Epidemiology of Atopic Eczema 3

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3.1 Definitions

The term "epidemiology" derives from the Greek "epi" (over) "demos" (the people) and "logos" (teaching). According to MacMahon and Trichopoulos, it can be defined as "the study of the distribution and determinants of disease frequency" [1]. Considering this definition, epidemiology does not only help to define the disease burden in the population by a valid estimate of the disease frequency in different subgroups and different populations, but also contributes to the understanding of the pathogenesis by identifying and investigating disease determinants that may play a role as risk factors and may serve as a basis for the development of specific prevention strategies.

Several synonyms exist to describe the chronic inflammatory skin disease atopic eczema (atopic dermatitis, endogenous dermatitis, neurodermatitis, etc.). A European working group has revised the nomenclature in allergy in 2001 and coined the term "atopic eczema/dermatitis syndrome" (AEDS) [2]. In 2003 the WAO, however, returned to the terms atopic and non-atopic [20].

3.2 Diagnostic Criteria

There is no single diagnostic parameter available that could validly discriminate cases and non-cases of atopic eczema. Therefore, the gold standard of a diagnosis of atopic eczema is still based on a clinical assessment, preferably by persons who are experienced with the disease. Such a clinical assessment, however, is mostly impractical in large epidemiological studies. Although a clear definition of what constitutes atopic eczema is lacking, several parameters that should help make a diagnosis have been determined over the past decades. Back in 1975, Rajka summarized such diagnostic major and minor criteria and later published a revision of these, which has gained wide acceptance as the Hanifin and Rajka criteria [3]. These criteria, however, have not been validated in large population-based settings and for this reason the UK working party on diagnostic criteria for atopic dermatitis has undertaken the task of thoroughly validating these criteria in clinical as well as population-based settings. As a result, the UK refinement of the Hanifin and Rajka criteria was published in 1994 [4–6]. According to this refinement, a diagnosis of atopic eczema can be made when an itching skin condition is present and at least three of the following five criteria are fulfilled:

1. History of involvement of skin creases such as folds at elbows, behind the knees, front of the ankles, or around the neck (including cheeks in children under 10).
2. Personal history of asthma or hay fever (or history of atopic disease in a first-degree-relative in children under 4).
3. A history of general dry skin in the last year.
4. Visible flexural eczema or dermatitis involving the cheeks, forehead and outer limbs in children under 4.
5. Onset under the age of 2 (not used if child is under 4).

These criteria have been validated in large clinical as well as population-based settings and in different countries with specificity ranging between 90% and 99% and sensitivity between 58% and 96% (exception, Iran 10%) [7–11]. The instrument therefore makes it possible to easily make a valid diagnosis of atopic eczema, especially in epidemiological studies.

3.3 Assessment in Epidemiological Studies

Atopic eczema can be assessed in several ways. The diagnosis made by a dermatological examination might be looked upon as gold standard, which has also been used for validation of the diagnostic criteria mentioned above. Since clinical examinations are not practicable in most epidemiological studies, information on atopic eczema is obtained from questionnaires or interviews. The corresponding questions may focus either on disease-specific symptoms or a history of a physician's diagnosis of atopic eczema. Several standardized instruments for the assessment of atopic eczema such as the questionnaire of the ISAAC (International Study of Asthma and Allergies in Childhood), used worldwide, exist [12, 13]. It is obvious that studies using different means of assessment are hardly comparable.

3.4 Measures of Frequency

Different measures of frequency are reported by different studies. A clinical examination would usually result in reporting a point prevalence, whereas questionnaires may assess eczema that has ever occurred during a given time period such as the previous year or during the lifetime, which results in reporting a period prevalence. Usually, in a prospective setting, the number of newly developed cases can be counted over a specific time period and reported, provided that the group under investigation was healthy at the beginning, as cumulative incidence or incidence rate. It becomes clear again that studies are not comparable when different measures of disease frequency were used.

3.4.1 Frequency of Atopic Eczema in Children

Some early international publications of the years 1939 to 1964 provide data on the frequency of eczema (not necessarily atopic) of samples of the general population. The frequency ranges between 1.1% and 3.1%. Numerous studies of the 1980s and 1990s revealed frequencies of up to 26% for questionnaire-based and 32% for studies that included a dermatological examination (summarized in [14]). Worldwide and profound data based on a standardized methodology were for the first time achieved by the ISAAC study. In 90 centers 256,410 children aged 6–7 years and in 151 locations 458,623 children aged 13–14 years were investigated in a total of 56 countries (Fig. 3.1). The study confirms a high worldwide variation of the disease, for younger children ranging between 1.1% in Iran and 16% in Japan and Sweden. For children 13–14 years old, the prevalence ranges between 1% in Albania and 17% in Nigeria. Overall, the prevalence seems to be higher in Australia and Northern Europe and lower in Asia and Central and Eastern Europe [12].

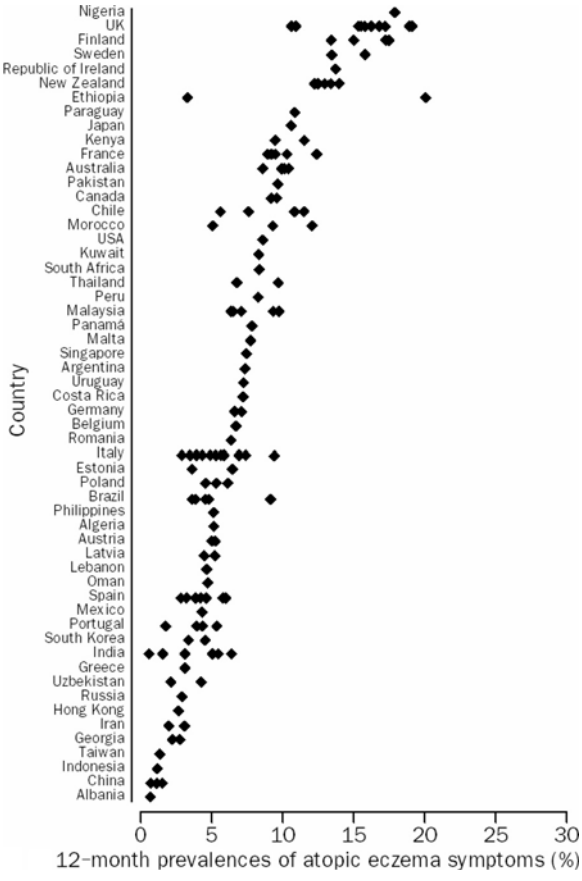

Fig. 3.1. Worldwide prevalence of atopic eczema in 458,623 children (aged 13–14 years). From ISAAC [13], with permission

3.4.2
Frequency of Atopic Eczema in Adults

Far fewer studies have evaluated the frequency of atopic eczema in adults either by questionnaire or clinical examination. The results range from 1 % in recruits at the time of inspection to 5.1 % for a lifetime prevalence according to a physician's diagnosis (summarized in [15]). The point prevalence of a sample of the inhabitants of the City of Hamburg was 3.4 % according to clinical examination [16]. Marked differences in the lifetime prevalence of reported physician-diagnosed atopic eczema in adults were reported between a region in Finland (17.7 %) and Russia (7.9 %) [17].

3.5
Trends and Frequency of Atopic Eczema

Several, especially European, studies have evaluated the prevalence for atopic eczema over a longer period of time using the same methodology. All studies resulted in a marked and mostly significant increase in the prevalence for atopic eczema. A summary of these studies is given in Fig. 3.2. The reasons for this increase, however, are still unclear, although several risk factors that were attributed to the Western lifestyle could be identified. Some recent studies suggest that the increase could level off to a plateau.

3.6
Atopic Eczema in East and West Germany

Between 1991 and 2000, over 33,000 preschool children were investigated in several locations of the Federal States of Saxony-Anhalt and North-Rhine-Westfalia. By questionnaire, an ever diagnosed atopic eczema and the occurrence of an itchy rash during the past year were recorded. In a subset of study sites, a total of 4,500 children were also examined dermatologically. Overall, 15.5 % of the children in East and 12.7 % of the children in West Germany gave a positive history of an atopic eczema ever diagnosed by a physician. This difference between both parts of the country was consistent for the entire observation period and statistically significant (OR 1.92; CI 1.09 – 1.31). In West as well as East Germany, the prevalence of physician-diagnosed atopic eczema increased significantly over the observation period. This trend, however, was more pronounced in East Germany and can in part be explained by a changing medical awareness and diagnosis (Fig. 3.3). The East–West-German differences are also reflected by reports of an itchy rash during the past year, which for the year 2000 was given as 6.2 % in East and as 4.7 % in

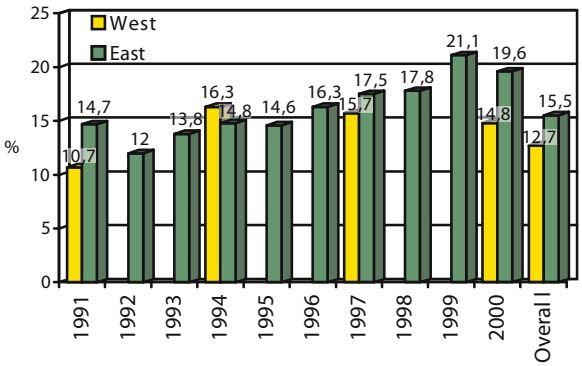

Fig. 3.3. Trends in the prevalence of physician-diagnosed eczema (ever) in 33,440 preschool children from West and East Germany. Time (increase) OR 1.71 (CI 1.51 – 1.93). East vs West OR 1.92 (CI 1.09 – 1.31)

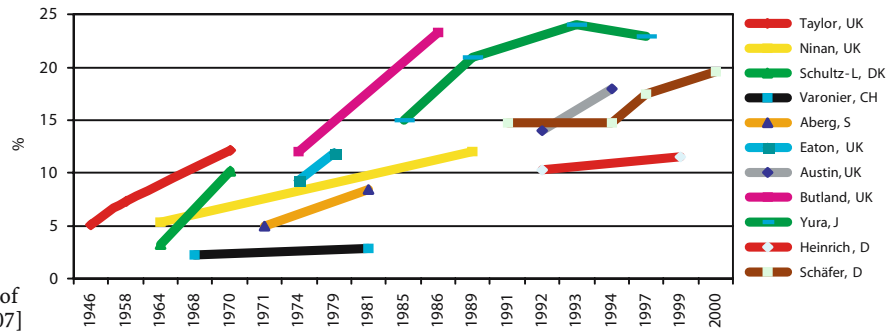

Fig. 3.2. Trends in the frequency of atopic eczema. From [27, 98 – 107]

West Germany. This difference was also statistically significant for the entire observation period (OR 1.34; CI 1.08 – 1.67). In the year 2000, a total 5.2 % of children suffered from actual atopic eczema according to clinical examination. Again, differences between East (5.9 %) and West Germany (4.5 %) were observed and significant for the whole group (OR 1.64; CI 1.34 – 2.02) [18 – 20].

3.7 Intrinsic and Extrinsic Atopic Eczema

Following the concept that has long been known for asthma, atopic eczema might be separated into extrinsic and intrinsic subtypes according to concomitant type I sensitization. Therefore, it is reasonable to assume that the proportion of extrinsic type atopic eczema is higher in hospital-based than population-based samples. Hospital-based estimates for the percentage of extrinsic eczema from Hungary and France range from 54.2 % [22] to 84.5 % [21]. According to a French report on 250 children, allergic sensitization to food allergens and aeroallergens was absent in mild cases and detectable in 33 % of moderate and all cases of severe eczema [23]. Summarizing the investigations in East and West Germany from 1991, 1994 and 1997 we have investigated subtypes of atopic eczema according to skin prick test reactivity to common aeroallergens. According to these results, 42 % of the children with atopic eczema exhibited an extrinsic type. Interestingly enough, the proportion of the extrinsic type was significantly higher in West Germany (50.4 % vs 36.5 %; OR 1.77, CI 1.12 – 2.79), indicating that factors other than type I allergy contribute to the excess of cases in East Germany [24].

3.8 Risk Factors and Characteristics

3.8.1 Genetic Risk

A parental predisposition still constitutes the largest single risk factor for the development of atopic eczema. This has been investigated intensively, including epidemiological studies in twins. The transmission of a genetic atopy risk has been attributed to several gene loci. The only conclusion at this point can be that the predisposition for allergy and also atopic eczema is not transmitted by a single but multiple gene loci. Ongoing large studies of the genetic epidemiology of atopic eczema may help to further elucidate that important issue [25 – 29].

For further information the reader is kindly referred to Chap. 23 in this volume, “Clinical Genetics of Atopic Eczema” by F. Schultz-Larsen.

3.8.2 Course of the Disease

It is well established that atopic eczema usually manifests very early in life, including the very first weeks after birth. Rajka and colleagues investigated 1,200 patients and reported that eczema occurred within the 1st year of life in 57 % and in 87 % before the 6th birthday [30]. Fortunately, the natural course is characterized by a remission in most cases. According to questionnaire-based follow-ups, the remission rates after 20 years varied between 26 % and 84 % [31 – 33].

This general course does not exclude the clinically well-known late onset of atopic eczema in adulthood. There are clinical impressions that cases with a late onset of atopic eczema have increased, but this has to be investigated systematically. Besides the typical cycling relapsing course of the disease, most patients (56 %–92 %) report a seasonal variation. Therefore, 48 %–65 % of patients notice that eczema regularly worsens during winter months and a similar proportion reports improvement during summer. There are cases, however, of pollen-sensitive atopic eczema, which, in contrast, exacerbate during pollen season, especially in skin areas not covered by clothes [25, 34 – 36].

3.8.3 Gender

In contrast to respiratory atopic diseases, atopic eczema affects more girls. Very few studies report a higher proportion of the male gender, whereas numerous recent studies show a predominance of girls, who are affected up to 2.6 times more often than boys (Table 3.1). Although the reasons for these gender differences are not understood, the results underscore that the characteristics and risk pattern of atopic eczema differ from that of respiratory atopic diseases.

Table 3.1. Gender ratio of atopic eczema in epidemiological studies

Study	Female : male
Eriksson-Lihr et al. [90]	1.4 : 1
Arbeiter et al. [91]	1.3 : 1
Turner et al. [92]	1.0 : 1
Kjellman et al. [93]	1.3 : 1
Larsson et al. [94]	1.7 : 1
Engbaek et al. [95]	1.4 : 1
Schultz-Larsen et al. [29]	1.2 : 1
Storm et al. [96]	1.5 : 1
Schultz-Larsen et al. [97]	1.4 : 1
Schäfer et al. [20]	1.3 : 1

3.8.4 Psychosomatic Factors

It is well established that psychosomatic factors contribute to the manifestation of atopic eczema, which is also indicated by the German term *Neurodermitis* [37, 38]. According to a population-based survey in adults, 35.5 % reported that their skin disease is affected by different moods, especially stress, conflict situations, and leisure time [16]. This might support observations of psychoneuroimmunological, i.e., humoral, associations in the sense of a central itch-stimulation as the chief complaint and primary efflorescence of atopic eczema [39, 40]. Psychosomatic aspects are successfully implemented in multiple educational and management concepts [41].

3.8.5 Socioeconomic Status

The influence of socioeconomic status (SES) and corresponding single parameters on the development of atopic diseases has been investigated in many ways [42]. A positive linear association between parameters of SES and allergic rhinoconjunctivitis or allergic asthma and allergic sensitization have been reported. Concerning atopic eczema, a study from Great Britain showed a significant association with higher social class expressed by the occupational groups of diseased adults [43]. A similar positive association between parental occupational group and atopic eczema in school children was reported in a Swiss study [44] and similarly, the prevalence of atopic eczema in German preschool children seems to be associated with the parental school education [20]. This was confirmed by a further large German study from the City of Hannover investigating 4,219 school entrances. Significant associations between the prevalence of atopic eczema and maternal education as well as paternal occupational category were observed [45]. Although many explanatory hypotheses have been generated, this consistent association between SES and atopic eczema remains largely unexplained.

3.8.6 Hygiene and Immune System

Results of studies concerning viral infections early in life or vaccination and development of atopic diseases are not consistent. Taking the example of measles infection and vaccination, a large population-based study from Denmark investigated the association with atopic eczema in 9,744 children aged 3 – 15 years. The cumulative incidence of atopic eczema in the 14-year-olds was 19.7 %. The majority of the children (93.3 %) had received measles vaccination and another 5 % developed the infection. An elevated eczema incidence was observed after measles, mumps, and rubella vaccination (OR 1.64; CI 1.24 – 2.16). However, the risk of atopic eczema was even higher for those who developed measles infection (OR 1.91; CI 1.04 – 3.51) [46]. A history of measles infection was found to be associated with both a higher and lower rate of different manifestations of atopy [47 – 49]. This makes it difficult to draw evidence-based conclusions at the present stage. Taking these conflicting study results and the large beneficial effects of vaccination into account, there is no reason to change the current recommendations on vaccination in the hope of achieving a preventive effect on atopic diseases.

Considering the concept of a TH1/TH2 dichotomy, the epidemiological observation of a negative association between juvenile diabetes (TH1) and atopic eczema (TH2) is of further interest [50, 51]. Similarly, it was reported that a higher gestational age increases the risk for atopic eczema (> 40 weeks vs 39 – 40 weeks; OR 1.32, CI 1.06 – 1.63) [52].

3.8.7 Nutrition

Atopic eczema is not a food allergy per se but in some cases the skin disease can be provoked by certain food allergens. The meaning of food allergens, however, might largely be overestimated especially by patients

or their carers, probably driven by the wish for a (single) cause that can be understood easily and be prevented. Investigations of hospital-based samples of children with atopic eczema revealed that food allergens were able to provoke an eczema exacerbation in 32 %–40 % [53 – 57]. Accordingly, this proportion is much lower in unselected patient groups (15 %–27 %) [23, 58]. Interestingly, the allergen spectrum that is responsible for more than 90 % of the reactions (hen's egg, cow's milk, wheat, soy, peanuts, and fish) remained the same when comparing investigations of the late 1980s to the late 1990s [59].

When it comes to prevention, the beneficial preventive effect of breast feeding is well confirmed. The meta-analysis of Gdalevich and co-workers revealed a significant preventive effect in the overall group and the subgroup of children with a genetic predisposition [60]. The beneficial effect has recently been shown in a large population-based randomized trial from Belarus. A total of 16,491 newborns were investigated over 1 year. In half of the participating obstetric clinics, a breast feeding-promotion program was implemented. As a result, children of the intervention group were breast-fed significantly more frequently and longer, and the prevalence of atopic eczema was almost halved (3.3 %) compared to the control group (6.3 %). This difference was statistically significant after control for genetic predisposition (OR 0.54; CI 0.31 – 0.95) and underscores the meaning of breast feeding as a measure of primary prevention [61]. Following the results of a Cochrane review, restrictions in the maternal diet during the last trimenon of pregnancy or during lactation have no significant influence on eczema prevalence [62, 63]. The delayed introduction of further food allergens in the child's diet, however, seems to have some preventive effect on atopic eczema [64, 65].

The prospective and randomized German Infant Nutrition and Prevention Study (GINI) provides valid data on the preventive effect of several formulas. In summary, all hypoallergenic formulas are capable of reducing the incidence of atopic eczema after 1 year in children without a genetic predisposition. In contrast, the incidence of atopic eczema was reduced in children with a positive history of atopic eczema in the family only when extensively hydrolyzed casein-based formulas were used [66].

The preventive potential of probiotics was investigated in a prospective randomized trial from Finland, in which 2×10^{10} CFUs of lactobacillus GG vs placebo were given to mothers 2 – 4 weeks before delivery and 6 months after to the lactating mothers or their children. After 2 years, the prevalence for atopic eczema was 23 % in the intervention group and half as high as in the control group [67]. Further studies will show whether this approach offers an easy and effective measure of prevention that obviously also has a therapeutic effect.

3.8.8 Aeroallergens: House Dust Mites

House dust mite allergens have long been known as a provocation factor for atopic eczema [68]. The efficacy of measures to reduce the allergen load of house dust mites was investigated in several randomized controlled trials focusing both on the allergen load and clinical endpoints. The majority of these studies indicate a beneficial effect, although some smaller studies were not able to confirm this [69 – 72]. The clinical association between atopic eczema and a sensitization to house dust mites was shown in an epidemiological study in 2,201 school children. A significant linear association between the degree of sensitization (kU/l) to house dust mites and the severity of atopic eczema (intensity score) was reported [73].

3.8.9 Pets and Farms

The impact of furry pets on the manifestation of atopic diseases is being discussed controversially at present. Prior studies support the current recommendations for prevention and indicate that pet keeping is a risk factor at least for at-risk babies [74]. On the other hand, more recent studies indicate that a specific allergen load might also have a preventive effect [75]. In contrast to respiratory atopic diseases, there is very little information on this issue for atopic eczema. According to some German epidemiological investigations, small rodents seem to be a risk factor for atopic eczema. For school children, an elevated risk for atopic eczema was reported when rabbits (for girls, OR 2.90, CI 1.36 – 6.19) [20] or guinea pigs (OR 3.56, CI 1.68 – 7.54) [76] were kept in the household.

A cohort study from Norway reported a preventive effect of cat keeping that was restricted to the genetically predisposed group and therefore raises questions whether differential behavior has led to this associa-

tion [77]. The review of German cross-sectional studies revealed preventive effects by dog keeping, which was again restricted to a group of genetically predisposed children [78]. Results of the prospective GINI study also indicate a preventive effect of dog keeping on atopic eczema. It is worth mentioning from a methodological point of view that the GINI cohort is enriched in at-risk children and that dog keeping was significantly less frequent in the genetically predisposed group [79]. A careful methodological interpretation of these results is necessary, since selective behavior of the genetically predisposed group might lead to false associations.

There is strong evidence from several studies that growing up on a farm can reduce the frequency of allergic sensitization and respiratory allergies [80]. The exposure to endotoxins is being discussed and investigated as a likely mechanism of action [81]. Such preventive effects, however, have not been reported for atopic eczema. The prospective birth cohort study LISA (investigation of Lifestyle on the development of the Immune System and Allergies, in East and West Germany) revealed that the prevalence of eczema, but not atopic eczema, was significantly reduced after 6 months under the condition of a high endotoxin load (OR 0.50, CI 0.28 – 0.88) [82].

3.8.10 Other Environmental Exposures

Several studies have linked the manifestations of atopic eczema with parameters of air pollution. Within the investigation in East and West Germany, a significant linear association between surrogate parameters of indoor NOx exposure (use of gas with/without hood, no gas) and the prevalence of atopic eczema (16.5 %, 14.9 %, 10.8 %; $p_{trend} = 0.02$) was observed. Similarly, the distance of the residence to a high-traffic road (< 50 m, 50 – 500 m, > 500 m) was linked with the frequency of atopic eczema (14.9 %, 11.7 %, 7.9 %; $p_{trend} = 0.04$) [20]. Results of the German part of the ISAAC study revealed significant linear associations between atopic eczema in 6- to 8-year-old children and the truck traffic density, i.e., the corresponding traffic noise [83]. Exposure to volatile organic compounds, especially toluene, was also found to be associated with atopic eczema in children [84].

Furthermore, environmental tobacco smoke (ETS) has been described as being associated with atopic eczema. According to a study in 421 preschool children, the risk for atopic eczema was more than doubled if the mother had smoked during pregnancy and lactation (OR 2.30, CI 1.32 – 3.12) [85]. Actual ETS exposure, as measured by cotinine levels, was also found to be associated with atopic eczema in preschool children (OR 1.97, CI 1.23 – 3.16) [86].

3.9 Prognostic Factors

Few studies have investigated prognostic factors of atopic eczema in a prospective fashion. An early report from Sweden suggests that persistent dry/itchy skin in adult life, widespread dermatitis in childhood, associated allergic rhinitis, family history of atopic eczema, associated bronchial asthma, early age at onset, and female sex were associated with persistence [87]. From the British Birth Cohort, it was reported that a personal history of respiratory atopic diseases, onset within the 1st year of life, and a history of pertussis are predictors of a poor outcome [88]. Similarly, a Swiss observation of patients concluded that an early onset (< 6 months) combined with severe eczema, single children, high IgE levels, and respiratory diseases are factors that lead to a poor prognosis [89].

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