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Migrants and allergy: a new view of the atopic march

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Introduction

Atopy march is usually interpreted as the progression of the clinical manifestations of atopic diseases through the different ages (1). Even if this concept is world-wide accepted and truly demonstrated by several papers (2), since a couple of decades the significance of the 'march' of atopy could be interpreted in an alternative way, that means the progression and widespread of atopic disorders through the world because of the expansion of formerly considered wellness-related diseases in "in march-populations". Migration flows in association with the progressive amelioration of life conditions in several countries with a previous subsistence economy, seem to be the new gateway of 'westernization'. Thus, movement of populations in a South-North and East-West gradient together with the shift from rural to industrialized economy along with the GDP gradient represent an interesting model to approach how the environment can modulate the genetic background. It is generally assumed that exposure to new allergens is the necessary pre-requisite to develop sensitization and eventually allergic disease, because immune recognition

Summary

Atopy is the result of the influence of environmental factors on genetically predisposed individuals. Migration flows represent an interesting model to study the possible reciprocal roles of genes and environment. In this review the following issues influencing the development of allergic sensitization and/or atopic disorders in migrants will be investigated: 1) ethnicity, genetic polymorphisms and risk of atopy; 2) double faceted effects of parasitic infestations; 3) biodiversity loss and industrial progress. Moreover, an extensive revision of the literature about the relationship between the migratory status and allergy development is provided.

of what was previously unknown is essential to develop memory, although of a non virtuous functional phenotype. However, in addition to the individual predisposition based on genes eventually shared with the personal ethnic membership, several external factors may influence this initial process of immune recognition. Actually, atopy also 'marches' along with climate changes and consequent spread of new allergens in previously 'untouched' countries. At the same time, climate-affecting emissions might enhance allergenicity of environmental proteins. Finally, biodiversity is impoverished that means not only the reduction of animal or vegetable variety, but also modification (and decrease) of our privileged relationship with the 'old friends' hosted inside our bowel, at the surface of our skin or respiratory tract. In this review these new concepts about the 'march' of atopy will be considered.

The 'march' of allergy: genetics and migration

Atopy might be interpreted as the result of the influence of environmental factors on a genetically predisposed individ-

ual. Twin studies have offered the best evidence of the heritability of this predisposition, with almost 80% concordance in monozygotic twins versus 20% in dizygotic ones (3). On the other hand, the higher prevalence of allergy in developed, rather than less affluent, countries may account for the influence of environmental factors (4). Which one of these two factors exhibits the prominent impact is still unknown (5). The study of migration flows may be a way to provide a more in-depth knowledge on this issue. In particular, it may help to replicate the concept of “atopy march”, that is the age-related progression of atopic disorders.

Differences in the rate of atopic disorders have been demonstrated among different ethnic groups but the impact of genetics might be underestimated because genome-wide association studies (GWAS) have been mainly focused on individuals of European ancestry (5). Atopic dermatitis (AD) has been extensively studied from a genetic point of view by GWAS approach and best represents a clear example of that underestimation. Suppression of filaggrin (FLG) in keratinocytes has been associated with skin barrier deficiencies and early-onset AD in Europeans (6). The higher prevalence of FLG mutations observed in Northern Europeans could indeed favor the penetration of UV-B rays with the consequence of more vitamin D3 synthesis or increased immunity towards infectious diseases, such as tuberculosis and plague (5). Similar FLG mutations have not been found in other ethnicities, but black children living in the United Kingdom show a 6-fold higher risk of AD when compared to the local population (7) and Chinese immigrated children have a 2-fold higher annual incidence of AD than local Australian population (8). Surprisingly, no *FLG* mutations were found in subjects of African descent who share the same rate of FLG level deficiency with Europeans (9). On the contrary, mutations in the *FLG2* gene, closely related to *FLG*, have been demonstrated in African Americans with AD but not in Europeans, but native Africans were not included in this study (10). These *FLG2* mutations are eventually completely different from those found in subjects of Chinese ancestry which, in turn, are even different from those found in Japanese people. Nevertheless, differences in the prevalence of atopy exist in different ethnicities (5). Studies from the United States highlight that African ancestry seems to be a risk factor for atopy (11). Disease-associated single-nucleotide polymorphisms (SNPs) may account for these disparities. Actually, SNPs variants in the *IL4*, *IL4* receptor and *IL13* coding genes, known to be strictly related to the type 2 immunity, were found to be more frequent in African subjects than in Europeans (48% vs 12%, respectively) (12), possibly representing an evolutionary footprint. It has been hypothesized that the *IL4* 589 variant (C>T) (rs2243250) may be associated with a lower risk of malaria infection (13) as well as the Gln551Arg (rs1801275) (14) and Ile50Val (rs1805010) (15) variants of the *IL4* receptor coding

gene and C-1112T (rs1800925) (16) variant of the *IL13* gene may confer increased resistance to parasitic infestation as skewing immunity towards the type 2 response is more protective. Several other genes have been related to atopic disorders in their whole (*IL5*, *TSLP*, *FOXP3*, *IL10*, *IFNG*, *CCL11*, *CCL26*, *FCER2*, *CD4*, *IGHG4*, *RNASE2*, *RNASE3*, *KCNE4*), but studies on their mutations in different ethnicities are still lacking (5).

The ‘march’ of allergy: parasites and migration

As stated above, these mutation differences might be explained by a balanced selection process of atopic-related genes as the result of multiple environmental factors, such as the pressure of pathogens (17). In this context, parasitic infestations have acquired a major interest during the last few years. Parasitic infestations can positively or negatively influence the development of atopy by respectively stimulating or suppressing the immune response. Factors claimed for this dual activity are the type of helminth, the concentration levels, the time of exposure and the genetic susceptibility of the host (17).

Few clear examples of this “Janus” activity of parasite infestation on allergy are present in the literature. A first example has been represented by the Falascia people, an Ethiopian ethnic group of Jewish faith. In 1984 and 1991 two immigration waves brought almost 30,000 Ethiopians to Israel (18). At their arrival, most of them presented parasitic infestation and very high IgE levels, with no symptoms of allergy or asthma (19). The entire population of immigrants received anti-parasite treatment and re-evaluation 3-years later found a 11% prevalence of allergy, mainly allergic rhinitis and asthma. In addition, in an Ethiopian cohort that lived in Israel for more than 8 years, the prevalence of asthma was higher than in the local population itself (20). Similarly, a regular anti-helminthic treatment of Venezuelan children was associated with the increase of atopic sensitization to house dust mite from 17% to 68% after a follow-up period of two years (21). Another study conducted in Ethiopia on 12,876 individuals, found that the presence of parasitic infestation independently reduced the risk of wheeze-onset in already atopic subjects (22).

On the other side, these data were not confirmed in other studies carried out in the Tropics, where urbanization, Western lifestyle and a great range of infections including heavy parasitic infestation are present at the same time (17). As an example, in Ecuadorian children a 12-month anti-helminthic treatment did not promote any allergic sensitization during the follow-up period (23). Moreover, and intriguingly, a study in China demonstrated that infestation with *A. lumbricoides* was a risk factor for the development of asthma and aeroallergen sensitization (24). Nonetheless, it is important to underline that the molecular basis of the high prevalence of sensitization to common allergens when assessed with specific IgE levels among population living in helminth-endemic areas can be due to cross-reactive

carbohydrate determinants (CCDs), complex N-glycans on plant and invertebrate glycoproteins, also present on parasites surfaces. This has been demonstrated analyzing molecular IgE profile on ImmunoCAP-ISAC in the serum of Indonesian children with virtually absent clinical allergy, but extremely high prevalence (65% to 85%) of sensitization to common airborne and food allergens (25). Although many epidemiological studies demonstrated that ascariasis is a risk factor for atopy and asthma as cross-reactive with house dust mite tropomyosin (26), basic research clearly demonstrated that helminths have immunomodulatory effects, playing a protective role against the development of allergy, through the induction of interleukin-10 and TGF-beta, the expansion of peripheral regulatory T cells and the production of high level of IgE and IgG4 by plasmacells (17,27,28) (**Figure 1**).

From an evolutionary prospective, parasitic products are able to downregulate T-cell receptor–MHC interactions favoring a Th2 response in the same way as long-lasting exposure to low-dose allergens with low affinity for the T-cell receptor activates the type 2 response in allergy (29). Actually, baseline levels of total IgE are usually high in immigrants from less developed countries (18). On this favored type-2 background, any change in lifestyle and habits and/or the exposure to new allergens instead of continuous exposure to parasite products, may make immigrants even more susceptible to atopic disorders than the local population itself. Indeed, in Western countries, pollutants, dietary changes and different socioeconomic factors in the absence of infectious stimuli may be able to redirect immunity towards the inappropriate type 2 response to allergens (**Figure 1**). This hypothesis is strengthened by the demonstration of

a direct proportion between rate of sensitization and time of residence in the new country (30-32).

Inclusion of different ethnicities in cohort studies and clinical trials as well as a clear definition of what the term atopy means (symptoms versus simple sensitization), would be key to defining the real impact of genetics, gene-environment connections and parasitic infestations on atopy development.

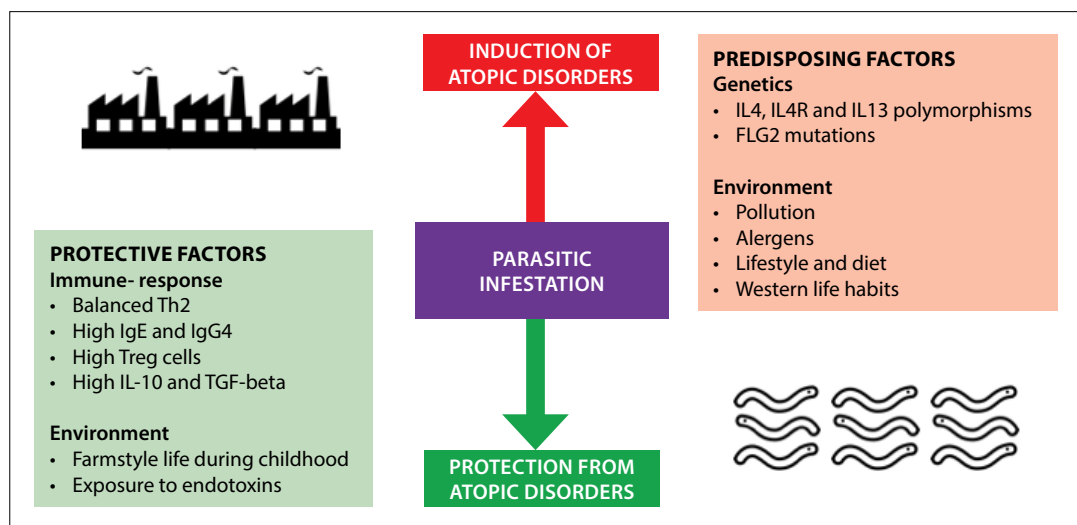
The “migration” of allergy: role of environmental factors

While it remains irrefutable that genetic predisposition has its weight, it is now widely accepted how genetics *together* with environmental exposure are key to shaping the immune system, especially during early life. Environmental exposure is in fact necessary to promote development and progression of allergic diseases (33). In 1958 Sherman stated that “Sensitization is never found to those allergens whose distribution precludes the exposure of the patient” (34). At that time, scientists were just beginning to deal with the consequences of imported ragweed pollen (*Ambrosia*) from America to Europe (35), and the sensitization that shortly followed exposure to an *Ambrosia*-naive population. The same could be witnessed the other way round, as described early on by Hughes in a series of 60 patients who immigrated to Canada, and developed sensitization to ragweed after at least one season of contact to the weed pollen (35).

The concept of biodiversity

Biodiversity is defined as the variability among living organisms from all sources, including *inter alia*, terrestrial, marine and oth-

Figure 1 - The “Janus” activity of parasitic infestation on the development of allergic diseases.



er aquatic ecosystems and the ecological complexes of which they are part. This includes diversity within species, between species and of ecosystems, a definition provided at the Convention on Biological Diversity in 1992. As a fact, the concept that biodiversity loss could lead to disease was introduced only recently in 2011, when the connection between two global megatrends, biodiversity loss and inflammatory diseases, was eviscerated (36). Although the neonate immune system has been vastly regarded as immature, it has been recently shown that strong antigenic stimuli can indeed induce efficient protective Th1 responses similarly to adults (37). The expression of cell activation markers, such as inducible T cell co-stimulator ligand (ICOS-L) and regulator markers, such as programmed death ligand 1 (PD-L1), has been found on dendritic cells of the neonatal lung in rats, implying the capacity of taking up antigens and processing them with a fine regulation of the immune response (38). On this basis, environmental exposure may exert an enormous impact on the immune system from an extreme early age onwards. This concept was evident from early on, when in 1989 the 'hygiene hypothesis' theory was introduced, stating that increased early-life exposure to infections and larger family size lead to a decreased risk of allergic disease development (39). Over a decade later, the 'old friends' hypothesis was proposed, where an explanation for the increase in allergic diseases was linked to the loss of symbiotic relationships with beneficial parasites and bacteria (1,40). Just a year later, in 2005, the 'microflora-microbiota' concept was introduced, blaming a reduced microbiome diversity for altered epithelial and immune cells (41). Indeed, numerous cohort studies dating back from 2001 to 2016, carried out in Europe and Australia, have shown that alterations in the gut microbiota during infancy and early childhood are associated with allergic disease (42-44). We now know that our intestinal tract is loaded with up to 10^{14} microbes (45) and data from metagenomic sequencing showed that every individual gives hospitality to at least 160 species of bacteria with a total number of bacterial species, identified in a sample of 124 Europeans, between 1000 to 1150 (46). Diminished early life exposure to the environmental microbiota could be responsible for priming the naïve immune system towards a Th2-predominant state, thus increasing the risk of developing allergic disorders. Indeed, microbiota has been claimed to modulate immune-responses through a so-called metabolic control (e.g. the action of short-chain fatty acids), being able to promote T regulatory cells and release hormones thus reducing the expression of pro-inflammatory cytokine (47,48).

Noteworthy, not only the number but also the variety of commensals seems to be relevant to prevent or favor allergies. Along with the 'biodiversity hypothesis', it is now accepted that "contact with natural environments enriches the human microbiome, promotes immune balance and protects from allergy and inflammatory disorders", as written by Haahtela T. in a recent

review on this topic (49). In this view two layers of biodiversity are identified: the *outer* (soil, natural waters, plants and animals), and the *inner layer* (gut, skin, airways). Biodiversity was further defined into three categories: macro-, micro- and genetic-diversity, the macro-diversity being the only easily observed, but the all three necessary for a global balance. Studies investigating the role of macro-diversity are important for understanding the delicate but intricate relationship between the inner-outer layer balance. In 1998 the Karelia Allergy Study began to substantiate the increase of the allergy incidence in the Finnish population (50). To this end a number of interesting studies were set up to evaluate the Finnish and Russian Karelia populations, living in adjacent areas of northern Europe, geoclimatically similar but socio-economically distinct. A once united population faced severe separation: the Russian population living in a small-scale agricultural lifestyle, while the Finnish population started to urbanize (51). Comparing the occurrence of asthma and allergy across the border, sensitization was low in both populations in individuals born at the time of the War. However, a linear increase was observed for allergy only in the Finnish younger generations (52). Another study carried out on children and adolescents from Finland and Estonia came to the same conclusion: the greener the environment, the lower the risk of allergy (53). These documented allergy gaps all presented in a relatively short period of time and between genetically close, if not identical, populations, supporting the view that not all can be explained by the genome, but rather in the change of lifestyle and environment (49).

Urbanization infallibly results in the loss of biodiversity and increased air pollution alongside improved socioeconomic conditions and better sanitation infrastructure, which in turn positively correlate with an increased incidence of atopy. In a large birth cohort in New Zealand, exposure to green areas and diverse vegetation has recently demonstrated to prevent from asthma development (54). However, these results have been not so clearly replicated and showed variations by region. In a study involving 2,472 children participating in the ongoing INfancia y Medio Ambiente (INMA) cohort located in Spain, higher residential surrounding greenness and higher proximity to green spaces were overall negatively associated with wheezing in the Euro-Siberian region. At the same time, in the Mediterranean region, higher residential proximity to green spaces was associated with a reduced risk for bronchitis (55). Opposite results on allergy risk were reported in a study based on individual data from Swedish (BAMSE), Australian (MACS), Dutch (PIAMA), Canadian (CAPPS and SAGE), and German (GINIplus and LISAPLUS) birth cohorts, involving a total of 13,016 individuals, which examined cohort-specific and combined associations of residential greenness with allergic rhinitis and aeroallergen sensitization. Here, residential greenness appeared to be associated with childhood allergic rhinitis and aeroallergen sensitization with the effect varying by location (56).

Inner layer modifications are also being associated with various adverse health effects. It was recently confirmed that alterations in the composition of the gut and skin microbiota as effect of reduced biodiversity are associated with various inflammatory conditions such as asthma, allergic and inflammatory bowel diseases (IBD), type 1 diabetes, and obesity (57), due to different immunopathologic mechanisms but all showing how tolerance mechanisms can rapidly become impaired in microbe-poor environments. These concepts has been acquired into the 2013 World Allergy Organization (WAO) Statement, where the loss of macro-diversity is associated with shrinking of micro-diversity, which is in turn associated with alterations of the indigenous microbiota (58). Their proposal highlighted an exponentially inverse relationship between biodiversity and the asthma/allergic rhinitis incidence: as biodiversity plummeted to record-lows, the incidence of allergic diseases sky-rocketed.

Finally, several epidemiological studies with large evidence suggested that exposure to high microbial loads in early life, such as a farming lifestyle, the presence of older siblings, and pet ownership, may be protective against atopy by shifting the immune milieu back towards a healthy Th1/Th2 balance (59).

Rural-Industrial Gap

As stated above, the phenotype of allergic diseases is heavily influenced by environmental exposure (33). When discussing the concept of biodiversity and its impact on the regulation of the immune system throughout an individual life, there is no better model to study than that of the consequences of immigration and/or emigration, a phenomenon which has lead hundreds of thousands across the world to become exposed to a complete new indoor and outdoor environment. Immigration and emigration to industrialized areas and the adoption of a more Western lifestyle has quickly led to behavioral, environmental, and dietary changes as the process of migration exposes immigrants to changes in socioeconomic, cultural, psychological, and, notably, environmental factors (60). The prevalence of diseases can greatly vary in settings with different socioeconomic conditions but also between regions, countries, and centers within a city or country (61). Studies have shown disparities in health and disease indices between migrant and native populations living in the same geographical location, especially regarding allergy (62). Comparisons between rural versus non rural microbial exposure in children in studies from all over the world, such as PAR-SIFAL and GABRIELA, or from studies conducted in Russia, China, Finland and more, have all come to one halting conclusion: early bacterial exposure carries a protective role in exposed individuals (52,63,64). One of the most striking study comparing microbial exposure in Amish and Hutterite children, respectively living on traditional or on large modern communal farms, showed a very low in the former and a significantly high-

er asthma incidence in the latter ones (5% vs 23%, respectively) (65). In this case, the importance of the origin and nature of bacterial exposure was highlighted, in fact it is supposed that the environmental protecting factor in Amish people consists of the higher endotoxin levels in household airborne dust. A Korean study involving 13,11 subjects divided into 3 groups according to the degree of urbanization (urban, semirural and rural) of the area where they resided, showed a positive correlation between sensitization to allergens (in particular house dust mite) and degree of urbanization (urban 17.2%, semirural 9.8% and rural 6.0%) (66).

The environmental and behavioral changes deriving, as an example, from urbanization, time spent indoors or antibiotic use result in increased exposure to air and traffic pollution, fungi, infectious agents, tobacco smoke, and other early-life and lifelong risk factors for the development and exacerbation of asthma and allergic diseases (33). Not surprisingly, migrants from rural areas moving to urban areas in developed countries actually show lower risks of allergic diseases compared to native urban residents.

This rural-urban gradient was well demonstrated also in a Danish study in which 1,236 male participants were divided into four groups depending on area of upbringing (city, town, rural area and farm) and assessed for allergy sensitization by skin prick tests (SPT) and specific serum IgEs towards inhalant allergens, clearly showing how exposure to a less urbanized childhood was associated with a lower risk of allergic sensitization and disease as an adult (67). Along with this first observation, a large body of evidence from Switzerland, Austria, Finland and Germany suggested that living on a farm and having contact with livestock is associated with protection against atopy, hay fever and asthma. The prevalence of atopy and hay fever has been reported to be reduced by between 31% and 69% in farmers' children (68–70). However, whether the presence of livestock or just agricultural farming is protective, still remains unclear. In a pioneering study from Italy, exposure to oro-fecal and food-borne microbes was inasmuch able to prevent the development of atopy (71). Moreover, a study carried out on Australian children found allergy protection depending on the type of farming (72). In another study carried out in China, rural children exposed to farming and higher endotoxin levels had decreased asthma risk compared with urban children (64). Although childhood farm-living have a lifelong protective effect on the prevalence of allergic rhinitis, it was also shown that an increasing prevalence of this disease goes hand in hand with the increasing degree of urbanization regardless of previous farm exposure (70). A cross-sectional study in the Chinese city of Suzhou observed that migrants from the countryside had lower rates of asthma and allergic symptoms compared to the local population (73). Interestingly enough, migrant children had higher rates of asthma compared to their parents, highlighting once again the critical role of early-life environmental

factors in the pathogenesis of allergic disorders. The concept of rural-industrial gap is somehow even clear in less affluent countries, where urbanization is relatively lower when compared to Western countries. Early studies conducted in South-East Asia in the 1980s, highlighted the higher prevalence of asthma in the cities (74,75). A study carried out in Mongolia in 2005 identified that the geographical distribution of allergic diseases was directly proportional to the level of urbanization of the area (76). Regarding Africa, a pioneering study in 1979 showed for the first time a greater prevalence of asthma in children of Xhosa ethnicity grew up in Cape Town when compared to peers residing in villages (3.17% versus 0.14%) (77). Subsequent studies in Kenya and Ethiopia broadly confirmed the urban-rural distribution of allergies (78,79). Similar data have been found in Latin America, with a prevalence of atopic dermatitis, allergic rhinitis and asthma up to 4-times higher than in the rural cohort (80). An interesting industrial-rural distribution for allergic-related diseases has been shown in several studies (81,82) carried also in Canada and USA.

Evaluating *when* and *what* happens when rurally-born and grown individuals move to a more industrial area is an intriguing point. A study conducted in Denmark demonstrated a decrease in the risk of allergic sensitization as well as rhinitis, and allergic asthma in adulthood with decreasing degree of an urbanized childhood (67). An Italian study better documented this concept in migrants from Albania. In spite of the low prevalence of allergic diseases in the country of origin, the prevalence of sensitization to local allergens and nasal symptoms increased in a time-dependent manner once migrants moved to the new urban setting (Italy)(83): more time passed, the higher the incidence of sensitization. Moreover, age at the time of migration does influence the risk of atopy and the rate of allergy acquisition (60). Subsequently, it was showed how children below the age of 4 years at the time of migration to Italy had a higher prevalence of rhinitis, atopic dermatitis, food allergy and allergic sensitization compared to children who migrated after the age of four (84). *Viceversa*, in this cohort an older age at the time of migration was associated with a shorter time to the onset of allergic symptoms from migration.

Migrants also offer a view on the environmental dynamics to the development of allergic diseases. It is clear that first-generation immigrants have a lower allergy prevalence compared to the native population, second-generation immigrants have a higher allergy prevalence compared to first-generation immigrants and second-generation immigrants with 2 foreign-born parents have a lower allergy prevalence than those with only 1 foreign-born parent (85-87). A clear correlation between immigration and insurgence of allergic symptoms was well shown in a study where first-generation immigrants acquired the sensitization profiles and allergic disease prevalence of the host country (88). These data were confirmed in another

cross-sectional Italian study, involving 21 allergy units in Italy, where the onset of allergic respiratory symptoms were shown to occur after immigration in 83% of adult immigrants, who had otherwise been asymptomatic while living in their native country (89).

Going back to the rural versus urban gap, it is possible that urbanization associated with high levels of vehicle emissions may be responsible of increased pollen-induced respiratory allergy in urban compared to rural populations (90). Literature vastly describes the role of outdoor (but also indoor) air pollutants in causing adverse health effects. It was claimed that moving from a rural to an urban area leads to exposure to a mixture of natural (wildfires, volcanoes, biological decay, dust storms) and human-made pollutants (motor vehicles, biomass burning, power plants, industrial facilities, waste incinerators, pesticides). In addition to this, sulfur dioxide, nitrogen oxides, carbon monoxide, and particulate matter are typical outdoor air pollutants from fuel combustion or motor vehicle emissions (91). Indoor air pollution is becoming increasingly troublesome due to the habit of some societies to spend the vast majority of time indoors, where tobacco smoke, solid fuels, stoves, construction materials, ambient particulate matter and biological materials can be found (92). Some studies investigated the pollutants capacity to directly promote the development of allergic disease. Traffic-related air pollution (TRAP) and tobacco smoke in allergic disease and asthma are indeed able to cause asthma exacerbation in children (93). Few studies have shown how near-roadway exposure is associated with increased asthma prevalence, chronic lower respiratory symptoms, phlegm production, bronchitis, wheeze, and medication use (94), decreased lung function, lifetime diagnoses and symptoms of allergic rhinitis or allergic sensitization among school-aged children (95). In another study, an estimated 14% of incident childhood asthma and 15% of childhood asthma exacerbations were caused by exposure to pollutants from roads with high vehicle traffic (96). Finally, other studies have shown how a large portion (40-83%) of the increased risk of aeroallergen sensitization by age 4 and increased risk of food allergy by age 8 could be linked to TRAP exposure (97). Despite the number of studies, however, meta-analyses of American and European cohorts observed substantial heterogeneity across studies that limited the ability to draw conclusions about the relationship between TRAP exposure and allergic outcomes (98). It has been claimed that air pollutants, such as CO₂, O₃ and NO₂ levels, interact with airborne allergens enhancing the risk of allergic sensitization and exacerbation of symptoms in sensitized individuals. Climate change, especially the global warming phenomenon, is one of the most important factors acting on allergic disease risk because it affects air quality, plant distribution and production, pollen count and fungal growth, being responsible for modifications of both allergenicity and season onset of aeroallergens spreading (4). Dietary factors may be

important in modulating immune-responses. Migration is usually associated with a change in dietary habits, and therefore the impact of these changes on allergy development has been investigated. Few studies have confirmed that the consumption of fast-food and take-away foods combined with the low intake of fruit and vegetables in the diet correlate with the increase in asthma and other atopic disorders prevalence (99). On the other hand, Mediterranean diet, especially if started since the first years of life, would exert to be a protective factor for atopic diseases (100). Some authors have observed that the alteration of the intestinal microbiota may represent one of the mechanisms by which the consumption of food in industrialized societies results in harmful effects (101).

Migration status and allergic disease

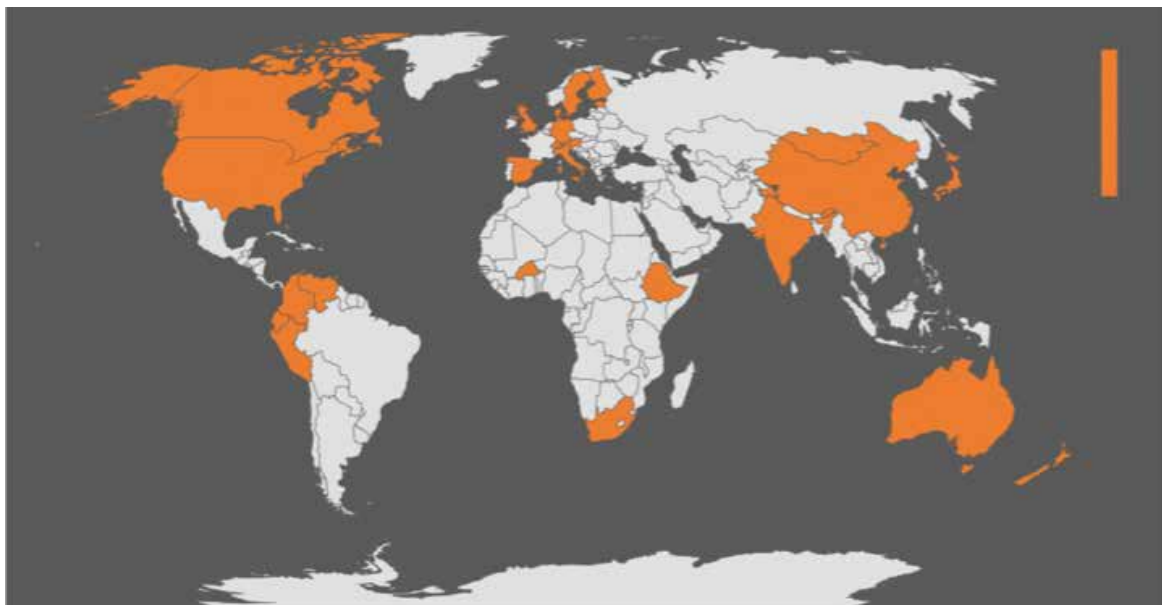
Despite infection and parasitic pressure, asthma and allergic diseases in general are also increasing in low and middle-income countries, where the complexity and severity of atopic diseases especially affect the youth population who carry on the greatest part of this epidemiological tendency (102). Migration status could heavily contribute to this trend, due to the abrupt exposure of the migrant populations to a new set of pollutants and allergens and the dramatic changes in diet, housing conditions and accessibility to medical services after the arrival in a new country (103). This phenomenon has an enormous economic impact as nearly one-seventh of the world population is now living in a different location from the birthplace. With one billion

people having moved in 2018, migration is a global reality and one of the greatest political issue in the contemporary world. The “disease load” among migrants is heterogeneous and dynamic because of a variety of interacting factors, such as genetic background as we have already touched on, pre-migration state of health, socio-economic and environmental conditions, local disease patterns, cultural norms and behaviours, access to medications before and during the migration process (81).

In the last two decades several papers on migrants have been published (**Figure 2**) with great heterogeneity regarding types of immigrant communities, comparison between local population and immigrants, which is often sporadic, possible lack of the country of origin. All these items may represent a big challenge for data synthesis (87). As a fact, the key variables affecting the external validity of migration studies and their results are represented by heterogeneity of immigrant population in terms of ethnicity and country of origin.

Overall, the findings of this great amount of published studies suggest that the burden of allergic diseases and asthma in immigrants from less affluent countries is lower than in the high-income host country. The ISAAC study involving 48 countries and 111 centres found that 6- to 7-year-old and 13- to 14-year-old individuals recently migrated to Western countries (high-income and high-allergy prevalence), had a lower prevalence of asthma and allergic disorders compared to local population (82). These results were not confirmed by the European Community Respiratory Health Survey (ECRHS), involving adults aged 20–45 years living in countries with high-asthma preva-

Figure 2 - A representation of the Countries where the studies about immigrants have been performed.



lence (Europe, USA, Australia, and New Zealand), founding no differences in asthma prevalence between resident migrants and non-migrants (104). However, these studies both present at least two limitations: sensitization instead of true allergy was taken into account in the ISAAC study, whereas in ECRHS asthma symptoms were considered, without any phenotyping into allergic and non-allergic one.

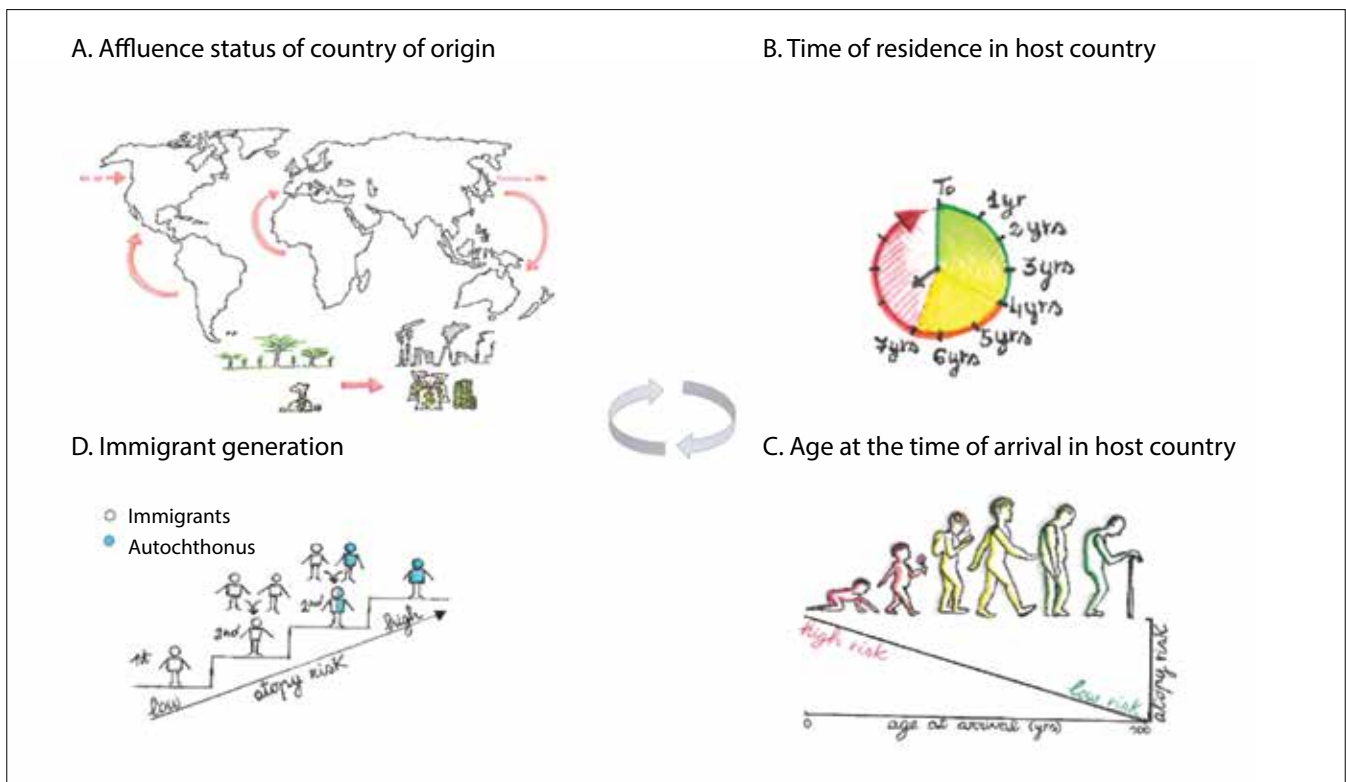
Most of the migration studies found that the prevalence of allergic disorders in immigrants tends to coincide with the general prevalence of the local population through a time-dependent process, confirming the strong role of the environment on the development of allergic sensitization and disease initiation. Analysing the ISAAC study, the protective effect of migration against allergy progressively declined with the increase of residence duration in the host country (82).

The main factors influencing atopic risk in migrant populations are resumed in **box 1** and **Figure 3**.

Box 1 Main factors influencing atopic risk in migrant populations

- The protective effect of migration is confined for migrants moving from a low-income country to a country with a high prevalence of allergic diseases
- The risk of developing asthma and allergic disease increases with the duration of residence in the host country (4-7 years)
- The risk of developing atopic disease is increased in people with younger age at the time of migration
- First-generation immigrants have a lower allergy prevalence compared to second-generation. Regarding the second generation, people with two foreign-born parents have a lower allergy prevalence compared to those with only one foreign-born parent

Figure 3 - Main factors influencing atopic risk in immigrant people: A. The protective effect of migration is confined to migrants moving from a low-income country to a country with a high prevalence of allergic disease; B. The risk of developing asthma and allergic disease increases with the duration of residence in the host country; C. 1st generation immigrants have a lower allergy prevalence compared to 2nd generation. Regarding the 2nd generation, people with two foreign-born parents have a lower allergy prevalence compared to those with only one foreign-born parent.



Asthma and Allergic Respiratory Diseases in migration studies

We summarize herein the principal findings of the most significant studies about asthma and allergic respiratory diseases in immigrants, grouping by the continent of the host country where the study was conducted and, when possible, dividing by ethnicity/country-of-origin of the immigrated study group.

North America

In 2007-2008 the National Survey of Children's Health studied 91,642 children with a cross-sectional questionnaire about atopic diseases, founding that children born outside the United States had significantly lower odds of any atopic disorders than their peers born in the USA (logistic regression OR, 0.48; 95% CI, 0.38-0.61), including ever-asthma (OR 0.53; CI 0.39-0.72), current-asthma (OR 0.34; CI 0.23-0.51) and hay fever (OR 0.39; CI 0.27-0.55) (105).

The National Health Interview Survey conducted early on between 1997 and 2011 demonstrated that foreign-born American adults from all regions of birth had lower odds of ever-asthma (adj OR 0.52, 95% CI 0.49-0.55) or current-asthma (adj OR 0.50, 95% CI 0.46-0.54) than US-born adults and that this risk increases after prolonged US residency. In fact, adult immigrants with prolonged residency in the USA (beyond 10 years) had greater odds of developing ever-asthma (OR 1.28, 95% CI 1.18-1.38) and current-asthma (OR 1.70, 95% CI 1.31-2.19) compared to those who had lived in the USA for less than 4 years (106).

Data analysis from the Canadian Community Health Survey demonstrated a lower prevalence of self-reported and physician-diagnosed non-food allergies among immigrants compared with non-immigrants, with diminishing difference along with the longer duration of residence (107).

A recent population-based retrospective cohort study in Ontario found that asthma incidence was lower among immigrants compared with long-term residents (IRR 0.30; 95% CI 0.30-0.30). On the other hand, Ontario-born children of immigrants from different world regions had significantly higher asthma incidence when compared to children of long-term residents (IRR 1.44; 95% CI 1.43-1.45).

Mexican Immigrants in USA

In the Chicago Asthma School Study, living in the USA instead of Mexico in the first year of life was associated with higher prevalence of physician-diagnosed asthma (OR 1.79, 95% CI 1.09-2.94). Along with this, long-term Mexican immigrants living in the USA for more than 10 years, had an increased risk of asthma compared with short-term immigrants, independently of country of residence in the first year of life (OR 1.93; 95% CI 1.00-3.73) (108).

Chinese Immigrants in USA

Adult Chinese immigrants living in the USA participating in the cross-sectional Community Assessment of Freeway Exposure and Health (CAFEH) study were less likely to have asthma (OR 0.20, 95% CI 0.09-0.48) compared to US-born whites thus showing that first generation immigrant status may be protective with a long-lived effect, as long as two decades (109).

Chinese Immigrants in Canada

Elaboration of data from the International Study of Asthma and Allergies in Childhood (ISAAC) phase III in 2008, comparing the prevalence of asthma and asthma-related symptoms (current wheezing, ever-wheezing, ever-asthma, wheezing attacks) in Chinese adolescents born in Canada, Chinese adolescents immigrated to Canada and Chinese adolescents living in China, demonstrated that asthma symptoms were lowest among mainland China residents, greater for Canada-immigrated and highest among Canada-born individuals. In detail, the prevalence of asthma in Chinese adolescent immigrants was 7.7% when residing in Canada for less than 7 years, 11.2% when living in Canada since more than 7 years and 15.9% when born in Canada (trend $p=0.006$) (110).

Australia

Early studies in the 1980s and 1990s observed that children born outside Australia had a lower incidence of asthma than natives. Moreover, foreign children tend to manifest a severe phenotype following a time-dependent pattern (111,112).

Asian Immigrants in Australia

It has been showed that in patients under 20 years of age the prevalence of asthma is distributed according to a gradient, from the more prevalent to the less prevalent, non-Asian Australians – Asian Australians – Asian migrants. However, this distribution was different when considering the prevalence of allergic rhinitis, which resulted more prevalent in Asian migrants and that was directly correlated with the levels of serum IgE (113,114).

Asia

The prevalence of allergic rhinitis in a cohort of new migrants from mainland China to Singapore was 9% compared to greater than 40% in Singapore-born subjects. The prevalence of allergic rhinitis increased up to 22% in the immigrated group after 8 years residence in Singapore. Moreover, less than 30% of China-born new immigrants were sensitized to house dust mites in comparison with 80% of Singapore-born subjects. However, after 3-8 years of residence, house dust mites in China-born migrants climbed to 50%, further increasing to 60% after more than 8 years. This study masterfully showed the

time-dependent influence of the environment on the allergic sensitization process (115).

The prevalence of asthma at age 17 on Israeli adolescents of the Israel defence forces was higher in native born Israelis compared with Ethiopians (4.7% vs 2.6% respectively, $p < 0.0005$) or immigrants from the former Soviet Union (FSU). The younger age of immigrants from Ethiopia and FSU when arriving to Israel, the higher was the prevalence of asthma at the age of 17 (20).

Europe

A different approach was used in a 2006 study, analysing the number of prescribed inhaled corticosteroids (ICS) as indicator of asthma in Swedish residents of different origin. A 3- to 4-fold higher rates of asthma medication was found in International adoptees and Sweden-born children from foreign-born parents when compared with foreign-born children. The odds ratios of asthma medication use declined persistently with age at immigration (116). More recently, in a selected disadvantaged immigrant population with highly precarious housing and potentially harmful environmental exposures (indoor moisture or mould, smoking), the atopic burden was indeed very high, also underlining the importance of unmet medical needs of certain immigrated communities (117).

One of the first Italian study conducted in Milan observed that a very high percentage of immigrants from outside Europe (84.5%) reported allergic/asthmatic symptoms developed after an average period of 4 years and 7 months from their arrival in Italy, while being asymptomatic in their country of origin. Aeroallergen sensitization patterns were similar to the local population (118). In 2011 it was found that new immigrants to Northern Italy compared to the resident population displayed a time-dependent increase in the number of sensitizing aeroallergens, which correlated with the duration of residence (30). The Viadana study, on the contrary, enrolled children aged 3–14 years living in Northern Italy who were compared to children born in Italy from Italian parents, demonstrating that immigrant children had a lower incidence rate of wheezing (7.9 vs. 36.6 per 1,000 persons/year) (119). In a wider cross-sectional study involving 21 Italian allergy units prevalently sited in the North and a very few in the Centre, taking into account immigrants referred to allergy services for respiratory symptoms, the onset of allergic respiratory disease occurred in 83% of previously asymptomatic adult immigrants. A higher rate of mono-sensitization was observed without any other relevant difference into the sensitization pattern, even though asthma and rhinitis were more severe in immigrants than in Italians (89). In a further and more recent cross-sectional multicentre study on rhinitis/asthma involving children born in Italy from Italian parents in comparison with children born either in Italy or abroad but from immigrants, the latter group showed a lower prevalence of rhinitis compared to Italians (68.3% vs. 87.6%, $p = 0.003$) with-

out any difference in terms of severity. However, significant differences in the pattern of sensitization was observed, inasmuch as immigrant children were more frequently sensitized to HDM than grass pollen (73.3% vs. 51%; $p = 0.002$) (120).

Albanian Immigrants in Italy

In a pioneering Italian study on the Albanian immigrant community living in Southern Italy, a lower prevalence of reported asthma and sensitization compared to the local Italian population was found (83). Over the time, the Albanian population developed allergic symptoms due to an increased prevalence of sensitization to local aeroallergens and acquired a pattern of sensitization typical of the host country (olive tree pollen).

Other Atopic Diseases in migration studies

The evidences about the prevalence, development and burden of atopic disorders other than respiratory diseases in migrant populations are definitely lower in numbers and more fragmented. We reported some interesting findings below.

Anaphylaxis

A Danish register-based study using nationwide data revealed that hospitalizations for anaphylaxis were less frequent in non-Western immigrants compared to Danish-born people (121).

In a recent study held in Australia about allergy and anaphylaxis, Asia-born children migrated to Australia exhibited a lower risk of food allergy (OR 0.33, 95%CI 0.20-0.55), eczema (OR 0.37, 95%CI 0.24-0.57) and asthma (OR 0.29, 95% CI 0.21-0.40) than non-Asian children. However, they were more likely at risk of anaphylaxis induced by both food and other triggers (122). The triggers of anaphylaxis differ between Asia- compared to non-Asian children, as lower for milk, peanuts and tree nuts but higher for soy, wheat and non-food related.

Food allergy

The population-based Health Nuts study in Melbourne (Australia) showed that peanut allergy was more frequent in infants with at least one parent born in East Asia than infants with both two Australia-born parents (OR 3.4, 95% CI 2.2–5.1) and comparable to children with at least one UK/Europe-born parent (OR 0.8, 95% CI 0.4–1.5) (123).

In the Canadian 2005-2006 National Health and Examination Survey investigating parental nativity, US-born children and adolescents had higher odds of sensitization to food, compared to outside US-born children, (OR 2.05, 95% CI 1.49-2.83, $p < 0.001$). In this case, levels of specific IgE to either milk, egg or peanuts of 0.35 kU/L or greater were considered. In foreign-born children, those arrived at 2 years of age or less had

higher odds of food sensitization than the older ones (OR 2.68, 95% CI 1.19–6.08, $p=0.02$), even if the US-born children with immigrant parents continued to be at the highest risk (OR 1.53, 95% CI 1.05–2.24, $p=0.02$) (86).

Eczema

Data from the German Interview and Examination Survey for Children and Adolescents (KIGGS) suggest that migration status has a significant inverse association with eczema (OR 0.63, 95% CI 0.49–0.80) (124).

This finding has been replicated in the multicentre ISAAC study, where children migrated at 10 years of age or older had lower odds of eczema (OR 0.69, 95% CI 0.56–0.86) compared to children migrated at the age of 2 years or younger. Nevertheless, eczema in children migrated at the age of 2 or older was more likely to be severe than earlier migration (82).

In USA the already mentioned National Survey of Children's Health found that outside US-born compared to US-born children had lower odds of eczema and food allergies in addition to lower respiratory allergic disorders (105).

In Italy, two already mentioned papers also accounted for allergic manifestations other than respiratory diseases. The first one is the cross-sectional multicentre study on adult immigrants with the finding of a lower prevalence of atopic eczema, food and drug reactions (89). The second one, the Viadana study, carried on children living in Northern Italy, confirmed that immigrant children had a lower incidence of eczema compared to Italy-born children from Italian parents (5.5 vs. 28.4 per 1,000 persons/year) (119).

Conclusion and future perspectives

Understanding the development of asthma and the allergic sensitization in the context of migration is a unique opportunity to reveal the complexity of gene-environment interactions, to identify risk factors and therefore to possibly find prevention strategies. In general, however, high-quality studies are still lacking, especially studies describing the longitudinal trajectory of illness in allergy (87). This should be advanced in future studies dealing more with basic immunological research, as unique findings might emerge following exposures and health status of immigrants before, during and after migration process and disclosing variation in their immune responses more in depth. Nevertheless, migration needs to be treated as a determinant of health and addressed as a global health priority, because the way the world will face human mobility in the near future will determine public health for the next decades (81).

A participatory approach in which migrants and local communities are included in the research process must be encouraged in order to best take care of the ever-rising number of sensitized patients, to predict who will become allergic and, among these, who will develop a more severe phenotype of atopy.

Conflict of Interest

The authors declare that they have no conflict of interest

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