



Epidemiology of adult atopic dermatitis

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Abstract Atopic dermatitis (AD) is driven by a complex gene–environment interaction. Many of the risk factors and genetic underpinning previously observed for pediatric AD may not apply to adult atopic dermatitis, suggesting that these may largely be different disorders. Whereas AD is classically thought of as a pediatric disease, recent studies have shown high rates of disease in adults as well. Risk factors for persistence of childhood-onset AD, as well as adult-onset AD, are reviewed. Adults with AD are particularly vulnerable to exogenous insults from the outside environment, including climate, ultraviolet exposure, pollution, irritants and pruritogens, and microbes. Finally, adult AD is associated with a substantial health care burden, with increased utilization, direct and indirect costs of care, and lost work productivity.

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Introduction

Atopic dermatitis (AD) is a common, chronic, inflammatory skin disease of adulthood. AD has a substantial symptom burden with pruritus in all patients, as well as pain, sleep disturbance, and mental health clinical manifestations.¹ The profound clinical manifestations and skin lesions can negatively impact health-related quality of life (QOL).² The high prevalence and patient burden of AD make it the most burdensome skin disorder globally, followed by acne and psoriasis.

AD is a heterogeneous disorder, which complicates investigation of its epidemiology. There is a wide spectrum of lesion morphology ranging from acute oozing

and crusting, subacute lesions with dryness and scaling, and chronic lesions with lichenification and/or prurigo nodules; erythema, excoriations, and dryness can occur at all stages of disease; dyspigmentation can also occur secondary to postinflammatory pigment alternation. The distribution of lesions is also heterogeneous.

In early childhood, lesions have a predilection for the face and extensor areas, whereas older children and adults tend to have flexural eczema, which is a major criterion according to Hanifin and Rajka³ and the United Kingdom Working Party (UKWP) criteria.^{4,5} Adults, particularly those with adult onset or recurrence, appear to have a lesional predilection on the head/neck and hands^{6,7}; moreover, the clinical course of AD is also heterogeneous, including varying ages of onset, severity and extent of lesions, remissions and recurrences, and long-term persistence of AD signs and clinical manifestations. All of these nuances are important considerations for the

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proper investigation and interpretation of the epidemiology of adult AD.

Most of the scientific discourse about the epidemiology and public health burden of AD has been limited to childhood disease; however, a number of recent and provocative studies have particularly modified our understanding of adult AD. This nonsystematic review will address the epidemiology of adult AD.

Definition of adult AD for epidemiologic study

The global prevalence of AD can be challenging to study, often due to limitations in the ability to accurately diagnose AD across a large population in a cost-effective manner. The current gold standard for diagnosing AD is a health care provider diagnosis of AD. The most frequently used criteria in clinical trials in the United States and internationally are the Hanifin and Rajka (HR) criteria; however, use of the HR criteria is impractical for large-scale epidemiologic studies due to their length (4 major and 23 minor criterion), as well as the high cost, poor scalability, and limited access of having physicians assessing all subjects. Additionally, HR criteria may not perform as well in certain AD phenotypes, including adult AD.⁸ In fact, diagnosing AD in adults can often be quite challenging.

The UKWP Criteria are an abridged version (6 criteria) of the HR criteria that have been validated internationally in the community and hospital based settings^{9,10} and are more commonly used in epidemiologic research¹¹ and the second most commonly used criteria in clinical trials. Certain racial/ethnic and other demographic groups may be prone to different phenotypes of AD. Recently, novel diagnostic criteria for AD have been proposed in China and were found to be more sensitive for the diagnosis of adolescent- and adult-onset AD. It is unclear how well these criteria may perform in other regions of the world.

The use of questionnaire-based diagnostic criteria is much more common in large epidemiologic AD studies due to ease of distribution, scalability, and lower cost; however, there is often significant variation in the content and performance of questionnaire-based approaches across studies. A commonly employed strategy is to use a single question assessing for self- or caregiver-reported AD clinical manifestations or physician diagnosis of AD. A multicenter dermatology-practice-based validation study found that a single question assessing self-report of health care–diagnosed “eczema or skin allergy” in the previous 12 months (used in the National Survey of Children’s Health and other studies) had very good sensitivity, specificity, and positive predictive value¹²; however, many other questionnaires used were not previously validated and may not be valid. In addition, validity of a questionnaire in one setting does not guarantee validity in all settings, locales, and study populations.

Multiquestion surveys allow for more robust criteria and often have greater validity. The International Study of Asthma

and Allergies in Childhood (ISAAC) and the National Health and National Examination Survey in the United States used a three-question definition for AD diagnosis:

1. Presence of itchy dermatitis for at least 6 months
2. Presence of the itchy dermatitis in the past year
3. Flexural distribution of the dermatitis.

Presence of all three was considered diagnostic of AD and fulfilled major criteria in both HR and UKWP criteria. This method has been shown to perform better in children¹³ than in adults¹⁴ in large international studies, likely due in part to a higher proportion of nontypical morphologic features and lesional distribution in adults. Development of questionnaires that are valid for defining adult AD would allow for more accurate investigation of the epidemiology of adult AD.

Prevalence of adult AD

AD has historically been regarded as a disease mostly relegated to children. Much of our knowledge of the global prevalence of childhood AD comes from the ISAAC studies of allergic disease in children aged 6–7 and 13 years. The prevalence of childhood AD was found to be as high as 30% in some countries within the ISAAC Phase 3 study, with large variations both between and within countries¹³; however, ISAAC and most other epidemiologic studies of AD did not include adults, and global prevalence estimates are lacking for adult AD. Recent studies from different countries or regions have suggested that adult AD is more common than previously thought.

United States

A study of 27,157 adults (aged 18–85 years) from a U.S. population-based study (2010 National Health Interview Survey [NHIS]) found the prevalence of “dermatitis, eczema, or any other red, inflamed skin rash” in the previous year to be 10.2%.¹⁵ This question likely overestimates AD prevalence by also including some dermatoses other than AD. When a composite definition of AD was used based on the above-mentioned question and a history of asthma and/or hay fever, the prevalence was found to be 3.2%¹⁵; however, this more restrictive definition underestimates the prevalence of AD, because it is analogous to so-called “extrinsic AD,” that is, AD with other atopic disease, but excludes a large subset of “intrinsic AD,” that is, those with AD and no atopic disease. From this study, it would appear that the prevalence of AD falls somewhere in the range of 3%–10%. A subsequent study of 34,613 adults (aged 18–85 years) from the 2012 National Health Interview Survey found the prevalence of “eczema or skin allergy” in the past year to be 7.2%.¹⁶ The question used in this survey was more focused than the one used in NHIS 2010 and similar to one previously validated for self-report of AD, but it did not include health care diagnosis.¹²

A study of 4972 adults aged 20-85 years from the National Health and Nutrition Examination Survey 2005-2006 found that the lifetime prevalence of health care–diagnosed eczema in adults was 7.4%¹⁷; however, this likely underestimates true lifetime prevalence owing to decreased recall of early childhood AD. The 7% estimates observed in NHIS 2012 and NHANES 2005-2006 are near the midpoint of the 3%-10% range observed in NHIS 2010; together, these studies suggest that AD occurs in approximately 7% of U.S. adults.

International

To date, there are very few high-quality studies that assess adult AD prevalence on a national level and even less on an international level. Additionally, international studies on AD prevalence often have wide variation in their study criteria.¹⁸ International studies of AD in adults found prevalences ranging from 2.0% to 17.6% with notable differences by region and study methodology.^{14,19–23} Globally, AD prevalence is often highest in high-income countries, that is, developed countries.^{13,24} This observation is shown in the ISAAC studies, where the prevalence of AD in Italy (10.0% in aged 6-7; 7.4% in 13-14), Sweden (22.3% in aged 6-7; 12.9% in 13-14), Australia (17.1% in aged 6-7; 10.7% in 13-14), and the United Kingdom (16% in aged 6-7; 10.6% in 13-14) is high in both children and adolescents.¹³ A similar assessment of international AD prevalence differences and risk factors in adults proves more challenging, as there is a lack of high-quality epidemiologic studies that have included adults in the analysis.

Some studies observed that the global prevalence of AD may be increasing,¹³ prompting researchers to understand trends of AD prevalence. A recent systematic review, including 69 cohort, repeated cross-sectional, and database studies, assessed global trends in AD prevalence.¹⁸ The study found that the prevalence of AD increased in Africa, Northern and Western Europe, and Eastern Asia¹⁸; however, most of these studies only analyzed pediatric AD, and there were insufficient studies to similar assessed time trends in the prevalence of adult AD.

To attain greater understanding of the prevalence of adult AD on a global scale, future epidemiologic AD and allergic studies should attempt to standardize study criteria and include adults into the study population.

Age

AD is extremely common in childhood and has often been regarded by clinicians and investigators as largely a pediatric disease; however, most epidemiologic studies of AD investigated children, but they did not simultaneously assess adults, thereby precluding comparison of pediatric versus adult AD. Although the epidemiologic data support the notion that AD prevalence is the highest in early childhood, they also show that AD is highly prevalent in adolescence and adulthood;

for example, the 2012 NHIS used similar questions about “eczema or skin allergy” in the previous year in both children using caregiver-report and adults using self-report. The use of nearly identical questions in both pediatric and adult populations allowed for direct comparison of the respective prevalences. In fact, the U.S. prevalence of AD was greatest in childhood (14%), decreased by approximately half during late adolescence (8%), and remained remarkably stable in adult years (7%-8%).¹⁶ This trend of prevalence by age may be present in Europe as well. Viewing pediatric data from ISAAC alongside adult studies, the prevalence of AD at ages 6-7, 13-14, and >18 years was 10%, 7.4%, and 6.6% in Italy and 5.9%, 4.3%, and 4.2% in Spain, respectively.^{13,14} Together, these studies suggest that the prevalence of AD does not decrease nearly as much as suggested by conventional wisdom. There are limitations of directly comparing prevalence estimates from studies that used disparate criteria and populations. Future international studies of both children and adults are needed to allow for direct comparison of prevalence estimates between childhood and adulthood.

Age of onset

AD is typically reported to first present early in life in a large majority of cases, with 50% of AD cases beginning in the first year of life and 85% beginning by age 5 years.²⁵ Most of these findings originated from studies of younger pediatric cohorts that neither examined adolescents or adults with AD. More recent studies have suggested that there is considerable heterogeneity with respect to the age of disease onset in adults with AD. Some adults may have had their disease since infancy or school age with persistence into adulthood, whereas others may report onset of AD signs and clinical manifestations during adolescence or adulthood.

Childhood onset AD persisting into adulthood

AD was once regarded as a predominantly pediatric disease that universally dissipates throughout later childhood and adolescence; however, recent findings have challenged this assumption. The PEER cohort is a phase 4 registry study that was set up to monitor U.S. children with AD who were treated with pimecrolimus for the development of malignancy over a 10-year period. The data included longitudinal self-reported data about AD activity in 7157 children for a total of 22,550 person-years.²⁶ The study showed that at every age, more than 80% of subjects had clinical manifestations of AD and/or were using medication to treat their AD.²⁶ It was not until age 20 years that 50% of patients had at least 1 lifetime 6-month symptom- and treatment-free period.²⁶ This cohort may have been biased toward greater persistence, as it comprised children from mostly urban locations, some with already long-standing disease, who received treatment for their AD by a

health care provider with a second-line nonsteroidal prescription topical agent, all of which may not be generalizable to the entire population.

A recent systematic review of 46 studies (mostly birth cohorts and a couple of very large health care claims-based studies) also assessed rates and risk factors of AD persistence, though it showed persistence is a less common event.²⁷ When combining the available studies in meta-analysis, 80% of cases of childhood AD experienced a period of observed disease clearance by 8 years and only 5% of cases had no observed clearance after 20 years of follow-up. This suggests that patients with AD may be more likely to have periods of disease clearance than suggested by the PEER cohort. Such a meta-analysis was limited by the original study observation period and was unable to assess disease activity after the initial disease clearance. It is likely that some persons with observed clearance had subsequent disease recurrence or flare-ups later in life; nevertheless, the approach of this meta-analysis allowed for the examination of a number of risk factors for disease persistence.²⁷ First,

1. Three studies stratified disease persistence by baseline disease severity and found that moderate to severe AD was more likely to persist than mild AD. These results highlight an important distinction between AD severity and persistence, because patients can have intermittent or persistent disease across the entire spectrum of AD severity.
2. The results of the meta-analysis showed that patients with already persistent disease are more likely to have ongoing persistent disease. This may have important therapeutic ramifications, because a patient presenting with already long-standing disease is more likely to have ongoing persistence and require a viable long-term treatment approach.
3. The results of the meta-analysis revealed that studies using self-reported disease showed greater persistence than those relying on clinician assessment alone. AD can have a relapsing course, and clinical manifestations may vary considerably between seasons, locales, and environmental exposures. As a result, clinician assessment at a particular visit may miss active disease between visits. This underscores the importance of factoring in patient-reported clinical manifestations into therapeutic decision making and not relying solely on the assessment of visible lesions during a clinical encounter.

Adult-onset or recurrent AD

Several international studies have shown high rates of adult-onset AD in adult cohorts. Among adults with current AD clinical manifestations, 60% in Italy,²⁸ 25% in Nigeria,²⁹ 22% in Korea,³⁰ and 54% in the United States³¹ reported the onset of clinical manifestations in adulthood. A recent systematic review and meta-analysis found that approximately 1 in 4 adults with AD report adult-onset disease, with similar proportions

across different countries.³² The issue of adult-onset AD remains controversial; that is, many patients who report onset of AD in adulthood might have had AD during early childhood that remitted and was long-since forgotten. As a result, they may have adult-recurrence of AD, rather than adult-onset AD *per se*. Alternatively, there may be specific triggers and/or pathomechanisms that lead to *de novo* adult-onset AD. The important clinical take-home message is that an adult patient with signs and clinical manifestations consistent with AD can report adult-onset of clinical manifestations and still have AD.

Adult-onset AD may have a differing clinical presentation compared with childhood onset AD. A prospective study of 59 Thai patients with adult-onset AD showed that 76% of patients presented with nontypical morphologic features, most commonly nummular lesions.³³ Adults may often present with lesional predilection for the hands and prurigo-like lesions.¹ These data suggest that adult-onset AD represents a specific disease phenotype.

Sex

It has been widely observed that AD shows a female preponderance, particularly in adolescence and adulthood.^{13,28,34} This increased prevalence in girls and women from puberty onward is also observed in other atopic disorders.³⁵ It may be that estradiol and other female sex hormones exacerbate Th2 inflammation in AD patients. Subcutaneous injection of estradiol was found to initiate allergic sensitization in mice *in vivo*.³⁶ Additionally, *in vitro* studies showed that estradiol directly promoted rat mast cell degranulation,^{37,38} whereas tamoxifen, a selective estrogen inhibitor, inhibited rat mast cell degranulation.³⁸ In adult women, both healthy controls and patients with AD undergoing skin prick testing had increased mast cell degranulation in response to administration of histamine and known allergens, respectively, during mid-ovulatory cycle when serum estradiol and LH are most elevated.³⁹

In contrast to the atopic effects of female estrogen, dehydroepiandrosterone (DHEA) is a steroid hormone with a male preponderance that appears to have an inhibitory effect on the development of atopy. In murine models of atopy, DHEA has been shown to reduce inflammation and Th2 response.^{40,41} *In vitro* studies show that human peripheral blood mononuclear cells exposed to DHEA produce significantly less IL-4, a key mediator in IgE synthesis.⁴² Additionally, men with AD have been shown to have significantly less serum DHEA concentrations compared with healthy controls.⁴² All of these observations suggest that DHEA is a key immunomodulatory hormone and is protective against the development of Th2 predominant atopic disorders.

Genetics

Genetic inheritance has an essential role in the predisposition and development of AD. Early twin studies show that

monozygotic twins have an AD concordance rate of ~80%, whereas dizygotic twins have only a ~20% concordance rate.^{43,44} These observations gave compelling evidence that genetics are implicated in the development of AD and served as the foundation for further research.

The *FLG* gene, which codes for the protein filaggrin, is the most well-studied genetic determinant of AD. *FLG* is broken down into natural moisturizing factor (NMF) in the stratum corneum and plays an integral role in skin-barrier function.⁴⁵ *FLG* null mutations lead to a deficiency of NMF⁴⁶ and xerosis in AD⁴⁷ and disrupt epidermal barrier function, allowing increased penetration of allergens and development of a Th-2 predominant phenotype.⁴⁸ An estimated 10% of people of European ancestry are heterozygous carriers and subsequently have a 42% chance to develop AD.^{49,50} Exon 3 of *FLG* is extremely large (~12.7 kb). As such, it has acquired numerous mutations throughout evolution. *FLG* loss-of-function mutations produce a severe phenotype defined by epidermal barrier malfunction.⁵¹ These mutations lead to a significantly earlier onset of AD and a more severe disease phenotype.⁵² *FLG* may also serve as a risk factor for persistence of childhood AD into adulthood.^{53,54}

The presence of *FLG* mutations alone may not account for the majority of AD cases. One study found that repeated single and tandem exposures to sodium lauryl sulfate and sodium hydroxide resulted in significantly lower levels of natural moisturizing factor in patients with AD, regardless of whether they had *FLG* mutations.⁵⁵ Although specific and persistent *FLG* mutations have been identified in European⁵⁶ and Asian⁵⁷ populations, they do not appear to have the same effect in other races. In South African and Ethiopian populations, *FLG* loss-of-function mutations are rare in patients with AD.^{58,59} A U.S. study detected *FLG* mutations in 27.5% of white and only 5.8% of African-American/black children with AD.⁶⁰

FLG and *hornerin* (*HRNR*) are just two of many genes that contribute to epidermal barrier function and cornification that are positioned closely together on chromosome 1 in a gene cluster that has had a dynamic evolution.⁶¹ Another nearby gene in this cluster, *FLG2*, is structurally similar to *FLG* and is comparably involved in epidermal barrier function. LoF mutations to *FLG2* have been shown to be associated with AD prevalence and persistence in black children, which were not present in patients of Northern and Western European ancestry.⁶² Children with *FLG2* loss-of-function mutations were less likely to be symptom-free over time.⁶²

The persistence of these mutations, in spite of the detrimental effects on skin barrier function and predisposition to AD that they confer, had perplexed investigators. Recently, a study on the evolutionary genetics of *FLG* loss-of-function mutations in Asian populations showed that *FLG* mutations are unlikely to confer evolutionary fitness to the individual and instead participated in a selective sweep with the *HRNR* gene.⁶³ It is hypothesized that the selected variants of *HRNR* did confer evolutionary fitness to an ancient ancestor who incidentally also carried *FLG* loss-of-function mutations.

Mast cell chymase (MCC) is a serine protease secreted by skin mast cells that appears to play a role in the development of adult onset AD. MCC plays a pivotal role in the immune system by regulating serum concentration of cytokines, particularly IL-4.⁶⁴ In murine models, addition of purified rat MCC increases IgE production *in vitro*.^{65,66} Additionally, addition of MCC inhibitor to a mouse model of AD *in vivo* has been shown to decrease the scratching response.⁶⁶ The -1903/A polymorphism of the *MCC* gene has been associated with adult AD but not allergic rhinitis or asthma.^{67,68} Additionally, two studies showed significantly lower serum IgE levels in adult AD patients with the -1903/A polymorphism.^{68,69} These results suggest that *MCC* polymorphism may play a role in adult-onset AD independent of an atopic phenotype.

Other important genetic factors linked to adult AD include the IL-4 receptor and vitamin D receptor. A small study in Japan found that the gain-of-function Gln551 Arg polymorphism in the *IL-4 receptor* gene was significantly associated with adult AD compared with healthy controls.⁷⁰ The vitamin D pathway is increasingly recognized for its role in epidermal barrier function and local immune response, and specific polymorphisms of the *vitamin D receptor* have been associated with severe adult AD.⁷¹ It is likely that these polymorphisms decrease skin barrier function, allowing allergen penetration, sensitization, and development of an atopic phenotype.⁷² As future research increases our understanding of the genetic influences in the predisposition and generation of AD, additional genes will likely be implicated.

Racial and ethnic differences

The prevalence of AD and other atopic diseases is not uniform in regard to race and ethnicity. In the United States and the United Kingdom, it is well documented that black children are more likely to be diagnosed with AD than white children.^{24,73,74} Additionally, Chinese infants in Australia have a significantly higher incidence of AD than white children living in similar environmental conditions.⁷⁵ Several studies have shown racial and ethnic differences with respect to AD severity. A study of children from the NSCH found in bivariate analyses that blacks and Hispanics were more likely to report moderate to severe AD than whites⁷⁶; however, in multivariate analyses, AD severity was associated with lower household income but not race/ethnicity *per se*.⁷⁶ This suggests that socioeconomic status plays an important role in AD severity and observed racial differences thereof.

There are also a number of distinguishing clinical features that occur more commonly in some racial and ethnic groups than others. Erythema in skin of color often appears hyperpigmented or violaceous. A previous study of Nigerian patients with AD found that 54.1% had lichenoid lesions and 70.3% had a perifollicular, micropapular eruption, on the extensor aspects of the joints.²⁹ It is unlikely that all these differences can be solely attributed to environmental or socioeconomic

factors and probably represent the summation of multiple risk factors influencing genetically predisposed individuals. These phenotypical differences may not be accurately diagnosed in the clinical setting. In addition, HR, UKWP, and other criteria do not address these phenotypical differences and may not perform as well in patients of African descent. Specific criteria have been proposed for use in Japan and China.

Foreign birthplace

Country of birth and current residence appear to play a role in the risk of AD in both children and adults. A U.S. population-based study found that children who were born in another country and immigrated to the United States had significantly lower prevalences of AD and allergic disease than those who were born and living in the United States.⁷⁷ The odds of AD and allergic disease significantly increased after 10 years of residence in the United States or longer.⁷⁷ These findings suggest that prolonged exposure to environmental or climate factors within the United States and perhaps other exposures related acculturation may increase the risk of AD in predisposed individuals. Previous studies in Italy, Israel, and Australia have also shown lower prevalences of allergic disease in immigrants compared with native-born persons in those countries.^{78–81} The increased odds of AD after immigration and prolonged residence in the United States and other countries suggest that foreign-born individuals may be at risk for later-onset AD. Anecdotally, one of the authors (J.I.S.) has seen dozens of adult AD patients who were born outside the United States and reported onset of clinical manifestations in adulthood after several years of residence in the United States. This subset of patients is a particularly interesting group to gain insight into the risk factors of adult-onset AD.

Risk factors

The wide international variation in adult AD prevalence suggests the implication of environmental factors. The hygiene hypothesis provides explanation on how environmental factors play a role in the generation of AD. It postulates that environmental antigens encountered during the early years of life are paramount in immune development. Industrialization and increased bathing and sanitization practices within affluent nations likely decrease this early exposure, resulting in immune dysfunction and propensity to develop autoimmunity and atopic disease.⁸² It is unclear how such environmental factors contribute to adult AD. It may be that environmental factors play a harmful role as exogenous triggers in AD, without the protective effects suggested in the hygiene hypothesis. Environmental risk factors are often geography dependent, and some of the better characterized ones are described below.

Climate and ultraviolet exposure

Some of the international variation in childhood AD prevalence may result from climatic differences. There are large variations in humidity, temperature, UV exposure, average time spent indoors, and average indoor humidity between and within countries. Humidity has been found to be negatively correlated with childhood AD prevalence in the United States.⁸³ This effect is likely explained by dry air impairing skin barrier function.^{84,85} Lower temperature and increased indoor heating days were found to be associated with increased AD prevalence,^{83,86} likely due to the increased time spent indoors with low ambient indoor humidity.

The amount of UV radiation that a geographic location is exposed to depends on both latitude and stratospheric ozone concentration (filters all ultraviolet C and most ultraviolet B radiation). Increased exposure to ultraviolet radiation was found to be inversely associated with childhood AD prevalence in the United States.⁸³ States with higher tropospheric ozone had increased AD prevalence.^{83,87} Ultraviolet radiation likely exerts protective effects against the generation of AD through its inherent cutaneous antiinflammatory properties.⁸⁸ Ultraviolet radiation may also increase stimulation of cutaneous vitamin D production, which plays an important immunologic role in the development of atopic disease.⁸⁹

A recent study of the hospitalization for AD or eczema in the United States found that admission rates were highest in the northeast during the winter and south during the summer.⁹⁰

Winter in the northeast is typified by low temperature, humidity, and ultraviolet exposure, accompanied by increased indoor heating, whereas summer in the south is typified by high temperature and humidity, which may provoke heat and sweat that are common triggers of pruritus in AD. Similarly, a recent population-based study in Italy showed that adult AD prevalence was significantly higher in northern Italy, which has a colder subcontinental climate, than in southern Italy, which has a warmer Mediterranean climate.²⁸

Airborne pollution

Urban living often increases exposure to environmental irritants. Nitrogen dioxide (NO₂) is a prominent component of airborne pollution that contributes to tropospheric ozone development and greenhouse gas formation. NO₂ damages the skin barrier and increases transepidermal water loss in patients with AD.⁹¹ A large prospective birth cohort showed significant positive correlation between NO₂ exposure and prevalence of AD at 6 years.⁹² Additionally, proximity to heavy traffic and exposure to diesel exhaust lead to increased IgE production,⁹³ and it has been shown to be an environmental risk factor associated with AD.^{94,95}

There are few studies regarding the association and interaction of adult AD and airborne pollution. It has been hypothesized that airborne pollution disproportionately affects adult AD greater than pediatric disease due to a greater percentage of extrinsic AD in adults.⁹⁶ Recently, a population-based

study showed a modest association between prevalence of adult AD and airborne particulate matter.⁹⁷ Further investigation is warranted to determine causality and identify specific irritants.

Farming

Living on a farm increases exposure to a wide variety of environmental and pet allergens. In line with the hygiene hypothesis, multiple studies have shown that living on a farm at an early age reduces the risk of sensitization and development of atopic disease later in life.^{98–101} In contrast, it has also been shown that current farm living increases the risk of allergic disease in later childhood, despite the early-life protective advantage being present.¹⁰² This effect is likely mediated through higher allergen load triggering atopy in predisposed individuals. The few studies focused specifically on the association between farming and adult AD are very heterogeneous. A recent systemic review on occupational farm exposure and the development of atopy was unable to perform meta-analysis given disparate study design.¹⁰³ Conclusions regarding farm exposure during adulthood and AD are currently undetermined, and further investigation is needed to discern whether farm exposure during adulthood is a risk factor for or protective against adult AD. It is unknown whether specific farming practices impact the inverse association between farming and AD.

Socioeconomics

In comparison to most chronic conditions, the prevalence of AD has been shown to increase with increasing socioeconomic status^{24,104}; moreover, much of these data come from child global epidemiology studies. Higher parental socioeconomic status is associated with childhood allergic sensitization and atopic disease,¹⁰⁵ likely due to the reduction in allergen exposure during immune development by residing in a more sanitary environment. Similar to childhood AD, data from the 2010 NHIS show that higher household education level and income are significantly associated with increased AD prevalence in adults.¹⁵ Additionally, a recent pooled meta-analysis of nine large-scale U.S. population-based studies showed that adult AD prevalence was significantly associated with increased household income, greater household education level, and households with more people.¹⁰⁶

Although high parental socioeconomic status increases the risk of acquiring AD in childhood, the presence of AD can negatively impact social interactions and work success throughout life. Children with AD are significantly more likely to report bullying¹⁰⁷ and have decreased productivity in the classroom.¹⁰⁸ Additionally, adult AD appears to negatively affect workday productivity,^{107,108} which may limit the career trajectory of patients. A U.S. population-based study, utilizing the 2012 NHIS, showed that adults with AD and sleep disturbance are more likely to miss work, have increased physician visits, and self-report their health as fair/poor.¹⁶ Additionally,

data from the 2010 NHIS showed that adults with AD were significantly more likely to be unemployed.¹⁵ Overall, this chronic disease imparts a large financial burden to adults in terms of both reduced work productivity and increased health care utilization.

Smoking

Early and current cigarette smoking, as well as childhood exposure to environmental tobacco smoke, has been associated with a higher prevalence of adult-onset AD in a case-control study.¹⁰⁹ These results were corroborated in a meta-analysis, which also found that patients with AD are more likely to be current smokers¹¹⁰; however, these studies are insufficient to determine causality. Possible explanations include tobacco smoke acting as an irritant to individuals genetically predisposed to AD, smoke causing initiation of AD through allergic sensitization, or a combination of both.

Stress

Psychologic stress has long been observed to influence the disease course of AD.¹¹¹ Acute stress has been shown to exacerbate clinical manifestations of AD in both adults and children.^{112,113} A complex network exists between stress response, the neuronal system, and the skin. Acute stress increases the release of neuromodulators, which act to increase sympathetic output and inflammation locally and systemically.¹¹⁴ Specifically, corticotrophic releasing hormone output from the hypothalamus increases during acute stress.¹¹⁴ This increases the systemic release of glucocorticoids, which favor a Th2 response and inhibit a Th1 response.¹¹⁵ At rest, patients with AD have been shown to have a significantly higher sympathetic tone in comparison to healthy controls.¹¹⁶ To balance this, resting parasympathetic tone is also consistently increased. Patients with AD may, therefore, be less able to cope with acute stress due to a reduction in parasympathetic reserve.¹¹⁶

The effect of AD on psychologic function is understudied but important, as adult AD has been shown to negatively affect psychologic outcomes. Adults with AD are more likely to be diagnosed with depression and possess poor coping mechanisms.^{117–119} There are few studies focused specifically on the association between stress and adult AD. Recently, a population-based study of Korean adults showed significantly increased odds of AD in adults self-reporting “high” or “very high” stress levels.¹²⁰ These limited data suggest an interaction between stress and adult AD, and further research is needed in this important topic.

Ethanol

Alcohol consumption has been considered an exacerbating factor of AD clinical manifestations. Addition of oral ethanol to the diet of a mouse model of AD has been shown to exacerbate itch response.^{121, 122} Murine models have also shown the

immunologic effect alcohol consumption has on systemic cytokine expression *in vivo*. In response to alcohol ingestion, serum concentration of IL-6, IL-10, and IL-18 increased in mice. These non-Th1/Th2-specific cytokines likely play a role in local inflammation, leading to an increase in itch response.¹²² The association and effect of alcohol consumption on AD is more poorly understood in humans. Adults with AD have been found to have increased alcohol consumption.¹²³ Further research is required to determine whether alcohol use is a risk factor for adult AD or if the association represents a psychosocial reaction of adults to self-medicate and relieve their itch.

Health care utilization

AD affects adult health and well-being on a physical, financial, and occupational level. Globally, AD is the greatest cause of disability-adjusted life years for nonfatal chronic skin conditions.¹²⁴ Just as prevalence of AD has increased nationally¹²⁵ and globally¹²⁶ over the past decade, so too have the health care costs required to treat this condition.^{127,128} Recent population-based studies have shown that adults with AD in the United States pay higher out-of-pocket costs per year, attend more outpatient physician visits, and are seen in the emergency department and hospitalized more frequently.^{129,130} A recent study of data from the 2002-2012 National Inpatient Sample found a high prevalence of hospitalization for AD or eczema, resulting in total inpatient costs of \$8,288,083 per year for adults and \$3,333,868 per year for children; moreover, the prevalence and total costs of hospitalization for AD or eczema significantly increased between 2002 and 2012.

In addition to increasing health care utilization, AD has been shown to affect performance in the workplace. Roughly one third of patients feel as if their disease affects their performance in their occupation, with 14% stating that AD has negatively influenced their career trajectory.¹⁰⁷ Previous studies have found that adults with AD are more likely to take sick leave,^{131,132} retire early,¹³¹ and change occupation.^{132,133}

The detrimental effects AD has on the physical health of patients are not skin specific. Patients with AD are more likely to have concurrent asthma and allergic rhinitis,^{130,134} insomnia and sleep disruption,¹⁶ obesity,^{135,136} poor cardiovascular outcomes,¹²³ type II diabetes mellitus,¹²³ ocular complications,¹³⁷⁻¹³⁹ osteoporosis and fracture of bone or joint disease,^{17,140} dental complications,¹³⁰ warts and extracutaneous infections,¹⁴¹ and psychiatric illness.^{24,142} Many of these comorbidities are related to AD severity and poor long-term disease control. Despite their increased health care utilization, patients with AD often have difficulty accessing the care they need. Adults with AD are often unable to access care in a timely manner^{129,143} and have difficulty affording prescriptions.¹²⁹ These studies show that many patients with AD have unmet needs and future research is needed to optimize delivery of care.

Conclusions

AD is common in adulthood and associated with a large patient- and population-based burden. Adult AD shares many common features with childhood AD, though it has a number of key differences with respect to genetics, risk factors, and sociodemographics. Future studies of AD should include adult patients in an effort to gain a more complete understanding of the epidemiology and risk factors for this unique disease.

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