Effects of Migration on Allergic Diseases

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Abstract

Studies in migrant populations provide vital opportunities to investigate the role of environmental factors in the pathogenesis of allergic disorders. Differences in allergy prevalence have been observed between migrants and native-born subjects living in the same geographical location. Immigrants who migrate from less affluent countries with lower allergy prevalence tend to have a lower prevalence of allergic disorders compared to native-born residents of the more affluent host country. The patterns of allergic disease prevalence also differ between first- and second-generation migrants. The timing of migration in relation to birth, age at migration, and duration of residence in the host country also influence one's atopic risk. A complex interplay of multiple environmental, socioeconomic, and cultural factors is likely responsible for these observed differences. Further research into the roles of various risk factors in modulating differences in allergic disease prevalence between migrant and native populations will enhance our understanding of the complex gene-environment interactions involved in the pathogenesis of allergic disorders.

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Introduction

Globalization and urbanization in modern societies are driving increasing volumes of migration worldwide. Migrant populations move within or between countries in search of enhanced career opportunities, a better quality of life, or to seek refuge from war or political unrest. Migration exposes individuals to changes in environmental exposures which can be traced to a specific temporal event, thus studies in migrant populations provide unique opportunities to evaluate the effects of different environmental factors on human health, as well as to identify potential gene-environmental influences which may contribute to the pathogenesis of disease.

Studies have shown disparities in health and disease indices between migrant and native populations living in the same geographical location [1, 2]. The process of migration exposes immigrants to changes in socioeconomic, cultural, psychological, as well as environmental factors. These include exposures to new pollutants and allergens, climate, diet, housing conditions, access to healthcare and health-seeking behaviours, all of which may contribute to the pathogenesis and/or influence the measured prevalence of allergic disorders.

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Table 1. Factors influencing allergic risk in migrant populations

Factor	Effect
Immigrant generation	1. First-generation immigrants have a lower allergy prevalence compared to the native population 2. Second-generation immigrants have a higher allergy prevalence compared to first-generation immigrants 3. Second-generation immigrants with 2 foreign-born parents have a lower allergy prevalence than those with only 1 foreign-born parent
Duration of residence in host country	Increased risk of atopy with increasing duration of residence
Age at the time of migration	Increased risk of atopy with younger age at the time of migration
Affluence status of country of origin	Lower risk of atopy in migrants moving from less affluent countries to more affluent countries
Migration in relation to birth	Birth after migration confers a higher risk of atopy than migration after birth
Rural childhood	Decreased risk of atopy in rural-to-urban migrants compared to those with an urbanized childhood

While it is known that allergic disease prevalence differs between migrant and native populations, differences in patterns between first- and second-generation immigrants and supporting proof-of-concept mechanistic studies have only recently been published. In this review we summarize the various patterns of allergic disease prevalence observed in migrant populations, highlighting novel observations on the differences in allergy prevalence between first- and second-generation immigrants, factors contributing to the observed differences, and supportive mechanistic studies which may explain these findings.

First-Generation International Immigrants

Studies in first-generation immigrants (individuals who immigrate to a foreign country) indicate that factors such as immigration during one's lifetime, the duration of time elapsed since migration, age at which migration occurred, and the affluence status of the country of origin all influence the development of allergic disorders (Table 1). The evidence also suggests that first-generation immigrants tend to have a lower prevalence of allergic diseases compared to the native population (the population born in the host country) of their host country if they migrate to a country with a higher prevalence of that particular allergic disorder (Fig. 1).

Overall Prevalence of Allergic Disorders

Asthma and Wheezing

The International Study of Asthma and Allergies in Childhood (ISAAC) found that the prevalence of all asthma-related symptoms in adolescents, such as current wheezing, ever wheezing, ever asthma, and wheezing attacks, was highest in Canadian born non-Chinese adolescents, followed by Chinese immigrants living in Vancouver, and was lowest in native Chinese adolescents living in mainland China and Hong Kong [3]. The National Health Interview Survey conducted between 1997 and 2011 also found that adults born outside the USA had lower odds of ever asthma (adjusted OR 0.52, 95% CI 0.49–0.55) or current asthma (adjusted OR 0.50, 95% CI 0.46–0.54) than US-born adults [4]. They also had a lower lifetime risk and point prevalence of asthma as well as significantly prolonged asthma-free survival compared to adults born in the USA. Adult Chinese immigrants living in the USA who participated in the Community Assessment of Freeway Exposure and Health (CAFEH) study were also less likely to have asthma (adjusted OR 0.20, 95% CI 0.09–0.48) compared to US-born whites [5].

Other Allergic Disorders

In a cross-sectional study comparing the prevalence of allergic disorders in Italian and immigrant children living in Italy, the latter group were found to have significantly

Fig. 1. Studies showing odds ratios of allergic diseases in immigrants versus non-immigrants.

lower rates of rhinitis and grass sensitization compared to native Italian-born children [6]. Asian immigrants to Australia, however, were reported to have a higher prevalence of seasonal allergic rhinitis compared to Australian-born non-Asians [7].

Adult Italian immigrants also had a lower prevalence of atopic eczema, food, and drug reactions as well as a family history of atopy compared to native Italians [8]. The Viadana study which enrolled children aged 3–14 years living in Northern Italy found that immigrant children had a lower incidence rate of wheezing (7.9 vs. 36.6 per 1,000 persons/year) and eczema (5.5 vs. 28.4 per 1,000 persons/year) compared to children born in Italy to Italian parents [9].

The 2007–2008 National Survey of Children’s Health which studied 91,642 children in the USA found that children born outside the USA had significantly lower odds of all allergic disorders, inclusive of ever asthma, current asthma, eczema, hay fever, and food allergies, than those born in the USA [10].

Assimilation Effect and Time Since Migration

Over time, first-generation immigrants acquire the sensitization profiles and allergic disease prevalence of the host country, which has been described as the assimilation or acculturation effect [11]. Increasing duration of residence in the host country is also associated with an increasing prevalence of sensitization and allergic disorders.

The prevalence of allergic disorders in the immigrant population gradually rises to match or even exceed that of the native population with time. In the ISAAC study, the protective effect of migration in children appeared to be greatest in those who had lived fewer years in the host country and declined with increasing duration of residence in the host country [12].

Asthma and Wheezing

In a cross-sectional multicentre study involving 21 allergy units in Italy, the onset of allergic respiratory symptoms occurred only after immigration in 83% of adult immigrants, who had otherwise been asymptomatic while living in their native country [8]. Another study in Milan, Italy, similarly observed that 84.5% of immigrants from outside Europe reported being asymptomatic in their country of origin, but developed allergic/asthmatic symptoms after arrival in Italy [13]. Likewise, Albanian migrants to Southern Italy had an initial low prevalence of reported asthma and sensitization compared to the local Italian population [14]. These migrants, however, developed increasing allergic symptoms and an increased prevalence of sensitization to local aeroallergens over time, gradually acquiring a pattern of sensitization typical of their host country.

The prevalence of asthma in Chinese adolescent immigrants residing in Canada for less than 7 years was 7.7%, compared to 11.2% for those who had lived in Can-

ada for more than 7 years and 15.9% in those who had been born in Canada ($p = 0.006$ for trend) [3]. Australian immigrant teenagers aged 13–19 years had a lower prevalence of self-reported wheeze (8.5%) compared to those born in Australia (19.2%). However, this risk increased 2-fold after 5–9 years of residence in Australia and 3-fold after 10–14 years (p for trend <0.001) [15]. Likewise, 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 [4]. Children of Mexican descent in the Chicago Asthma School Study who were born in the USA, as well as those who had migrated from Mexico to the USA for longer than 10 years, had an increased risk of asthma (adjusted OR 2.57, 95% CI 1.68–3.95) compared to those who had lived in the USA for less than 10 years [16].

Allergic Rhinitis

A cross-sectional telephone survey which examined the associations between atopic disorders and length of stay in Asians and non-Asians living in Melbourne, Australia, found that the prevalence of hay fever and asthma in Asian immigrants increased significantly with duration of residence in Australia (p for trend <0.05) [17]. In fact, in those older than 20 years, the prevalence of hay fever in Asian immigrants was almost twice that of Australian-born non-Asians ($p < 0.002$).

The prevalence of allergic rhinitis in a cohort of migrants from mainland China to Singapore was only 9% compared to greater than 40% in Singapore-born subjects [18]. However, over time the prevalence of allergic rhinitis in Chinese migrants increased to 22% after 8 years of residence in Singapore.

Allergic Sensitization

Around 80% of Singapore-born subjects were sensitized to house dust mites, compared to less than 30% in China-born subjects [18]. However, house dust mite sensitization rates climbed from less than 30% in China-born migrants with less than 3 years of residence in Singapore to 50% after 3–8 years, and increased further to 60% after living in Singapore for more than 8 years. New immigrants to Northern Italy also displayed a time-dependent increase in the number of sensitized aeroallergens, which correlated to the duration of residence in their host country, compared to the resident population [19]. Aeroallergen sensitization patterns in Italian migrants likewise bore greater similarity to that of the local general popula-

tion in their host country rather than that of their home country [13].

Other Allergic Disorders

Foreign-born children who had lived in the USA for more than 10 years had significantly higher odds of developing any allergic disorder (adjusted OR 3.0, 95% CI 1.08–8.60), eczema (adjusted OR 4.93, 95% CI 1.18–20.62), and hay fever (adjusted OR 6.25, 95% CI 1.70–22.96) compared to those who had migrated less than 2 years before [10]. The Canadian Community Health Survey (CCHS) studied associations between immigration status and non-food allergies in individuals above 12 years of age living in 122 provinces and territories across Canada [20]. The highest prevalence of non-food allergies was reported in non-immigrants (29.6%) followed by long-term immigrants – those who had lived in Canada for more than 10 years (23.9%, adjusted OR 0.73, 95% CI 0.68–0.78) and the lowest prevalence was observed in recent immigrants who had migrated to Canada less than 10 years before (14.3%, adjusted OR 0.35, 95% CI 0.30–0.40).

Age at Migration

Age at the time of migration also appears to influence the risk of atopy and the rate of allergy acquisition. An earlier age at the time of migration was generally associated with increased risks of developing atopic diseases compared to migration later in childhood. Children who were below the age of 4 years at the time of migration to Italy had a higher prevalence of rhinitis, atopic dermatitis, food allergy, and sensitization compared to children who had migrated after the age of 4 years [6]. However, an older age at the time of migration was associated with a shorter time from migration to the onset of allergic symptoms in this cohort.

Foreign-born Swedish young men who had been adopted into Swedish families before 7 years of age presented at the compulsory Swedish military service conscription medical examination at 17 years of age [21]. The prevalence of reported hay fever (31 vs. 19%, RR 1.6, 95% CI 1.4–1.9), asthma (9 vs. 3.6%, RR 2.5, 95% CI 1.7–3.8), and eczema (4.9 vs. 2.1%, RR 2.1, 95% CI 1.2–3.7) was higher in the boys who arrived in Sweden before 2 years of age compared to those who arrived between 2 and 6 years of age. The prevalence of purchased prescribed inhaled corticosteroids obtained from the Swedish Prescribed Drug Register, used as a surrogate indicator of asthma prevalence, also decreased with older age at the time of migration in both internationally adopted chil-

dren and foreign-born children of foreign-born immigrant parents who had migrated to Sweden [22].

Children in the multicentre ISAAC study who had migrated after 10 years of age had lower odds of current wheeze (adjusted OR 0.71, 95% CI 0.52–0.96), ever asthma (adjusted OR 0.68, 95% CI 0.55–0.83), current rhinoconjunctivitis (adjusted OR 0.76, 95% CI 0.62–0.92), and ever eczema (adjusted OR 0.69, 95% CI 0.56–0.86) compared to children who had migrated before 2 years of age [12]. However, eczema in those who had migrated after 2 years of age was more likely to be severe compared to those who had migrated before 2 years of age.

A study of 17-year-old Israeli adolescents drafted into the Israeli defence forces found an inverse correlation between immigration age and asthma prevalence in immigrants from Ethiopia and the Former Soviet Union (p for trend = 0.006 and <0.0005, respectively) [23].

Affluence Status of the Country of Origin

The observed protective effect of migration appears to be confined to migrants moving from a less affluent to a more affluent country but not vice versa. The ISAAC study involving 48 countries and 111 centres found that 6- to 7-year-old and 13- to 14-year-old recent immigrants to countries of greater affluence or a higher allergy prevalence had a lower prevalence of asthma, rhinoconjunctivitis, and eczema compared to those who were born in that country [12]. However, the European Community Respiratory Health Survey (ECRHS), which surveyed adults aged 20–45 years of age living in developed countries with an overall high asthma prevalence (Europe, USA, Australia, and New Zealand), found no differences in asthma prevalence between migrants and non-migrants living in these countries [24].

Rural to Urban Migration

A number of studies have now investigated the rural-urban gradient in the prevalence of allergy disorders. In general, migrants from rural areas moving to urban areas in developed countries showed lower risks of allergic diseases compared to native urban residents. A study conducted in Denmark demonstrated a decrease in the risk of allergic sensitization, rhinitis, and allergic asthma in adulthood with decreasing degree of urbanized childhood [25]. Evidence from a number of studies suggests that being born and raised in a farm environment confers a protective effect against the development of allergic diseases in children [26, 27]. A Swedish study of adults aged 16–75 years showed that subjects living on a farm during the first 5 years of life had a reduced prevalence of allergic

rhinitis across all groups [28]. An increasing prevalence of allergic rhinitis was also observed with increasing urbanization [29]. These findings were supported by a large population-based study where subjects living on a farm with livestock exposure during the first 5 years of life had significantly reduced rates of allergic rhinitis and symptoms in adulthood compared to those who had a city-based childhood, independent of differences in farming structure [30]. In agreement with these studies, the European Community Respiratory Health Survey II also reported a lower prevalence of atopic sensitization, atopic asthma, and atopic rhinitis in adulthood for subjects with farm exposure before 5 years of age as compared to those with an urban childhood [31].

Another cross-sectional study conducted in the Chinese city of Suzhou observed that domestic migrants (children and parents) from the countryside had lower rates of asthma and allergic symptoms compared to the local population [32]. Interestingly, migrant children had higher rates of asthma compared to their parents, highlighting the critical role of early-life environmental factors in the pathogenesis of allergic disorders. Other studies have also demonstrated correlations between urbanization and high levels of vehicle emissions with increases in pollen-induced respiratory allergy in urban compared to rural populations [33].

The duration and intensity of exposure to a farming environment have also been proposed to be associated with the development of atopy. In a Mongolian study, subjects aged 10–60 years who moved from rural villages into a town demonstrated trends towards a decreased risk of allergen sensitization compared to those who lived in a town from birth [34]. Results from another Swiss study showed that children of full-time farmers had lower risks of atopic sensitization as compared to children of part-time farmers [35].

However, contrasting observations were found in studies conducted in less developed or less affluent countries. A cross-sectional study conducted in 2,510 school-children aged 5–16 years living in Ecuador showed that rural-to-urban migrants had a higher prevalence of wheeze compared to non-migrants [36]. Age at migration and time since migration were again important determinants of subsequent allergic disease development in this group. Children who had migrated after 3 years of age had an increased risk of developing wheeze compared to non-migrants and migrants with less than 5 years of residence in their host city had a higher prevalence of wheeze compared to non-migrants. Another study on adolescents aged 13–14 years in an urban area of Argentina showed

Table 2. Proposed mechanisms for differences in allergy prevalence between migrant and native populations

Factor	Effect
Shifts in innate and adaptive immunity	Reduced immune responses and reduced exposure to microbial diversity in long-term immigrants living in Westernized environments may attenuate immunoregulatory mechanisms essential in modulating allergic predisposition
Pollution	1. Increased air pollution in urbanized regions associated with increased prevalence of asthma 2. Airborne pollutants interact with aeroallergens to enhance airway permeability and allergen penetration, leading to increased asthma exacerbations
Climate change	Longer pollen seasons, changes in crop patterns and pollen distribution patterns in different countries
Microbial exposures (hygiene hypothesis)	Increased exposure to microbes in early life, such as a rural childhood, is protective against allergy development
Dietary changes	Adoption of Westernized diet of host country may result in pro-inflammatory states leading to increased risk of allergic disease
Health-related beliefs Health-seeking behaviour Access to healthcare	1. Migrants from ethnic minorities may display lower health awareness and decreased adherence to prescribed medications 2. Migrants with lower socioeconomic status may have limited access to quality healthcare 3. Language barriers may hinder understanding and reporting of disease conditions, which may result in decreased reported disease prevalence in this group
Intergenerational and transgenerational epigenetic inheritance of allergic predisposition	Maternal epigenetic changes in the antenatal and preconception period influence immune responses in offspring

that the adolescents with a history of rural residence had the same rates of wheeze as compared to those who had been living in urban areas [37].

Possible Mechanisms

Changes in environmental influences, such as climate change, pollination patterns, air pollution, lifestyle factors, and health-seeking behaviours may influence allergic risk and disease reporting among migrant populations (Table 2). Recent proof-of-concept studies have shown that migration from a low-risk country, such as China, to a Westernized environment with a higher prevalence of allergic disorders such as Australia resulted in differential shifts in innate and adaptive immune responses between long-term and recent immigrants, which might explain the differences in allergic predisposition in these two groups. Chinese immigrants who had resided in Australia for more than 5 years demonstrated attenuated innate cytokine responses following TLR stimulation [38], in-

creased genome methylation, and decreased gene expression compared to newly arrived immigrants [39]. Furthermore, the intensity of innate cytokine responses to TLR ligands and correlations between innate and adaptive antibody responses to pathogen-associated antibodies were significantly weaker in the long-term Chinese immigrants compared to newly arrived immigrants [40]. This supports the hypothesis that prolonged reduced exposure to microbial loads and biodiversity present in Westernized environments over time may attenuate key immunoregulatory mechanisms involved in modulating susceptibility to allergic disease.

Local environmental factors such as air pollution, climate change, and pollination also influence atopic risk, particularly in immigrants migrating from less affluent to more affluent Westernized countries. Increasing urbanization and enhanced transportation infrastructure, particularly in developed countries, are inevitably accompanied by an increase in air pollution, especially in regions

where the adoption of environmentally friendly practices has not kept pace with the rate of technological advancement. Ambient air pollutants such as ozone, carbon monoxide, nitrogen dioxide, sulphur dioxide, and particulate matter in urban areas have been associated with increased prevalence of paediatric asthma and related morbidity [41]. Residence in areas with a high traffic density and industries, in particular, were found to be associated with wheeze, asthma, and increased total IgE levels in children [42, 43]. Furthermore, animal [44–47] and human studies [48–50] showed that exposure to diesel exhaust particles induced a Th2-dominant response and allergen-specific IgE production, which may predispose to the development and exacerbation of allergic disorders.

Climate change and air pollution also impact upon ecological systems and pollination patterns. Global warming has resulted in longer pollen seasons, changes in crop patterns, and pollen distribution patterns [33]. Environmental conditions specific to urban regions such as high nocturnal temperatures, increased atmospheric carbon dioxide, and nitrogen deposition provide favourable conditions for agriculture, leading to increased production of pollen and airborne allergenic protein loads [51–54]. Furthermore, airborne pollutants interact with aeroallergens, enhancing airway permeability and allergen penetration, which compound their detrimental effects on asthma exacerbations [55]. These may explain the higher prevalence of allergic respiratory disorders observed in individuals living in urbanized, developed environments for a longer period of time compared to migrants with a shorter duration of exposure.

Comparative studies of rural-to-urban migrants have shown significant differences in lifestyle such as family size, dietary habits, exposure to livestock, and mode of delivery between children raised on farms versus urban environments [56]. Urbanization also results in loss of biodiversity and increased air pollution alongside improved socioeconomic conditions and better sanitation infrastructure [57]. The “hygiene hypothesis” proposes that diminished early life exposure to environmental microbiota primes the naïve immune system towards a Th2-predominant state which increases the risk of developing allergic disorders [58]. Conversely, epidemiological studies suggest that exposure to high microbial loads and increased biodiversity 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 [59–62]. These suggest that the lower prevalence of allergic disorders in individuals with rural childhood origins may be

attributed to the protective immunoregulatory effects of greater microbial exposures and biodiversity in early life.

Lifestyle factors such as diet, health beliefs, and health-seeking behaviour may also play an equally important role in modulating allergic risk. Many immigrants to Western countries gradually adopt the Westernized diet of their host country, which is characterized by high salt, high saturated fat, food additives and preservatives, and low fibre. Over time, these dietary imbalances lead to nutritional deficiencies or obesity, resulting in a pro-inflammatory state associated with increased airway reactivity and enhanced susceptibility to asthma and allergic diseases [63, 64]. In contrast, the Mediterranean diet, which is low in pro-inflammatory omega-6 fatty acids and high in anti-inflammatory omega-3 fatty acids, fruits, and vegetables, has been associated with decreased risks of wheeze and asthma [65].

A multicentre Danish study found that several reversible lifestyle factors such as younger age, male gender, heavy drinking, smoking, and higher education levels were positively associated with atopy [66]. The Dutch KOALA Birth Cohort study also found that parental atopic status influenced their family lifestyle patterns in relation to perceived allergic risk factors, such as environmental tobacco smoke exposure, pet ownership, and infant vaccination practices, which may in turn modulate allergic predisposition in their offspring [67].

Cultural or religious beliefs about health, disease and its management also influence disease recognition, health-seeking behaviours, and compliance to treatment in ethnic populations. Studies have shown that systemic corticosteroids and self-management education programs reduce the risk of asthma exacerbations [68, 69]. However, individuals from ethnic minorities displayed lower awareness of these benefits [70] and decreased adherence to the use of anti-asthmatic medications [71–73]. Studies showed that South Asians tended to hold opinions that most drugs were “addictive” and could do more harm than good, and were also less likely to take the preventive medications as prescribed compared to white parents [71, 74].

Ethnic minorities or migrants living in adverse socioeconomic circumstances often have a poor understanding of asthma, underestimate the importance of its control, and also have limited access to high-quality asthma care [75]. This may explain the perceived lower measured prevalence of disease in this group observed in epidemiological studies but yet greater asthma severity, which may be due to under recognition of underlying poorly controlled asthma or delayed presentation to medical attention [76].

Fig. 2. Studies showing odds ratios of allergic diseases in children of foreign-born parents (second-generation immigrants) versus children of native-born parents.

Additionally, language barriers in healthcare communication may hinder the translation and understanding of certain medical terms such as “wheeze” into other languages [77]. Inconsistencies in the understanding of wheezing presented in videos and written study questionnaires have also been reported, which may underestimate the reported prevalence of the disorder in certain ethnic populations [77, 78]. In a cohort study performed in the UK, families that were less proficient in English communication were found less likely to report asthma and wheeze compared to those fluent in the English language [79]. The multicentre ISAAC study also observed that asthma prevalence was higher in English-speaking countries and lower in the Indian subcontinent, Asia-Pacific region, Eastern Mediterranean, Northern Africa, and Eastern Europe [80]. The ISAAC study was limited by a lack of objective measures of asthma, such as lung function testing and difficulties in maintaining questionnaire validity during translation into multiple languages, which might have impacted upon differential reporting between countries.

It could also be speculated that underdiagnosis of allergies in migrants from less developed home countries and subsequent improved access to healthcare and accuracy of disease diagnosis after migration might manifest in an apparent increase in the prevalence of allergies over time in their host country. Holguin et al. [81] observed that increasing duration of residence in the USA was associated with increased access to healthcare services.

Comparative studies of allergy prevalence between individuals from the same ethnic background living in countries with different levels of access to healthcare also lend support to this observation. The prevalence of self-reported wheezing in the phase 3 ISAAC study in China was only 3.6% in Chinese adolescents [12], but 14.5% in new Chinese adolescent immigrants who had lived in Canada for less than 7 years [3].

Second-Generation International Immigrants

Overall Prevalence of Allergic Disorders

There are comparatively fewer studies on the prevalence of allergic disorders in second-generation immigrants (children of migrant parents who are born in the host country itself) and the evidence is conflicting (Fig. 2). A systematic review comparing first- and second-generation immigrants found that the prevalence of allergic disorders was generally higher in second-generation immigrants compared to first-generation immigrants [82].

However, in comparison to native-born families, the prevalence of allergic diseases appears to be lower in children with foreign-born parents compared to children whose parents were native to that country. Of US-born children surveyed in the US National Survey of Children’s Health, those with foreign-born parents had a significantly lower prevalence of allergic diseases than those with US-born parents [10]. Furthermore, children with 2

foreign-born parents had a lower prevalence of allergic disorders than those with just 1 parent born outside the USA.

Children born in Italy of foreign parents had lower incidence rates of wheezing (24.6 vs. 36.6 per 1,000 persons/year) and eczema (16.3 vs. 28.4 per 1,000 persons/year) compared to those born to native Italian parents [9]. The incidence rates were likewise lower in those with 2 foreign-born parents than those with 1 foreign-born parent.

The German Health Interview and Examination Survey for Children and Adolescents (KiGGS) also observed that children and adolescents with two migrant parents had lower risks of atopic dermatitis and sensitization to birch, soybean, peanut, rice, potato, and horse dander compared to children with only 1 migrant parent, or native-born children without any history of migration [83, 84].

The prevalence of allergic disorders in second-generation Asian immigrants living in Australia, however, bears a striking contrast to the above patterns. The HealthNuts study in Melbourne, Australia, found that challenge-proven peanut allergy was three times more common in infants with parents born in East Asia (adjusted OR 3.4, 95% CI 2.2–5.1) compared to infants with 2 Australian-born parents and those with parents born in the UK or Europe (adjusted OR 0.8, 95% CI 0.4–1.5) [85]. Panjari et al. [86] also found that children born in Australia of ethnic Asian mothers had a higher risk of parental-reported nut allergy than native non-Asian children. This also contrasts with the low nut allergy prevalence observed in ethnic Asians living in Asia [87, 88]. A cross-sectional study in Melbourne, Australia, also observed that the prevalence of hay fever and allergic sensitization, particularly to pollen and dust mites, in children below 20 years of age was higher in Australian-born Asians than in Australian-born non-Asians [17]. It is still, however, unclear whether these differences might be attributed to an unmasking of a genetic predisposition to these allergies in ethnic Asians due to exposure to certain environmental factors while living in Australia.

Timing of Migration in Relation to Birth

The timing of migration in relation to birth in individuals of the same ethnic group also influences allergy risk. Migration after birth appears to confer a protective effect compared to birth after migration.

Asthma and Wheezing

Children of US immigrant families in which both generations were born outside the US had a significantly low-

er prevalence of any allergic disease (18.2 vs. 33.4%, adjusted OR 0.45, 95% CI 0.25–0.78) and lower odds of ever asthma (adjusted OR 0.38, 95% CI 0.19–0.78), current asthma (adjusted OR 0.37, 95% CI 0.16–0.95), and hay fever (adjusted OR 0.35, 95% CI 0.16–0.77) than those whose parents were born in the USA [10].

The Hispanic Community Health Study/Study of Latinos found that second-generation US-born individuals of Mexican and Dominican ethnicity had 1.49 (95% CI 1.19–1.85) and 1.37 (95% CI 1.12–1.69) times the odds of reported asthma by the age of 18 and 30 years, respectively, compared to those who were born outside the USA and subsequently moved to the USA in their childhood [89]. The Third National Health and Nutrition Examination Survey (NHANES III) and National Health Interview Survey (NHIS) also found that US-born Mexican Americans were more likely to report ever having asthma (7 vs. 3% in NHANES III and 8.1 vs. 2.5% in NHIS) than Mexican-born Mexican Americans [81]. The Chicago Asthma School Study in children of Mexican descent found that children born in the USA and who had lived there in the first year of life had a 2.39-fold increased risk of physician-diagnosed asthma compared to those who had been born in Mexico and migrated to the USA only after the first year of life [16].

Among ethnic Chinese adolescents, the prevalence of ever wheezing (adjusted OR 2.27, 95% CI 1.55–3.33), current wheezing (adjusted OR 1.93, 95% CI 1.18–3.15), and ever asthma (adjusted OR 2.72, 95% CI 1.75–4.23) was higher in Canadian-born Chinese compared to Chinese immigrants who had migrated to Canada after birth [3]. Adolescent immigrants from Ethiopia and the former Soviet Union to Israel also had a significantly lower prevalence of asthma compared to children born in Israel of the same ethnicity [23]. A Swedish study using inhaled corticosteroid prescriptions as a surrogate indicator of asthma prevalence found that these prescriptions were higher in Swedish-born children of foreign-born parents (adjusted OR 3.36, 95% CI 3.10–3.66) compared to foreign-born children who had migrated to Sweden after birth with their biological parents [22].

Food Allergy

A state-wide school entrance health questionnaire survey administered in Melbourne, Australia, found that among ethnic Asian children those born in Asia with subsequent migration to Australia were at a lower risk of parental-reported nut allergy compared to those who had been born in Australia [86].

Possible Mechanisms

There is now an emerging body of evidence for the intergenerational and transgenerational epigenetic inheritance of allergic disorders, in which gene-environmental interactions induce modifications in the epigenome before conception or in utero, which can then be transmitted to the next generation and beyond [90] (Table 2). Intergenerational murine models have shown that allergen sensitization in the preconception period influences antigen-specific immune responses in the offspring and predisposes to the development of asthma and atopy [91]. Studies have also shown that antenatal particulate exposure in mice resulted in distinct methylation changes and increased susceptibility to allergic airway diseases in up to three subsequent offspring generations [92, 93]. In a murine model of peanut allergy, offspring of peanut-sensitized mothers were more susceptible to the development of peanut allergy, through epigenetic alterations of the IL-4 gene promoter [94].

These observations provide insights into the possible mechanisms behind the above-mentioned epidemiological differences in asthma prevalence and food allergies in second-generation compared to first-generation immigrant children, and also in the timing of migration in relation to birth. The periconception and antenatal environment may thus induce differential epigenetic effects on offspring which likely influence their ensuing risk of allergic respiratory disorders and food allergies after birth.

Conclusions

The varying patterns of allergic disorders in first- and second-generation migrant populations and factors influencing allergic risk, which have been illustrated in this review and are summarized in Table 1, underscore the essential role of the environment in modulating allergy risk. The differences in allergy prevalence seen even in

individuals of the same ethnic group living in different environments suggest that gene-environmental interactions, particularly during the critical window of opportunity in early life, influence immune regulation and determine health and susceptibility to disease in later life [95]. Evidence supporting this hypothesis is now emerging in the form of mechanistic studies which demonstrate immune alterations and epigenetic changes which can be passed down through generations. Further studies on the epigenetic mechanisms controlling the role of environmental factors on disease outcomes will enhance our understanding of the complex gene-environment interactions involved in the pathogenesis of allergic disorders.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

E.H. Tham conceptualized the review, performed data acquisition and interpretation, and drafted and revised the manuscript. E.X.L. Loo and Y. Zhu were involved in data acquisition, drafting, and revising the manuscript. L.P.-C. Shek was involved in revising the work critically for important intellectual content. All authors gave final approval for the manuscript.

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