among girls equalized the male to female ratio recently, even being more prevalent when considering eczema [11, 12].

By the age of 11, male sex is still stronger when considering current wheezing [18]. As the age of the sample evaluated increases, the predominance reverses. In a cohort evaluation, male in childhood declined by adolescence and early adulthood, considering female sex as one of the major risk factors for having asthma [19]. It was also a predictive factor for persistence of asthma symptoms from childhood [20], but this conclusion needs to be reinforced in larger populations because the odds obtained revealed evidence of a wide confidence interval.

Not only the former but also allergic rhinitis shows similar transition from male in childhood to female in adolescence. Having those repeated observations reinforced by evaluations in large population samples, the fact that estrogen has pro-inflammatory and testosterone anti-inflammatory effects could explain this trend [21, 22].

Diet

Recently, Garcia-Marcos et al. [23] evaluated the relationship of the Mediterranean diet (vegetables, pulses, cereals, potatoes, pasta, and rice) with asthma and rhinoconjunctivitis in more than 20,000 children, adjusting for exercise and obesity, finding its protective effect against current severe asthma in girls. Also, seafood and fruit were protective against having rhinoconjunctivitis.

In the same direction, Wickens et al. [24] corroborated that fast food intake was related with asthma symptoms in a frequency-dependent manner. Takeaway consumption greater than once a week showed an increased (although not significant) bronchial hyper-responsiveness, but had no effect on atopy.

Not only animal fat consumption was implicated as a risk factor for atopic diseases expressions. Vegetable oils contain linoleic acid, an Omega 6 polyunsaturated fatty acid (PUFA) precursor of arachidonic acid and consequently of eicosanoid metabolites, promoting the Th2 imbalance while decreasing interferon γ (IFN γ); omega 3 PUFA found in fish oil inhibits PGE2 formation, modulating the production of immunoglobulin E (IgE) indirectly [25]. However, the clinical relevance of adding fish oil in pregnancy diet demonstrated just a decrease in the severity of eczema in infants at high risk of atopy [26].

Feeding habits in the UK over the last decades, where atopic expressions grew, evidenced diminished saturated fat consumption [27]. This growing could then be attributed to a reduction of antioxidants in the diet, since only the fatty acids deregulations could oversimplify the frame. Anyway, more studies are needed in this field as interventional strategies have been disappointing as of date.

Could Diet Effect Be Related to Overweight?

As atopy, asthma, and obesity increased in the last decades, it was reasonable to speculate that maybe they are linked. When evaluating the effect of the Mediterranean diet [23], it was reported that obesity was a risk factor for current severe asthma in girls. A practical measurement of total body fat is the estimation of body mass index (BMI)–weight/height ratio [28].

However, controversies about the relationship of BMI with the presence of atopy and asthma is shown by a report from Australia [29], which states that increased BMI was a risk factor for cough, ever wheezing and atopy (predominantly in girls), but not for diagnosed asthma or bronchial hyper-responsiveness. Without these last two conditions, it is difficult to be conclusive, as gastro-esophageal reflux, sleep disorders, being unfit, or altered mechanical ventilation could explain symptoms, and all are associated with overweight.

So some meta-analysis was required to elucidate the real impact of overweight in the incidence of asthma, and 1 with a sample larger than 300,000, evidenced a dose–response increasing odds for incident asthma: odds ratio (OR) 1.38 for normal versus overweight comparison, and OR 1.92 for obesity; none of them was affected by sex [30]. These odds have a huge impact on populations like the USA, where more than 60% of adults are overweight/obese, and in consequence at risk of developing asthma.

Also considering a meta-analysis in children, the same evidence was reported. The relative risk (RR) of high birth weight on developing asthma later was $RR = 1.2$ (95% confidence interval (CI) 1.1–1.3), while the effect of overweight in middle childhood was $RR = 1.5$ (95% CI 1.2–1.8) [31]. Misclassification, diagnostic bias, and individual confounders are always doubts emerging from meta-analysis; however, the results from an enormous cohort study, from childhood to adulthood, are the only possibility to corroborate or contradict this evidence.

What About Environmental Pollution and Work Exposure?

The effects of air pollution have been described some years ago as significantly harmful in children with elevated IgE and bronchial hyper-responsiveness. Airborne particulate of a size of less than $10\ \mu\text{m}$ (PM10), sulfur dioxide, black smoke, and nitrogen dioxide provoked lower airways symptoms in these patients (wheezing and dyspnea), as well as a decrease in peak expiratory flow greater than 10% while particulate amounts increased [32].

PM10, nitrogen dioxide, and carbon monoxide showed a considerable correlation with emergency assistance in children, but not in adults [33]. In children under 5 years, peak carbon monoxide level was predictive of hospitalization because of asthma attack [34].

Going from an epidemiological to a bio-immunological approach, one of the risk factors that could explain the increasing prevalence of atopic diseases in industrialized countries has been the exposure to diesel exhaust particles, recognized as enhancer of IgE-dependent allergic inflammation, and the consequent symptoms of asthma and rhinitis [35]. Once again, a recent revision cannot be conclusive in considering these particles as a significant risk factor for having atopic diseases [36].

About indoor pollution, there is no doubt that tobacco smoke constitutes the key factor to be considered, since it has been implicated in the development of asthma in children and non-smoking adults exposed [37]. About those smoking actively, the RR for incidental asthma was reported as high as 3.9 (95% CI 1.7–8.5) [38].

Work Exposure

With an obvious gap in concentration, some same outdoor pollutants could be found at working places. But time and dose exposure could promote the starting of irritant asthma, like sulfite mill workers in whom sulfur dioxide established a risk of four to six times greater for new-onset medical-diagnosed asthma [39]. Not only pollutants are capable of inducing asthma, instruments and surface cleaners, adhesives and latex particles have been implicated in that process within healthcare workers [40]. The list of demonstrated provoking agents, as well as mechanism involved, goes beyond the present analysis.

What About Infections and the Hygiene Hypothesis?

In 1989, Strachan [41] proposed that allergic diseases could be prevented by infections in early childhood, and the transmission of them by unhygienic contact with older siblings. Smaller family size, higher standard of living, and personal cleaning

reduced the chances of spreading “protective” infections, originating the *hygiene hypothesis*.

A recent comparison of two genetically related but cultural and socio-economic different populations (Russian and Finnish) evidenced higher specific IgE levels in Finnish but more total IgE and specific microbial antibodies in Russians. Enterovirus infection represented the strongest protective factor against allergen sensitization [42].

In this direction, farmers’ children from a rural environment were evaluated for atopic symptoms (by questionnaire) and atopy (by skin test), as well as endotoxin measurement. Compared to non-farmers’ children, they presented significantly fewer symptoms of current asthma (adjusted OR 0.67; 95% CI 0.49–0.91; $P = 0.01$) and rhinitis (OR 0.50; 95% CI 0.33–0.77; $P = 0.002$). If having unpasteurized milk also, a significant reduction of atopy (OR 0.24; 95% CI 0.10–0.53; $P = 0.001$) and current eczema symptoms were added (OR 0.59; 95% CI 0.40–0.87; $P = 0.008$), while reducing IgE ($P < 0.001$) and increasing IFN γ ($P = 0.02$) [43]. Pasteurized milk, vaccinations, early use of antibiotics, and the westernized lifestyle with less exposure to infectious agents could contribute to this lack of stimulation, essential in the first years of life to change the initial Th2 profile toward a Th1 just not to favor atopy development.

Ten years ago the hygiene hypothesis was suggested, an extensive analysis was done to determine its current relevance, and the conclusions were [44]: (a) atopic diseases, but not necessarily asthma, are highly prevalent in smaller and more affluent families; (b) the postulate of protective infections against atopy is immunologically plausible; the reversal is inconclusive; (c) the modulating effects of antibiotic therapy and diet influencing intestinal flora need to be evaluated extensively; (d) The inverse association of family size and allergic sensitization could potentially help to discern underlying causes of the increasing prevalence of atopic diseases.

However, the Th1/Th2 paradigm and how it fits in the hygiene hypothesis must be analyzed. Table 1 considers how all these factors affect both Th2 and Th1 illnesses, and its scheme outlines factors influencing immune system development at different time points [45].

In this context, genetically inheritance should be the beginning, while the attributable genetic risk ranges from 30% to 80% depending on the disease considered. Then, susceptibility to multiple exposures will determine if “western and industrialized world” affects the development of atopic diseases in these individuals. There, developing countries with the objective of reaching a better quality of life increase their risk as shown by the increased atopic prevalence in people who migrated to developed regions and in urban cities when compared to rural [7, 45, 46].

As a conclusion, we do not need to go back in evolution, we must maintain the control over infections, but need to clarify the role of each microbial stimulus (especially at the gastrointestinal tract), in parallel with genetic background and every co-factor. Large longitudinal birth cohort studies, getting representative biological and environmental samples, will help us in the future.

Table 1 Discrimination of factors influencing Th1 and Th2 diseases; scheme below: factors that could manipulate immune system development, at different periods. (From [45], with permission.)

	Atopic disease	Auto-immune disease
Epidemiological findings		
Decreasing family size	↑↑	↑↑
Number of older siblings	↑↑	↑↑
High socio-economic status	↑↑	↑↑
Decreased day-care exposure	↑↑	↑↑
Evidence of cleaner houses		↑↑
Evidence of previous oro-fecal infection (as a marker for poor hygiene)	↓↓	?
Higher frequency of viral “cold” in early childhood (parentally reported)	↓↓ ⇒	?
Environmental measurements		
High endotoxin exposure (e.g., on farms)	↓↓	?
GI-flora		
Decreased Lactobacilli, Bifidobacteria	↑↑	?
Supplementation with <i>Lactobacillus</i> CG	↓↓	?
Increase in Clostridia (esp <i>Costridium difficile</i>)	↑↑	?
GI-parasite infection		?
Active/chronic infection	↓↓	
Treatment of parasite infection	↑↑	

GI, gastrointestinal.

Is Atopy Per Se a Risk Factor for Having Atopic Diseases?

Taking the former proposal to consider longitudinal studies, to elucidate the attributable risk of different exposures, a cohort of more than 1,000 children was evaluated by their atopic status, and related to asthma, rhinitis, and eczema. Sensitization to dust mites was the strongest independent risk factor for having asthma (OR 8.07, CI 4.6–14.4), to grass pollen for having rhinitis (OR 5.02, CI 2.21–11.41), and to peanut for having eczema (OR 4.65, CI 1.02–21.34). Even though less than half of the original cohort was skin tested at the age of 4, some relevant tendencies were evident: the prevalence and severity of asthma correlated with allergen sensitization, the risk of all allergic diseases increased with the number of positive prick tests, there was a predominance of male sex at this age, but they conclude that only 30–40% of allergic diseases is attributable to atopy, and the rest to the affected organ or other factors [47]. A recent report suggests that asthma attributable to atopy could vary depending on allergen exposure and its modifications because of the environment such as climate [48].

But atopy alone does not explain much of the real life, where multiple factors could influence the development of atopic diseases, such as respiratory viral infections and the development of asthma. In a cohort of more than 2,000 children,

where the presence of current asthma at 6 years of life was correlated with atopy and respiratory tract infections in first year, concluded that both conditions were independently associated with a significant risk of having asthma by the age of 6 [49]. Also, maternal feeding evidences a protective behavior.

Another longitudinal study demonstrated the association of infantile chest infections with wheezing and asthma, and the importance of early life atopic status for the presence of wheezing, asthma, and bronchial hyper-responsiveness at 10 years of life [50]. Other conditions such as familiar asthma, early passive smoking, and having eczema at the age of 4 were also significantly associated with asthma and wheezing but not with bronchial sensitivity.

We must preliminary conclude that atopy per se is not enough, neither to express atopic diseases nor to justify the increased incidence of them.

But What Is the Natural History of Asthma and Allergy?

A prevalence of positive skin test ranging from 8% to 30% in general asymptomatic population has been described; from them, one to two out of three will develop an atopic respiratory disorder in the future [51]. Multiple risk factors associated with the development of allergy and asthma have been detailed.

Genetic polymorphism and their environmental interaction, premature aeroallergen sensitivity, exposure to tobacco smoke, presence of eczema and rhinitis, and lower respiratory viral infections are all risk factors for developing chronic asthma [50, 52]. Once asthma is present, several predictors have been detailed for persistence and severity of the disease *in children* [53]: (a) severe wheezing in preschool age, (b) the onset at school age, (c) familiar history of asthma and allergy, (d) elevated serum IgE levels, (e) early sensitization to aeroallergens, (f) early development of bronchial hyper-responsiveness, (g) frequency of respiratory infections, (h) lack of contact with older children, (i) familiar discrepancies with psychological involvement. For persistence and severity *in adults*, predictors described are [53]: (a) constant exposure to sensitized allergens (including occupational), (b) older age of the onset, (c) aspirin intolerance, (d) socio-economic status, (e) smoking, (f) coexisting pulmonary diseases provoking COPD (like bronchiectasis or aspergillosis).

Some absolutely relevant cohort studies allowed to discriminate phenotypes of asthma that can be grouped in: (a) intermittent wheezers associated with respiratory infections, (b) transient or persistent wheezers (the latter associated with atopy), (c) atopic and intrinsic asthma (invariably persistent), (d) occupational or drug-induced asthma (mainly adults with prognosis related to severity) [53–56]. This differentiation has important therapeutic implications as supposed.

Regarding the other atopic disorders, atopic march described that while in the first years of life the prevalence of food allergy and eczema is present but declines progressively, giving respiratory allergy the chance to persist [57, 58]. The first

atopic expressions being eczema and food allergy, maternal diet restrictions and food avoidance have both been recommended as primary prevention without conclusive and strong evidence [59, 60]. Indeed, a recent evaluation of the delay in solid food introduction could not demonstrate a protective effect against food or any allergen sensitization and/or eczema by the age of 2 [61].

Allergic rhinitis is undoubtedly an independent risk factor for having asthma; moreover, treating rhinitis with allergen immunotherapy reduced the risk of developing asthma [62]. Eczema (together with familiar history of asthma) was considered to be a major predictor for having asthma [63].

Has Any Therapeutic Intervention Been Demonstrated to Alter This Natural Course?

One of the most controversial issues to date is the use of ICS to alter the natural development of asthma, specifically when to begin its use and for how long. There is no doubt that persistent asthma must be treated chronically with ICS [64–66], and significant reduction in its impact is remarkable, in any case, considering hospitalizations or mortality [67, 68]. However, the convenience of early introduction of them in intermittent asthma and the regular versus intermittent use in mild persistent cases are not conclusive yet; robust evidence is needed to conclude that early introduction and permanent use of ICS prevent a significant decline in lung function in such a mild profile, with truly clinical relevance, and a strong risk–benefit ratio [69–74].

About primary prevention of atopic diseases, we mentioned that no concluding recommendations should be given regarding maternal diet and feeding of babies [59–61].

In clinically relevant aeroallergen sensitization, measures for avoidance of house dust mites may benefit in reducing symptoms only [75]. However, specific immunotherapy can prevent new sensitizations while maintaining an asymptomatic condition for many years; moreover, it has been demonstrated to prevent the onset of asthma in children with rhinitis [76–78]. Sublingual immunotherapy has an excellent safety profile while having same immunological effectiveness as subcutaneous, emerging then as the only interventional option that can modify the natural course of allergic diseases [77, 78].

Concluding Remarks

1. The prevalence of allergic diseases is still slightly increasing, with different profiles in the developed world (stabilization) and the developing world (increasing). The direct implication must be analyzed in the context of the regions where population is growing.

2. Urgent global networks and programs must be implemented, to allow admission to all people for prevention, diagnosis, and treatment. This is the only possibility for reversing this trend.

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