

EDITORIAL

Clinical & Experimental Allergy

Do migrant studies help to identify causes of asthma?

This editorial discusses the findings in the paper by Braback et al. [14] pp. 1108–1115.

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The question how migration, ethnicity and socio-economic position influence development and severity of asthma is receiving increasing scientific interest. Prevalence of asthma shows large international variations and has steeply increased during past decades [1]. Despite a large body of research, the causes underlying regional differences and time trends are poorly understood. Migrating populations provide a natural experiment to differentiate between genetic and environmental causes of a disease. These populations undergo, within a few years, environmental and lifestyle changes that in native populations have taken decades or centuries to happen. Therefore migrant studies might help to understand geographic differences and secular trends of asthma.

Published papers on this topic fall into two main categories. The first set of papers present data from populations emigrating from less-developed countries with low asthma prevalence (South Asia, East Asia, Eastern Europe, South America) into developed countries with a western lifestyle and high asthma prevalence (Australia, Israel, Sweden, UK, US) [2–6]. Unanimously, these papers describe an increasing frequency of ‘asthma’ with longer duration of residence in the host country or younger age at emigration. Prevalence in people who had been born in the host country or had immigrated as toddlers usually approached prevalence in the native population [5, 7–9].

The second set of papers, mainly from the United States, describe a higher prevalence, more severe disease, increased emergency health-care utilization and poorer outcomes in ethnic minority groups or people of other ‘races’ [10]. These data tend not to be from new immigrants, but from families who arrived decades or generations ago and who remained in relative poverty, social

seclusion and poorer health care compared with whites. Therefore, results do not necessarily contradict the findings from recent immigrants, but might reflect the situation further down the time line.

Outcomes studied

Authors presenting data from migrants generally concluded that environmental exposures during intrauterine life or early childhood influence developmental pathways of immune system (allergy vs. host defence), airway responsiveness and lung growth, facilitating the development of atopy and asthma [2, 5–7, 8]. However, in none of the studies specific environmental exposures could be identified.

Figure 1 illustrates why many studies are difficult to interpret. *Asthma-related outcomes* typically assessed in studies are symbolized by *blue squares*. First in the chain of outcomes come (1) measurable objective traits related to asthma, such as lung function, atopy, bronchial responsiveness (BR) or airway inflammation. These can but need not lead to (2) symptoms, such as cough, wheeze or difficulty breathing. Symptoms can but need not lead to (3) a visit to the doctor. The doctor can (4) make a diagnosis and prescribe a treatment. Finally (5) the family may or may not buy and use the prescribed treatment. Progression to the next step in the chain depends on many factors: symptoms must be perceived by the child or the parents; parents must understand that these problems need medical attention and decide to visit the doctor; the doctor's diagnosis and treatment decision then depend on the presented symptoms, on objective asthma correlates if these are measured, and on socio-cultural and psychological factors affecting communication with the family.

Categories of causative factors for these asthma outcomes are symbolized by *red circles*: (A) genetic background; (B) macro-environment, comprising factors such as climate, infectious agents, outdoor allergens or air pollution; (C) micro-environment including factors related to family lifestyle and indoor environment, such

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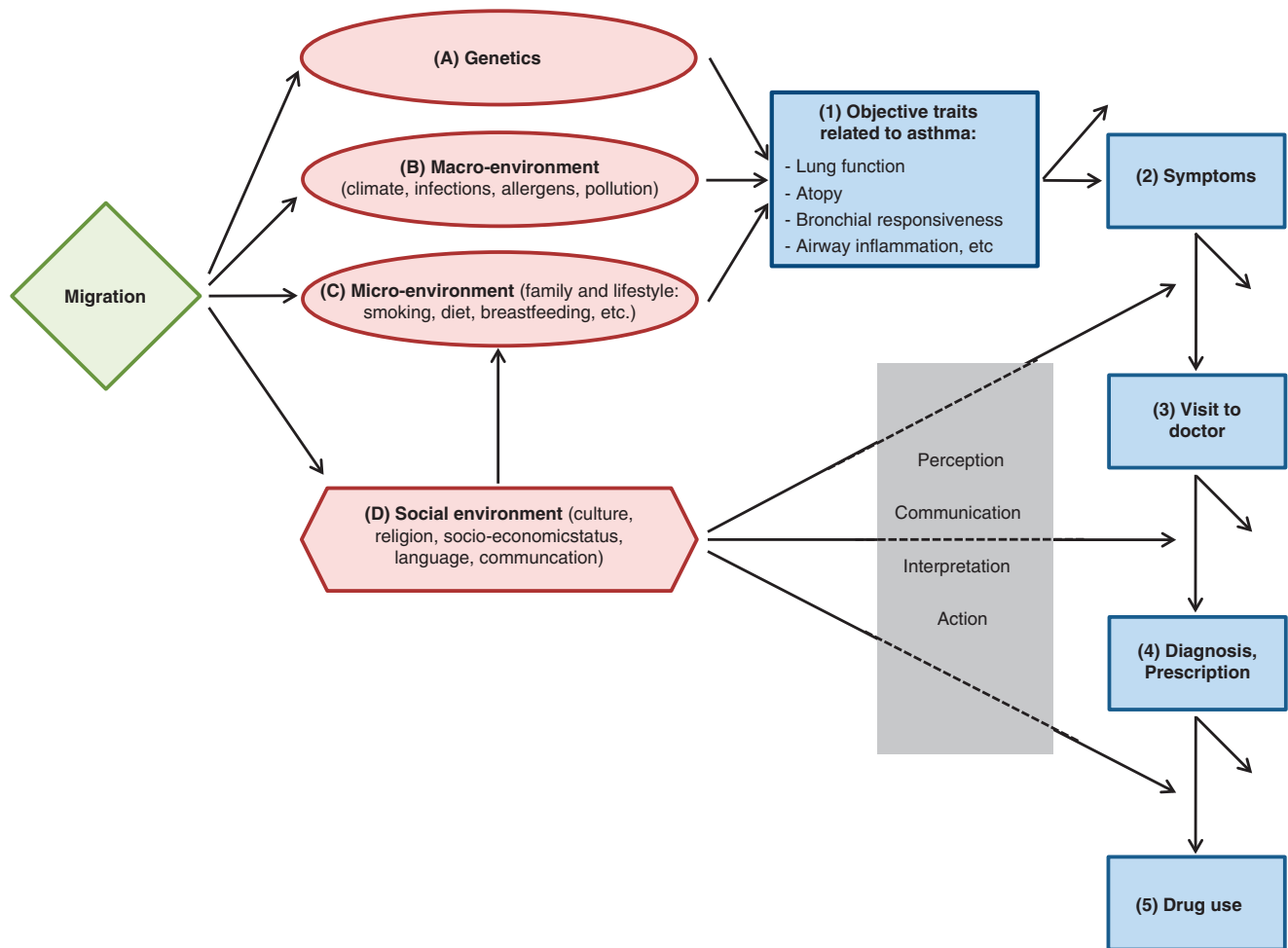


Fig. 1. Causal mechanisms and asthma-related outcome measures in migrant studies. Red circles: different categories of potential causative factors related to migration (A–D); blue squares: asthma-related outcomes typically assessed in studies (1–5).

as breastfeeding, diet, tobacco-smoke exposure or indoor allergens. The *red hexagon* (D) symbolizes the social environment built up by culture, religion, language, communication or socio-economic factors. These can affect family environment and lifestyle, but also modulate the way symptoms are perceived, reported, diagnosed and treated [11–13].

To identify environmental causes for asthma, it is easiest to focus on objectively measurable outcomes that are close to the causative factors and mechanisms (1). Instead, most migrant studies reported on outcomes further down the chain (symptoms, health-care visits, treatment). In asthma, diagnosis is difficult and the line between normal and pathological blurred. Most cases are mild and survive with or without treatment. In this type of disease, socio-cultural factors might in fact be much stronger determinants of treatment than the subtle influences of the physical environment, which lead to small developmental deviations of immune system and lung growth. Other common limitations of published studies on

migrants include: insufficient assessment and analysis of socio-economic factors; unknown age at immigration and duration of residence in the host country; a study population of mixed ethnicity; small sample sizes; poor response rates (participation bias) or language problems for self-reported outcomes (differential misclassification).

The Swedish study

In this issue of *Clinical and Experimental Allergy*, Bråbäck, Vogt and Hjern analysed the association between migration and asthma medication (inhaled steroids) in Sweden [14]. They had access to routine data on region of birth, date of immigration, socio-economic characteristics and parental origin from all 6- to 25-year-old residents of Sweden (nearly 2 million people), leaving little room for participation bias. Using a personal identifier, the authors linked this information to the database of all dispensed drugs in Sweden and assessed type and number of dispensed asthma inhalers. The study population included

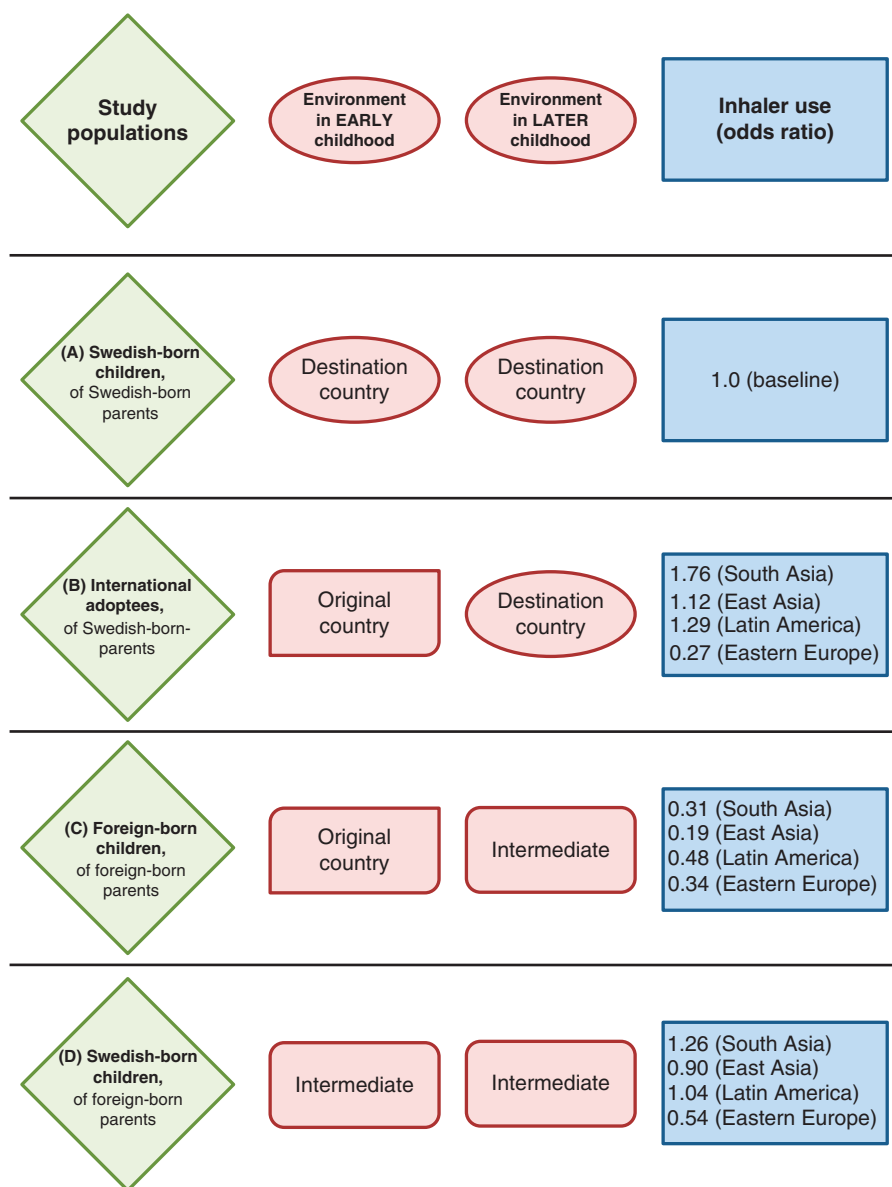


Fig. 2. Environmental exposures in early and later childhood in four groups of participants. Native population (A), international adoptees (B) and first- (C) and second- (D) generation immigrants (adapted from Braback et al. [14]). Original country: environmental and social exposures typical for the country of origin; destination country: exposures typical for the host country; intermediate: exposures typical for first- (much less for second-) generation immigrants (family environment, lifestyle, language and other socio-cultural factors).

four distinct groups (Fig. 2): 1.77 million Swedish-born children with Swedish-born parents (A), 24 252 international adoptees of Swedish-born parents (B), 47 986 foreign-born children of foreign-born parents (C) and 40 971 Swedish-born children of foreign-born parents (D). Immigrants came from four distinct regions, one with a temperate climate (Eastern Europe) three with tropical or subtropical climates (South Asia, East Asia, Latin America).

Environmental exposures in early and later childhood (Fig. 2) differed between these groups. Group A was exposed to the macro-, micro- and social environment of

Sweden (destination country) during both periods. Groups B and C both passed their first years in an environment typical of their country of origin (original country) and experienced a sudden change when they immigrated. While children adopted by (mainly upper class) Swedish families (B) were immersed into a Swedish micro- and macro-environment, children who immigrated together with their parents (C) proceeded to live in an intermediate situation, with a Swedish macro-environment but a micro-environment and social environment still influenced by their place of origin. The last group (D), Swedish-born children of foreign-born parents, spent both early and late

childhood in such an intermediate situation. This study design thus has potential to disentangle effects of early environmental exposures (before migration) from later environmental and socio-economic influences after migration.

What did they find?

Inhaled corticosteroids (ICS) during the past year were purchased by 7.5% of native Swedish people (group A). Most of these must have mild episodic asthma, as only one-third purchased two or more prescriptions in the past 12 months. This means that they needed inhalers only for days or weeks and some might have been wrongly diagnosed. Compared with this group, ICS use was (Fig. 2):

- higher in international adoptees (group B) from South Asia, East Asia and Latin America [odds ratio (OR) of 1.76, 1.12 and 1.29], but lower in those from Eastern Europe (0.27);
- markedly lower, with OR between 0.19 and 0.48 in new immigrants (group C), for all regions of origin;
- comparable or lower for Swedish-born offspring of foreign-born parents (group D), depending on region of origin (OR of 0.54 for Eastern Europe, 0.90 for East Asia, 1.04 for Latin America and 1.26 for South Asia).

Adjusting for age, sex, urban residency and socio-economic factors, younger age at immigration remained strongly associated with ICS use. Similarly, origin from South Asia remained associated with a higher and origin from Eastern Europe with a lower treatment frequency.

These data allow some cautious conclusions:

1. Low prevalence of 'asthma' in new immigrants is likely to be explained to a large extent by micro-environment (family lifestyle and indoor exposures) and socio-cultural factors, both acting during later childhood. This follows from the large differences in asthma prevalence between international adoptees and children who immigrated with their families. Both had a similar early environment and similar late macro-environment, so that differences in outcomes can only be caused by differences in family and social environment in later childhood.
2. This paper, together with earlier publications [15–17], suggests that there are important differences between regions of origin. In particular, adoptees from Eastern Europe had a lower and adoptees from South Asia a higher use of ICS than natives or immigrants from other regions. One explanation for this is genetic. Le Souef suggested that populations whose immune system has adapted to a tropical environment with more parasitic disease might deviate towards an allergic response when relocating to an environment with less microbial exposures [18]. An alternative, more prosaic explanation is diagnostic bias: doctors diagnose asthma (and prescribe ICS) preferentially in patients with lower lung function and more allergies. South Asians have up to 15% lower lung volumes than whites for the same age and height [19]. As spirometers lack ethnic-specific norm values, lung function of

these children wrongly appears to be abnormal. Similarly, the high prevalence of allergies in South Asian immigrants [16, 20] might contribute to a physician's decision to prescribe ICS, even though only a proportion of asthma, if any, is attributable to allergy [21]. The low rates of ICS use in immigrants and adoptees from Eastern Europe are consistent with reports from Finnish and Russian Karelia [17], where strikingly different proportions of atopy among asthma patients suggest important differences in aetiology.

3. In international adoptees and children who immigrated with their parents, lower age at immigration was associated with higher ICS use [14]. Again, this can be explained at least in two ways. First, a causative effect of early environment, which would not be restricted to prenatal environment – rather the results suggest a dose response to cumulative life years. The second explanation is a 'healthy immigrant effect': as parents tend to adopt healthy children and asthma usually begins in the first years of life, children adopted (still healthy) at a later age will be less likely to have asthma at school age or adulthood than their peers adopted earlier.

What lessons can we learn for planning future studies?

Even such an extraordinary national dataset as the one from Sweden therefore leaves a number of open questions and leads to speculations rather than firm conclusions.

1. Research including simultaneously international adoptees and children raised by their own (migrated) parents is helpful to disentangle early environmental from later social exposures.
2. Region of origin matters. Further research could profit from investigating differences between immigrants from different regions (particularly South Asia and Eastern Europe).
3. Age at immigration and duration of living in the country should be assessed and, if possible, looked at separately.
4. Objectively measurable outcomes (lung function, BR, atopy or inflammatory measures) are preferable for investigating environmental effects in migrants, because they are relatively close to causes and mechanisms and not affected so much by the social environment as are asthma diagnosis or treatment.
5. However, these traits are related to but not identical with asthma. The extent to which these traits contribute to complex phenotypes, such as atopic multi-trigger wheeze or non-atopic viral wheeze [22], seems to differ between populations [16–17]. Looking at complex phenotypes might be necessary to gain more insight into asthma pathogenesis.

An ideal study would collect serial prospective measurements of several outcomes in migrants, beginning at the time of immigration or even before. This could show whether and how these measurements deviate from the norm with increasing duration of residence in the host country. Age-matched peers from both the host country and the country of origin with similar serial measurements could serve as control groups. Given the

largely uncontrollable dynamics of human migration, such a project is unlikely to happen. However, if some of the elements discussed above will be systematically incorporated in future migrant studies, these might indeed contribute important pieces to the big puzzle of the aetiology of bronchial asthma.

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