Clinics in Dermatology (2015) **33**, 281–288

ELSEVIER

Clinics in Dermatology

Epidemiology of childhood atopic dermatitis

Nitin Garg, MD[a], Jonathan I. Silverberg, MD, PhD, MPH[b,*]

[a]*Department of Dermatology, Northwestern University Feinberg School of Medicine, Chicago, IL*
[b]*Departments of Dermatology, Preventive Medicine and Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL*

Abstract Atopic dermatitis (AD) or eczema is a chronic inflammatory skin disorder with significant morbidity and quality of life impairment. Elucidating the epidemiology of AD is important for understanding disease risk factors and facilitates development of interventions for disease prevention. This contribution aims to summarize recent developments in the epidemiology of AD, including the US prevalence, regional differences, and secular trends of disease prevalence, genetic and environmental determinants, distribution, and determinants of disease severity and health care use for AD.
© 2015 Elsevier Inc. All rights reserved.

Introduction

Atopic dermatitis (AD or eczema) is a chronic inflammatory skin disorder with significant morbidity and quality of life impairment. In addition to an exasperating itch-scratch cycle, AD is associated with numerous comorbidities and a significant risk of secondary complications, such as infection.[1–4] Although considered by many a "minor" disease of childhood, the burden of disease extends into adulthood as well[5] and profoundly affects overall family functioning. It is, therefore, of minimal surprise that there are tremendous health care costs associated with AD.[6]

Observations over the last few decades have found increasing trends of AD over time, with prevalence distributed unequally across the globe. Although genetic disposition clearly plays a role, gene-environment interactions likely explain much of the international variation in prevalence rates. Examples of potential environmental modulators include climactic variation, pathogen exposure, allergen exposure, and diet, factors which may confer protection, or on the other hand, act as risk factors. Further, genetic modulation likely plays a role in the geographic differences associated with the disease.

Elucidating the epidemiology of AD will facilitate efforts to identify modifiable risk factors and improve patient health by preventing future disease. Research over the last decade has made substantial contributions to this effect. We summarize recent important developments in the epidemiology of AD, including prevalence values, genetic and environmental determinants, distribution and determinants of disease severity.

Prevalence of childhood AD

Until recently, epidemiologic data about AD were lacking in the United States. In contrast, estimates of AD prevalence in most other countries were generated from the International Study of Asthma and Allergies in Childhood (ISAAC). This international epidemiologic research collaboration provided a global map of AD, allowing for comparison of prevalence estimates between different countries by using standardized methodology.[7] One study analyzed data from 385,853 participants ages 6 to 7 and 663,256 participants ages 13 to 14 in the ISAAC phase 3 study.[7] They found a wide variation

* Corresponding author. Tel.: +1 312 503 4985.
E-mail address: JonathanISilverberg@gmail.com (J.I. Silverberg).

http://dx.doi.org/10.1016/j.clindermatol.2014.12.004
0738-081X/© 2015 Elsevier Inc. All rights reserved.

in prevalence values worldwide, from 0.9% in India to 22.5% in Ecuador at ages 6 to 7 years and from 0.2% in China to 24.6% in Colombia at ages 13 to 14 years. This study, along with other smaller population- and/or community-based studies suggest overall higher AD prevalence in wealthier, developed nations compared with poorer, developing nations.[7–17]

In recent years, major strides have been made with respect to the epidemiology of childhood AD in the United States. A study of Oregon schoolchildren ages 5 to 9 years found AD prevalence of 17.2% using a self-administered questionnaire and 11.8% using the question "has a doctor ever said that your child has eczema?"[18] There were limitations of low response rates in certain regions and the survey was limited to a single state, which left a number of unanswered questions about the epidemiology of AD in other pediatric age groups and other states.

Subsequently, another study used self-administered surveys of 42,249 households in 1998. Using complex weighting based on ethnicity and other demographic factors and response bias, the study was found to be representative of 116,202 individuals, including children and adults. They found that 17.1% of individuals had at least one of four eczematous symptoms, 10.7% had empirically defined eczema, and 6% had empirically defined AD.[19] Extrapolation of these prevalence estimates to the total US population of 296 million in 2005 indicated an affected population of 31.6 million people with empirical eczema criteria and 17.8 million people with empirical AD criteria. This study did not distinguish between children and adults and did not present prevalence estimates stratified by age, which precluded definitive conclusions about the prevalence of eczema or AD in children per se.

In 2010, the first AD prevalence estimates from a true US population-based study were published. They analyzed data from 102,353 children ages 0 to 17 from the National Survey of Children's Health (NSCH), which randomly sampled >1800 households in each of the 50 states. This study used complex weighting based on race, ethnicity, gender, age, etc. to generate prevalence estimates that were generalizable to the entire pediatric population in the United States. AD was defined by a positive response to the question "during the past 12 months, have you been told by a doctor or other health professional that (child's name) had eczema or any kind of skin allergy?" They demonstrated a 10.7% prevalence of AD in the United States, with significant variation between states and districts (8.7%-18.1%).[17] Although limited by the caregiver-reported nature of eczema, this study provided the first US population-based study of childhood AD.

It is difficult to compare the previously mentioned estimates to those from other countries due to differences in methodology, including varied questionnaires, sampling, age groups, and scale. The ISAAC phase 1 study (data from 1994 to 1995) sampled more than 7000 US children age 13 to 14 years and found that the United States had the 17th highest prevalence of AD in the world.[20] Of note, the children were recruited from Chicago and Seattle, which may not reflect the entire US population and perhaps underestimate the prevalence of AD in the United States compared with other countries. Nevertheless, the prevalence of AD appears to be higher in the United States than most developing countries.

The conventional dogma has been that childhood AD dissipates or "burns out" as one approaches adulthood. Epidemiologic data on adult AD in the United States has been even sparser than childhood AD. International studies of AD in adults found prevalence ranging from 2.0% to 6.9%,[21–25] likely attributable to a combination of methodologic and regional differences.

Recently, a study of adults (ages 18–85 years) from the 2010 National Health Interview Survey randomly sampled 27,157 adults from a nationally representative cohort from all 50 states and assessed for self-report of eczema using an in-person survey. The 1-year prevalence of eczema was 10.2%,[5] which was dramatically higher than expected. The prevalence of adult eczema remained high (9.8%) even after exclusion of occupationally related dermatitides (unpublished data).

Is the prevalence of childhood AD increasing?

For the last few decades, evidence has suggested a genuine increase in the prevalence of AD worldwide.[26] The CDC recently released a report analyzing NHIS data from 1997 to 2011 to assess US trends in the prevalence of eczema, which was defined as a positive response to the question, "During the past 12 months, has your child had eczema or any kind of skin allergy?" Among children ages 0 to 17, the prevalence of eczema increased from 7.4% in 1997 to 1999 to 12.5% in 2009 to 2011.[27] A recent questionnaire-based survey of schoolchildren ages 7 to 14 in Norway also demonstrated increases in AD prevalence over time. They compared a 2008 parental questionnaire (n = 4150) to identical questionnaires distributed in 1985 (n = 4870) and 1995 (n = 4456), demonstrating an increase in the prevalence of "current eczema" from 6.4% in 1985 to 13.5% in 2008.[28]

The above studies have been limited to a single population, however, which limits generalizability to other populations. One cannot extrapolate the results of these studies to the other countries. In fact, recent evidence pooling data from different centers across the world (as opposed to single populations) has challenged the notion that eczema prevalence is increasing. A comparison of ISAAC phase 1 (1994–1995) and ISAAC phase 3 (2001–2003) data showed that average prevalence changes were generally small, with prevalence in the 13 to 14 age group leveling off or decreasing in areas with previously high AD prevalence.[29] In comparison, AD levels in developing countries continued to increase for the 13 to 14 age group, and AD levels in the 6 to 7 age group showed consistent increases for most centers. This may suggest a finite number of individuals are

susceptible to atopic dermatitis, and therefore, areas of previously high prevalence are now leveling off.[29] A recent systematic review also reveals no clear trends in the worldwide incidence and prevalence of AD from 1990 to 2010, but did provide evidence for prevalence increases in areas of Africa, Eastern Asia, and areas of northern Europe, including the UK.[30] Overall, there was inadequate study coverage worldwide, with the existing evidence complicated by a large variety of outcome measures and varying disease definitions used across different studies. If AD is truly increasing, a variety of factors, such as the rapid demographic transition of developing nations, vaccination campaigns, modernization, improving sanitation, and increased use of western medicine and antibiotics may play a role. Further, the secular increase of AD prevalence across the world is likely not related to genetic factors alone.

Determinants of childhood AD

Studies over the last few decades have revealed racial disparities in the expression of AD. A study in 1995 examined racial disparities in 693 London schoolchildren ages 3 to 11. The group administered parental surveys and employed dermatologists to independently examine each child, attempting to account for bias that may be present in self-reported surveys. They found that London-born black children of Caribbean descent had a higher prevalence of AD than white children.[31] This study was limited to only black children of Caribbean descent in London, and may therefore not be generalizable to most other populations.

Subsequently, the aforementioned US population-based study, which analyzed data from the NSCH, also found that African-American/black race was significantly associated with higher prevalence of AD, even after controlling for several potential confounding factors, such as household income, health insurance coverage, and parental education level.[17] Similarly, eczema severity was worse in African Americans/blacks and Hispanics.[32] One study found that blacks and Asians in the United States had increased health care use for AD, as they had higher numbers of pediatric visits dedicated to AD compared with whites.[33] Other studies also suggested that African Americans/blacks may be prone to more severe disease compared to Caucasians/whites.[34,35]

The reasons for these racial disparities are unclear. Perhaps there exist differences in genetic susceptibility between races, as studies have found that filaggrin mutations have significantly lower prevalence in black populations.[36–38] Some authors posited there is greater transepidermal water loss (a sign of defective barrier function), higher immunoglobulin E (IgE) serum levels, and larger mast cell granules in African Americans.[34] Future research regarding the expression, distribution, and characteristics of AD in minority populations is needed. This would allow for a better understanding of the underlying disease processes and may lead to improved targeted interventions for these populations.

Evidence also suggests a slight preponderance of AD in women. A 1996 study examined 3000 school children (age 7) in Denmark, Germany, and Sweden.[14] The researchers administered parental questionnaires in public and private schools in representative cities of each country, finding that girls more often had flexural AD, compared to boys.[14] Of note, this study was limited to a single age group among schoolchildren. The ISAAC phase 3 study evaluated more than 1 million children in numerous countries worldwide in two distinct age groups (6–7 and 13–14) and also demonstrated that "current eczema" was higher in girls than boys, especially for the 13–14 age group.[7] The authors suggested that misclassification of irritant or allergic dermatitis, which may be more common in girls (secondary to earrings, bracelets, necklaces, etc.), may be responsible for these reported gender disparities.[7] Even so, increased irritant reactions may be attributable to AD, as there is a lower irritant threshold.[39,40]

Several studies found no associations between gender and AD.[9,17,41] Multiple US population-based studies found no association between gender and AD.[17,41] Similarly, a questionnaire-based study of 12,323 schoolchildren ages 7, 12, and 16 in Singapore, found no differences of AD prevalence by gender.[9] This was a nonpopulation based study, which may not be generalizable to the entire population. The differences between these studies may be related to regional or racial/ethnic variation in gender association.

Differences in socioeconomic status appear to be key determinants of AD prevalence. In 1994, a national birth cohort study in the UK analyzed the influence of "social class" on the prevalence of AD. They followed up on 8279 children at ages 7, 11, and 16, examining the prevalence of parental-questionnaire reported AD, validated by a general physical exam by experienced school medical officers. They found higher prevalence of AD in advantaged socioeconomic groups.[42] This study was limited by the reliance on school medical officer definition of AD. Subsequently, a 2004 study of 4947 children ages 13 to 14 in Cape Town, South Africa found no association with socioeconomic status using the self-administered ISAAC questionnaire.[43] These findings, however, were limited by significant reporting and diagnostic biases, as the authors reported a variety of language barriers that may have made it difficult for study subjects to understand diagnostic terminology. The previously mentioned study of children from NSCH also found higher prevalence of caregiver-reported AD associated with increased household incomes, higher education levels, and smaller family sizes.[17] Finally, the prevalence of AD levels appears to be higher in wealthier, developed nations.[7–17] Together, these findings support a harmful role of a higher socioeconomic status in AD. Future research is needed to determine whether these differences are related to behavioral factors or health care disparities.

Other possible risk factors of uncertain significance include maternal history of atopy and lower birth order.[8,44] In addition, urban and metropolitan living may be associated with AD,[17,45] which may have significance as a part of the broader "hygiene hypothesis," as discussed in detail below.

Genetic epidemiology of AD

The recent discovery of filaggrin gene (FLG) mutations being associated with AD provides support for the role of genetic predisposition for AD. FLG is a protein that binds to and aggregates the keratin cytoskeleton, ultimately allowing for a condensed protein-lipid epidermal barrier.[46] FLG plays a vital role in skin barrier function, allowing for protection against environmental insults and minimal transepidermal water loss. When FLG mutations are present, however, skin barrier function is suboptimal and skin becomes vulnerable to insult by irritants and/or other environmental factors. Multiple meta-analyses subsequently demonstrated that FLG mutations are powerful predictors of the development of AD, and are also associated with increased severity and persistence of disease.[47–49]

Further, it has been suggested that impaired barrier function allows for increased transepidermal penetration of allergens and resulting sensitization, which appears to play a role in the "atopic march" toward asthma and other atopic disease.[50] This is supported by FLG only being associated with asthma in the presence of AD.[48] FLG mutation is even more strongly associated with eczema herpeticum, supporting the role for defective skin barrier function against infections.[51]

The two most prevalent loss-of-function FLG gene mutations, R501 X and 2282 del4, along with several other less prevalent mutations, are present in approximately 10% of people of European origin.[46,52] It is not surprising, therefore, that people with AD have particularly high prevalence of FLG mutation. Small, nonpopulation-based cohort and/or cross-sectional studies of patients with AD have demonstrated varying prevalence of FLG mutation worldwide, ranging from 26% in Northern China,[53] 25% in Japan,[54] 15% in Denmark,[55] 21% in Germany,[56] to up to 46% in the UK.[57] This sharp contrast in prevalence between regions may be in part due to selection biases secondary to patient recruitment from outpatient hospitals and other health care settings, which may select for more severe cases. Different populations do, however, appear to have their own unique mutation spectra.[52] It has, therefore, been suggested that new FLG-null mutations likely arise after one population has split away from another.[52]

A recent longitudinal cohort study examined the prevalence of filaggrin mutations in US children. Eight hundred and fifty-seven children with AD who were enrolled in the Pediatric Eczema Elective Registry (a postmarketing study of pimecrolimus in children age 2 or older) provided DNA samples from saliva, and the authors found that 16.3% of children possessed one or more FLG-null mutations.[36] This nonpopulation-based study was also prone to selection biases, as those with a certain genotype may have been preferentially enrolled.

A population-based design in the UK to attempted to generate accurate prevalence estimates. Eight hundred and eleven children ages 7 to 9 were recruited from a population cohort and assessed for the prevalence of AD along with the presence of 5 common FLG mutations. Overall, 14.2% of children carried one or more FLG mutations. Of AD cases, 18.4% carried 1 or more mutations compared to 12.9% of control subjects.[58] Subsequently, a population-based study of 3301 preadolescent children (aged 11–14) extracted from a longitudinal cohort in Sweden demonstrated that FLG mutations were found in 7.3% of children; 13.5% of children with AD had at least one mutation, compared to 6.5% of children without AD.[59] Because many children are affected by AD at an earlier age than accounted for by the above studies, and may therefore have "grown out" the disease, estimates including earlier age groups may be even more helpful.

Of note, the prevalence of FLG mutations is significantly lower in black populations. Researchers have found that the two most common FLG mutations (R501 X and 2282 del4) were absent in a sample of 124 North Africans.[38] It has also been demonstrated that 27.5% of white children with AD had FLG loss-of-function mutations, as opposed to only 5.8% of African American subjects with AD.[36] A subsequent study by the same group compared the prevalence of FLG mutations between white and African American children with AD and asthma, finding that 4.7% of African Americans in the cohort had any FLG mutation, as opposed to 18.8% of whites.[37] These findings suggest that there may be different genetic profiles in different demographics. More importantly, it suggests that FLG may not be the only genetic modulator in effect.

FLG is the strongest genetic association found to date, but other genes likely play key roles. A 2010 review paper reported a total of 46 genes that have been demonstrated to have an association with AD.[60] Some genes were found to be involved in antigen presentation and immune response, including CD14, interleukin-4 receptor, toll like receptor-2 (TLR-2), etc.; others were involved in cell signaling/movement, including brain-derived neurotrophic factor (BDNF), chemokine (C-C motif) ligand 5 (CCL-5), interleukin-5, etc.[60] One study found that 11.5% of 78 patients with AD had a TLR-2 polymorphism, compared to 2.5% in a control group. Patients carrying this specific gene variant were found to have more severe disease.[61] Later studies demonstrated that impaired TLR-2 expression decreased the secretion of certain inflammatory cytokines, such as interleukins-6, 8, and 2 B,[62,63] suggesting that this may contribute to the increased susceptibility to secondary skin infections with staphylococcus. Similarly, six of 27 AD patients in Japan had a specific polymorphism in the IL-4 R gene, compared to 0 of 28 non-AD controls,[64] although the mechanism of action of this variant is unknown. A recent study found that a missense single nucleotide polymorphism in the human gene *MATT* confers a small, but significant, increase in AD risk.[65] It is likely that a combination of genes involved in the innate and adaptive immune system and skin barrier function interact to produce the phenotype of AD.

Environmental epidemiology of AD

The striking variation of AD prevalence between countries[7,20] and even states within the United States[17] suggests that there are environmental factors that trigger or

flare the disease. Some authors have proposed that this may be due to higher numbers of metropolitan centers with increased pollution.[17] Alternatively, there may be lower exposure to microorganisms in the soil of metropolitan areas compared to their rural counterparts. There are likely a wide variety of factors that cause variation in prevalence of AD from one region to another, such as microbial exposure, dietary habits, or even environmental factors, such as climate and indoor/outdoor environment.

A recent study analyzed data for 91,642 children ages 0 to 17 years from the NSCH. They found that American children born outside the United States had significantly lower odds of developing AD compared with those born in the United States.[66] There was an additive protective effect against AD when the child and parents were born outside the United States. This suggests that behavioral practices in different cultures and ethnicities, such as diet, influence expression of AD. One of the most intriguing findings was that prolonged residence in the United States for 10 years or longer was associated with increased risk for AD. This suggests that prolonged exposure to environmental factors within the United States and perhaps other exposures related to acculturation trigger or aggravate AD. Previous studies in Italy, Israel, and Australia also showed lower prevalence of allergic disease in immigrants compared with native-born persons in those countries.[67–70]

Climate factors are a particular example of environmental factors that may play a role in AD. There is significant variation of climate factors between states and countries, which might account for varying AD prevalence. Researchers have provided evidence for the influence of climate factors on the statewide variation of the prevalence of AD.[41] They performed analyses of merged data from the 2007 to 2008 NSCH and climate factors for the preceding 1 to 2 years from the National Oceanic and Atmospheric Administration. They found significantly lower AD prevalence in areas with higher relative humidity, higher mean temperatures, less indoor heating, higher ultraviolet (UV) index, and lower precipitation. It is possible that higher humidity improves skin barrier function.[71,72] In addition, studies have in fact shown that vitamin D deficiency may contribute toward atopic disease.[73–75] As such, it is possible that greater exposure to UV light enhances cutaneous photoimmunosuppression and synthesis of vitamin D,[73] thereby lowering the risk of AD.

There are likely complex gene-environment interactions that account for the waxing and waning and often variable course of disease. Filaggrin protein appears to be modulated by the environment, possibly amplifying AD risk.[76] Studies in hairless mice show that transfer from a high to low humidity environment may reduce the expression of filaggrin. In humans, areas of the skin that are more exposed to the environment (the cheeks and back of hands) tend to be preferentially affected in those with filaggrin mutation.[76] Future studies are needed to better understand the role of gene-environment interactions in AD and what effect they have on varying prevalence of AD worldwide.

Hygiene hypothesis

The prevalence of AD appears to be higher in wealthier, developed regions, such as the United States, UK, Japan, Australia, and New Zealand, as opposed to developing regions, such as India, China, Iran, and areas of Africa.[7–17] This suggests that some environmental exposures may be harmful toward the development of AD, while others may protect against disease. One example of such protective exposures is early life exposure to certain infections and/or microbial exposures.[77] This is known as the "hygiene hypothesis," which posits that early life exposures steer the immune system away from a proallergic or inflammatory state, thereby decreasing the risk of AD and allergic diseases. It may be that residents of developing countries are exposed to unhygienic exposures, which account for regional differences.

Multiple systematic reviews demonstrated evidence that exposure to endotoxins, helminthes, farm animals, dogs, unpasteurized milk, and early day care is protective against AD.[78–80] In a case–control study, a single episode of varicella-zoster virus (chickenpox) infection in childhood decreased the odds of subsequent AD.[81] This protection existed in cases occurring up to 8 to 10 years of age, not just in the first year of life. A subsequent study reported that varicella-zoster virus (chickenpox) infection up to the age of 8 years is associated with subsequently decreased total IgE levels, peripheral blood lymphocyte, monocyte, and basophil counts,[82] which supports the theory that a change in the milieu of the immune system subsequent to microbial exposure protects against subsequent allergic disorders. These studies emphasize that potentially protective and/or harmful exposures should not be viewed as "all or nothing." Rather, it is necessary to model the age on onset and duration of exposure, which is a key concept of life-course epidemiology.

Of note, not all microbial exposures increase the risk of AD, and some studies found infections, such as respiratory syncytial virus that may actually increase the risk of disease.[81–85] Further work needs to be done to elucidate which types of infections confer protection against AD and to determine whether such protection is also conferred by nonpathogenic bacteria.[78,79]

Severity of AD

Little is known about the distribution and determinants of AD severity in the United States and abroad. A recent study[1] examined the distribution of parentally-reported AD severity in US children ages 0 to 17. Using data from the NSCH, they found that 67% of children had mild, 26% had moderate, and 7% had severe disease throughout the country. There was also significant statewide-variation of the distribution of AD severity with highest prevalence of severe disease in Northeastern and Midwestern states.[32] It is noteworthy that the distributions for the prevalence of AD overall and severe

AD were distinct. Further, some of the factors that were associated with severe AD were different than previously demonstrated associations with AD prevalence. For example, older age, lower household income and lower paternal/maternal education level were all associated with severe AD. In contrast, younger age, higher household income and higher parental education level were all associated with higher prevalence of AD. Together, these studies suggest that there may be different factors that drive the severity of AD in the US population.

Previous studies in the UK found varying distributions of AD severity.[86,87] One study using a novel eczema severity score found that 82% had mild, 12% moderate, and 6% severe disease.[86] Another study using clinician assessment of severity found 84% mild, 14% moderate and 2% severe.[87] The different distributions may reflect population-based differences of eczema severity between the United States and UK and/or methodologic differences.

AD severity is multifactorial, including the subjective impact of itch, extent, and distribution of AD lesions and the effects of a variety of related comorbid health disorders. Until recently, there were few validated and well-accepted measure of severity and other outcomes in AD. This gap has contributed to a relative lack of data on the epidemiology of AD severity in the United States and abroad. Fortunately, recent attention has been given to forming a consensus about the best outcome measures for AD, which is known as Harmonizing Outcome Measures of Eczema (www.homeforeczema.org). Future research is needed to better understand what drives the severity of AD in the United States and abroad.

Health care use for AD

AD is often considered a minor "skin problem" without major associated health care costs. In reality, the economic burden of AD is comparable to other chronic diseases, such as emphysema, asthma, epilepsy, and psoriasis.[6,88] Studies estimating the total national cost of AD in the United States have ranged widely, from $364 million to $3.8 billion US dollars per year.[6] These estimates are based primarily on direct costs related to medical attention and treatment.

There are a number of "hidden" costs that have not been addressed in previous studies. A recent US population-based study from the NSCH found that children with AD, particularly severe disease, have a higher number of chronic health conditions, poorer overall health, more sleep impairment and higher rates of asthma, hay fever, food allergy, visual problems, recurrent ear infections, and dental health problems.[1] Another US population-based study from the NSCH found that children with AD have a higher number of mental health comorbidities, including depression, anxiety, attention deficit disorder or attention deficit hyperactivity disorder, conduct disorder, opposition defiant disorder, autism, and developmental delay.[3] AD has also been found to be associated with a slew of extra-cutaneous infections, including strep throat, other sore throat, head or chest cold, influenza/pneumonia, sinus infections, recurrent ear infections, chickenpox, urinary tract infections,[2] obesity,[89] and epilepsy.[90] It is therefore not surprising that children with AD also had significantly increased health care use, including medical, mental, dental, and therapy related services, and frequently sought specialist care.[1] Children with severe disease had even more comorbidities than those with mild to moderate disease.[1]

Previous estimates of the cost of AD failed to include the costs of the multitude of comorbid disorders mentioned above, as well as many other indirect costs of disease.[6,91] A British questionnaire-based study of parents of children with AD examined their use of medical services and found that indirect family care costs accounted for 36% of total disease cost, including changes in the home environment, purchase of over-the-counter medications, transport costs, and salary loss.[92] Because these indirect costs are often not included in estimates, the cost of AD is likely much greater than previously reported.[6] Given the increasing prevalence of AD and rapidly growing population in the United States, the state- and nation-wide costs of AD are likely to skyrocket. Increased support for research into preventative and more effective therapeutic modalities for AD is therefore indicated. Such research has the potential to dramatically reduce the economic and social burden of the disease.

Conclusions

Significant strides have been made in recent years on understanding the epidemiology of AD. Although the prevalence of AD has been steadily increasing over time, we now know that some developed nations with high disease burden appear to be leveling off, an intriguing finding with unknown implications. Recent population-based and other wide-scaling studies have confirmed the influence of socioeconomic status on the prevalence of AD, while also revealing that the determinants for severity of disease are distinct from those of prevalence, including lower household income, lower paternal/maternal education level, and older age. In addition, we are beginning to expand our research to account for demographic populations that have been sorely neglected; for instance, African-American/black populations tend to have greater burden of disease, more severe disease, and a different genetic profile. The powerful influence of genetics has been demonstrated by the recent discovery of the filaggrin mutation, showing that genetics interacts with the environment to modulate the expression of the disease.

The challenge that remains is to build on this information and eventually attempt to develop interventions for disease prevention and to reduce the public health burden of disease. The association of AD with higher socioeconomic status raises intriguing questions about whether specific modifiable risk factors are present. Given the substantial economic costs of AD and the added "hidden" burden of associated comorbidities, continuing efforts to understand risk and exacerbating factors for AD should be a top priority.

References

1. Silverberg JI, Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased health care utilization. *Pediatr Allergy Immunol.* 2013;24:476-486.
2. Silverberg JI, Silverberg NB. Childhood atopic dermatitis and warts are associated with increased risk of infection: A US population-based study. *J Allergy Clin Immunol.* 2014;133:1041-1047.
3. Yaghmaie P, Koudelka CW, Simpson EL. Mental health comorbidity in patients with atopic dermatitis. *J Allergy Clin Immunol.* 2013;131:428-433.
4. Simpson EL. Comorbidity in Atopic Dermatitis. *Curr Dermatol Rep.* 2012;1:29-38.
5. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: A US population-based study. *J Allergy Clin Immunol.* 2013;132:1132-1138.
6. Mancini AJ, Kaulback K, Chamlin SL. The socioeconomic impact of atopic dermatitis in the United States: A systematic review. *Pediatr Dermatol.* 2008;25:1-6.
7. Odhiambo JA, Williams HC, Clayton TO, et al. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. *J Allergy Clin Immunol.* 2009;124:1251-1258. [e1223].
8. Purvis DJ, Thompson JM, Clark PM, et al. Risk factors for atopic dermatitis in New Zealand children at 3.5 years of age. *Br J Dermatol.* 2005;152:742-749.
9. Tay YK, Kong KH, Khoo L, et al. The prevalence and descriptive epidemiology of atopic dermatitis in Singapore school children. *Br J Dermatol.* 2002;146:101-106.
10. Martin PE, Koplin JJ, Eckert JK, et al. The prevalence and socio-demographic risk factors of clinical eczema in infancy: A population-based observational study. *Clin Exp Allergy.* 2013;43:642-651.
11. Xu F, Yan S, Li F, et al. Prevalence of childhood atopic dermatitis: An urban and rural community-based study in Shanghai, China. *PLoS One.* 2012;7:e36174.
12. Belyhun Y, Amberbir A, Medhin G, et al. Prevalence and risk factors of wheeze and eczema in 1-year-old children: The Butajira birth cohort, Ethiopia. *Clin Exp Allergy.* 2010;40:619-626.
13. Kay J, Gawkrodger DJ, Mortimer MJ, et al. The prevalence of childhood atopic eczema in a general population. *J Am Acad Dermatol.* 1994;30:35-39.
14. Schultz Larsen F, Diepgen T, Svensson A. The occurrence of atopic dermatitis in north Europe: An international questionnaire study. *J Am Acad Dermatol.* 1996;34:760-764.
15. Sugiura H, Umemoto N, Deguchi H, et al. Prevalence of childhood and adolescent atopic dermatitis in a Japanese population: Comparison with the disease frequency examined 20 years ago. *Acta Derm Venereol.* 1998;78:293-294.
16. Kanwar AJ, De D. Epidemiology and clinical features of atopic dermatitis in India. *Indian J Dermatol.* 2011;56:471-475.
17. Shaw TE, Currie GP, Koudelka CW, et al. Eczema prevalence in the United States: Data from the 2003 National Survey of Children's Health. *J Invest Dermatol.* 2011;131:67-73.
18. Laughter D, Istvan JA, Tofte SJ, et al. The prevalence of atopic dermatitis in Oregon schoolchildren. *J Am Acad Dermatol.* 2000;43:649-655.
19. Hanifin JM, Reed ML, Eczema P, et al. A population-based survey of eczema prevalence in the United States. *Dermatitis.* 2007;8:82-91.
20. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet.* 1998;351:1225-1232.
21. Muto T, Hsieh SD, Sakurai Y, et al. Prevalence of atopic dermatitis in Japanese adults. *Br J Dermatol.* 2003;148:117-121.
22. Saeki H, Tsunemi Y, Fujita H, et al. Prevalence of atopic dermatitis determined by clinical examination in Japanese adults. *J Dermatol.* 2006;33:817-819.
23. Marks R, Kilkenny M, Plunkett A, et al. The prevalence of common skin conditions in Australian school students: 2. Atopic dermatitis. *Br J Dermatol.* 1999;140:468-473.
24. Dotterud LK, Falk ES. Atopic disease among adults in Northern Russia, an area with heavy air pollution. *Acta Derm Venereol.* 1999;79:448-450.
25. Herd RM, Tidman MJ, Prescott RJ, et al. Prevalence of atopic eczema in the community: The Lothian Atopic Dermatitis study. *Br J Dermatol.* 1996;135:18-19.
26. Williams HC. Epidemiology of atopic dermatitis. *Clin Exp Dermatol.* 2000;25:522-529.
27. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997–2011. *NCHS Data Brief.* 2013:1-8.
28. Hansen TE, Evjenth B, Holt J. Increasing prevalence of asthma, allergic rhinoconjunctivitis and eczema among schoolchildren: Three surveys during the period 1985–2008. *Acta Paediatr.* 2013;102:47-52.
29. Williams H, Stewart A, von Mutius E, et al. Is eczema really on the increase worldwide? *J Allergy Clin Immunol.* 2008;121:947-954. [e915].
30. Deckers IA, McLean S, Linssen S, et al. Investigating international time trends in the incidence and prevalence of atopic eczema 1990–2010: A systematic review of epidemiologic studies. *PLoS One.* 2012;7:e39803.
31. Williams HC, Pembroke AC, Forsdyke H, et al. London-born black Caribbean children are at increased risk of atopic dermatitis. *J Am Acad Dermatol.* 1995;32:212-217.
32. Silverberg JI, Simpson EL. Predictors of pediatric eczema severity in the United States: A population-based study. *J Invest Dermatol.* 2012;132:S44.
33. Horii KA, Simon SD, Liu DY, et al. Atopic dermatitis in children in the United States, 1997–2004: Visit trends, patient and provider characteristics, and prescribing patterns. *Pediatrics.* 2007;120:e527-e534.
34. Vachiramon V, Tey HL, Thompson AE, et al. Atopic dermatitis in African American children: Addressing unmet needs of a common disease. *Pediatr Dermatol.* 2012;29:395-402.
35. Ben-Gashir MA, Hay RJ. Reliance on erythema scores may mask severe atopic dermatitis in black children compared with their white counterparts. *Br J Dermatol.* 2002;147:920-925.
36. Margolis DJ, Apter AJ, Gupta J, et al. The persistence of atopic dermatitis and filaggrin (FLG) mutations in a US longitudinal cohort. *J Allergy Clin Immunol.* 2012;130:912-917.
37. Garrett JP, Hoffstad O, Apter AJ, et al. Racial comparison of filaggrin null mutations in asthmatic patients with atopic dermatitis in a US population. *J Allergy Clin Immunol.* 2013;132:1232-1234.
38. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet.* 2006;38:441-446.
39. Nassif A, Chan SC, Storrs FJ, et al. Abnormal skin irritancy in atopic dermatitis and in atopy without dermatitis. *Arch Dermatol.* 1994;130:1402-1407.
40. Darlenski R, Kazandjieva J, Tsankov N, et al. Acute irritant threshold correlates with barrier function, skin hydration and contact hypersensitivity in atopic dermatitis and rosacea. *Exp Dermatol.* 2013;22:752-753.
41. Silverberg JI, Hanifin J, Simpson EL. Climatic factors are associated with childhood eczema prevalence in the United States. *J Invest Dermatol.* 2013;133:1752-1759.
42. Williams HC, Strachan DP, Hay RJ. Childhood eczema: Disease of the advantaged? *BMJ.* 1994;308:1132-1135.
43. Mercer MJ, Joubert G, Ehrlich RI, et al. Socioeconomic status and prevalence of allergic rhinitis and atopic eczema symptoms in young adolescents. *Pediatr Allergy Immunol.* 2004;15:234-241.
44. Gibbs S, Surridge H, Adamson R, et al. Atopic dermatitis and the hygiene hypothesis: A case–control study. *Int J Epidemiol.* 2004;33:199-207.
45. Schram ME, Tedja AM, Spijker R, et al. Is there a rural/urban gradient in the prevalence of eczema? A systematic review. *Br J Dermatol.* 2010;162:964-973.
46. Irvine AD, McLean WH. Breaking the (un)sound barrier: Filaggrin is a major gene for atopic dermatitis. *J Invest Dermatol.* 2006;126:1200-1202.
47. van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: Systematic review and meta-analysis. *BMJ.* 2009;339:b2433.

48. Rodriguez E, Baurecht H, Herberich E, et al. Meta-analysis of filaggrin polymorphisms in eczema and asthma: Robust risk factors in atopic disease. *J Allergy Clin Immunol.* 2009;123:1361-1370. [e1367].
49. Baurecht H, Irvine AD, Novak N, et al. Toward a major risk factor for atopic eczema: Meta-analysis of filaggrin polymorphism data. *J Allergy Clin Immunol.* 2007;120:1406-1412.
50. Leung DY. New insights into atopic dermatitis: Role of skin barrier and immune dysregulation. *Allergol Int.* 2013;62:151-161.
51. Gao PS, Rafaels NM, Hand T, et al. Filaggrin mutations that confer risk of atopic dermatitis confer greater risk for eczema herpeticum. *J Allergy Clin Immunol.* 2009;124:507-513. [513 e501–507].
52. Brown SJ, McLean WH. One remarkable molecule: Filaggrin. *J Invest Dermatol.* 2012;132:751-762.
53. Li M, Liu Q, Liu J, et al. Mutations analysis in filaggrin gene in northern China patients with atopic dermatitis. *J Eur Acad Dermatol Venereol.* 2013;27:169-174.
54. Nomura T, Akiyama M, Sandilands A, et al. Prevalent and rare mutations in the gene encoding filaggrin in Japanese patients with ichthyosis vulgaris and atopic dermatitis. *J Invest Dermatol.* 2009;129:1302-1305.
55. Carson CG, Rasmussen MA, Thyssen JP, et al. Clinical presentation of atopic dermatitis by filaggrin gene mutation status during the first 7 years of life in a prospective cohort study. *PLoS One.* 2012;7:e48678.
56. Weidinger S, Rodriguez E, Stahl C, et al. Filaggrin mutations strongly predispose to early-onset and extrinsic atopic dermatitis. *J Invest Dermatol.* 2007;127:724-726.
57. Brown SJ, Sandilands A, Zhao Y, et al. Prevalent and low-frequency null mutations in the filaggrin gene are associated with early-onset and persistent atopic eczema. *J Invest Dermatol.* 2008;128:1591-1594.
58. Brown SJ, Relton CL, Liao H, et al. Filaggrin null mutations and childhood atopic eczema: A population-based case–control study. *J Allergy Clin Immunol.* 2008;121:940-946. [e943].
59. Ballardini N, Kull I, Soderhall C, et al. Eczema severity in preadolescent children and its relation to sex, filaggrin mutations, asthma, rhinitis, aggravating factors and topical treatment: A report from the BAMSE birth cohort. *Br J Dermatol.* 2013;168:588-594.
60. Barnes KC. An update on the genetics of atopic dermatitis: Scratching the surface in 2009. *J Allergy Clin Immunol.* 2010;125:16-29. [e11-11; quiz 30–11].
61. Ahmad-Nejad P, Mrabet-Dahbi S, Breuer K, et al. The toll-like receptor 2 R753 Q polymorphism defines a subgroup of patients with atopic dermatitis having severe phenotype. *J Allergy Clin Immunol.* 2004;113:565-567.
62. Mrabet-Dahbi S, Dalpke AH, Niebuhr M, et al. The Toll-like receptor 2 R753 Q mutation modifies cytokine production and Toll-like receptor expression in atopic dermatitis. *J Allergy Clin Immunol.* 2008;121:1013-1019.
63. Niebuhr M, Lutat C, Sigel S, et al. Impaired TLR-2 expression and TLR-2-mediated cytokine secretion in macrophages from patients with atopic dermatitis. *Allergy.* 2009;64:1580-1587.
64. Oiso N, Fukai K, Ishii M. Interleukin 4 receptor alpha chain polymorphism Gln551 Arg is associated with adult atopic dermatitis in Japan. *Br J Dermatol.* 2000;142:1003-1006.
65. Saunders SP, Goh CS, Brown SJ, et al. Tmem79/Matt is the matted mouse gene and is a predisposing gene for atopic dermatitis in human subjects. *J Allergy Clin Immunol.* 2013;132:1121-1129.
66. Silverberg JI, Simpson EL, Durkin HG, et al. Prevalence of allergic disease in foreign-born American children. *JAMA Pediatr.* 2013;167:554-560.
67. Marcon A, Cazzoletti L, Rava M, et al. Incidence of respiratory and allergic symptoms in Italian and immigrant children. *Respir Med.* 2011;105:204-210.
68. Tedeschi A, Barcella M, Bo GA, et al. Onset of allergy and asthma symptoms in extra-European immigrants to Milan, Italy: Possible role of environmental factors. *Clin Exp Allergy.* 2003;33:449-454.
69. Farfel A, Green MS, Shochat T, et al. Trends in specific morbidity prevalence in male adolescents in Israel over a 50 year period and the impact of recent immigration. *Isr Med Assoc J.* 2007;9:149-152.
70. Leung RC, Carlin JB, Burdon JG, et al. Asthma, allergy and atopy in Asian immigrants in Melbourne. *Med J Aust.* 1994;161:418-425.
71. Sato J, Denda M, Chang S, et al. Abrupt decreases in environmental humidity induce abnormalities in permeability barrier homeostasis. *J Invest Dermatol.* 2002;119:900-904.
72. Denda M, Sato J, Tsuchiya T, et al. Low humidity stimulates epidermal DNA synthesis and amplifies the hyperproliferative response to barrier disruption: Implication for seasonal exacerbations of inflammatory dermatoses. *J Invest Dermatol.* 1998;111:873-878.
73. Vahavihu K, Ala-Houhala M, Peric M, et al. Narrowband ultraviolet B treatment improves vitamin D balance and alters antimicrobial peptide expression in skin lesions of psoriasis and atopic dermatitis. *Br J Dermatol.* 2010;163:321-328.
74. Peroni DG, Piacentini GL, Cametti E, et al. Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children. *Br J Dermatol.* 2011;164:1078-1082.
75. Frieri M, Valluri A. Vitamin D deficiency as a risk factor for allergic disorders and immune mechanisms. *Allergy Asthma Proc.* 2011;32:438-444.
76. Langan SM, Irvine AD. Childhood eczema and the importance of the physical environment. *J Invest Dermatol.* 2013;133:1706-1709.
77. Strachan DP. Hay fever, hygiene, and household size. *BMJ.* 1989;299:1259-1260.
78. Flohr C, Yeo L. Atopic dermatitis and the hygiene hypothesis revisited. *Curr Probl Dermatol.* 2011;41:1-34.
79. Flohr C, Pascoe D, Williams HC. Atopic dermatitis and the 'hygiene hypothesis': Too clean to be true? *Br J Dermatol.* 2005;152:202-216.
80. Pelucchi C, Galeone C, Bach JF, et al. Pet exposure and risk of atopic dermatitis at the pediatric age: A meta-analysis of birth cohort studies. *J Allergy Clin Immunol.* 2013;132:616-622. [e617].
81. Silverberg JI, Norowitz KB, Kleiman E, et al. Association between varicella zoster virus infection and atopic dermatitis in early and late childhood: A case–control study. *J Allergy Clin Immunol.* 2010;126:300-305.
82. Silverberg JI, Kleiman E, Silverberg NB, et al. Chickenpox in childhood is associated with decreased atopic disorders, IgE, allergic sensitization, and leukocyte subsets. *Pediatr Allergy Immunol.* 2012;23:50-58.
83. Illi S, von Mutius E, Lau S, et al. Early childhood infectious diseases and the development of asthma up to school age: A birth cohort study. *BMJ.* 2001;322:390-395.
84. Welliver RC, Wong DT, Sun M, et al. The development of respiratory syncytial virus-specific IgE and the release of histamine in nasopharyngeal secretions after infection. *N Engl J Med.* 1981;305:841-846.
85. Williams H, Flohr C. How epidemiology has challenged 3 prevailing concepts about atopic dermatitis. *J Allergy Clin Immunol.* 2006;118:209-213.
86. Emerson RM, Charman CR, Williams HC. The Nottingham Eczema Severity Score: Preliminary refinement of the Rajka and Langeland grading. *Br J Dermatol.* 2000;142:288-297.
87. Emerson RM, Williams HC, Allen BR. Severity distribution of atopic dermatitis in the community and its relationship to secondary referral. *Br J Dermatol.* 1998;139:73-76.
88. Ellis CN, Drake LA, Prendergast MM, et al. Cost of atopic dermatitis and eczema in the United States. *J Am Acad Dermatol.* 2002;46:361-370.
89. Silverberg JI, Kleiman E, Lev-Tov H, et al. Association between obesity and atopic dermatitis in childhood: A case–control study. *J Allergy Clin Immunol.* 2011;127:1180-1186. [e1181].
90. Silverberg JI, Joks R, Durkin HG. Allergic disease is associated with epilepsy in childhood: A US population-based study. *Allergy.* 2014;69:95-103.
91. Carroll CL, Balkrishnan R, Feldman SR, et al. The burden of atopic dermatitis: Impact on the patient, family, and society. *Pediatr Dermatol.* 2005;22:192-199.
92. Emerson RM, Williams HC, Allen BR. What is the cost of atopic dermatitis in preschool children? *Br J Dermatol.* 2001;144:514-522.