Clinical Management of Atopic Dermatitis

Second Edition

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Epidemiology

Atopic dermatitis (AD) is a chronic, inflammatory skin disease that commonly affects both children and adults. AD is associated with a heavy symptom burden, including pruritus, in addition to pain, sleep disturbance, and mental health symptoms.[1] The 2010 Global Burden of Disease survey found that AD had the highest disability-adjusted life-years among skin disorders, reflecting both the high prevalence and patient burden of the disease.[2,3]

Challenges to Studying the Epidemiology of AD

There are several challenges to studying the epidemiology of this disorder. First, there is considerable heterogeneity with respect to the morphology (ranging from acute oozing and crusting, subacute lesions with dryness and scaling, and chronic lesions with lichenification and/or prurigo nodules), distribution (flexural, extensor, head and neck areas, and generalized), time course (intermittent, chronic persistent disease, seasonal variation, and episodic flares), intensity, and associated comorbidities. There are also no widely accepted biomarkers or objective diagnostic tests for AD. Further complicating diagnosis, standardized international nomenclature for AD does not exist, with the term eczema having several different uses in addition to the lay synonym for AD. Due to these challenges, several approaches have been used to study the epidemiology of AD, but there is no single valid approach.

Prevalence of Childhood AD

The prevalence of childhood AD has been increasing over the past few decades, both in the United States and internationally. The 1-year

prevalence of caregiver-reported healthcare diagnosed eczema increased from 9.8% to 12.2% in the National Survey of Children's Health (NSCH) 2003 and 2007 studies, respectively, with significant variation between states and districts (**Figure 1.1**; 7.7% to 19.8%).[4,5] Similarly, the prevalence of childhood AD steadily increased from approximately 8% in 1997 to more than 12% in 2010 and 2011 in the National Health Interview Survey (NHIS), but may have plateaued in 2012 and 2013 (**Figure 1.2**).

The International Study of Asthma and Allergies in Childhood (ISAAC) found wide variation in the global prevalence of childhood AD, ranging 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 (**Figure 1.3**).[6] Comparison of prevalence estimates between Phases 1 and 3 of the ISAAC study suggest increasing prevalence of AD among 6- to 7-year-olds in both developing and developed nations, and increasing prevalence in 13- to 14-year-olds in developing nations.[7] A systematic review examining international trends in AD between 1990 and 2010 demonstrated childhood AD prevalence rates of more than 20% in some developed nations, with increasing rates of AD in Africa, eastern Asia, western Europe, and parts of northern Europe.[8] A survey-based study of more than 65,000 children and adolescents (6 months to <18 years old) in 18 countries also reported a wide range of AD prevalence internationally.[9] The 12-month prevalence of diagnosed AD (based on ISAAC criteria and self- or parent-reported AD diagnosis by a physician) ranged from 2.7% in Israel to 20.1% in Brazil.

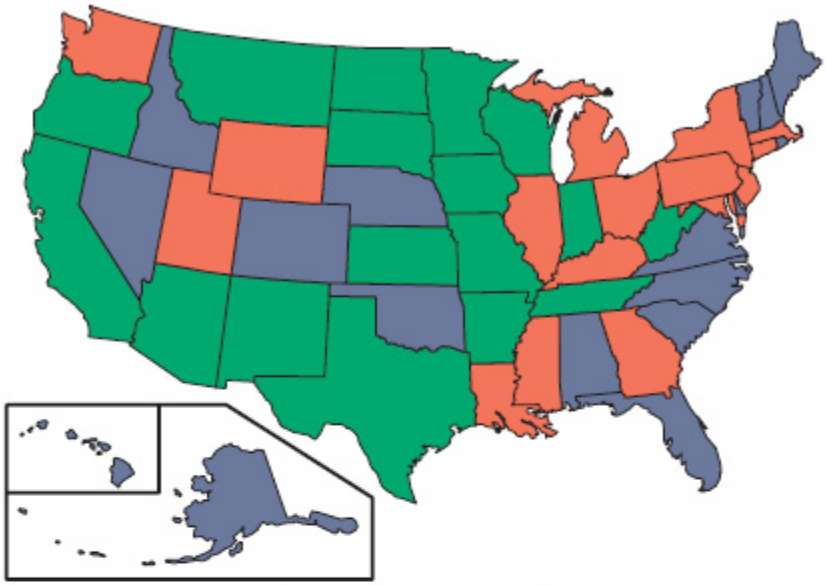
Prevalence of Adult AD

AD is commonly thought of as being a pediatric disorder. As it turns out, recent studies found that AD is far more common in adults than previously thought. Recent studies of adults from NHIS found 1-year prevalences of AD ranging from 7.2% to 10.2%.[10,11] The true prevalence is likely closer to 7.2%, and appears to be 6% to 8% throughout adulthood (**Figure 1.4**). Another US population-based study found an AD prevalence of 7.3% among adults.[12]

The high prevalence of AD in adults is likely related to a combination of both persistence of childhood AD and adult onset/recurrent AD. Recent studies have suggested that childhood AD may not "burn out" or dissipate

as much as previously thought.[13] A systematic review found that children whose AD started later in childhood or adolescence, was more severe, or already persistent for many years were more likely to have persistent AD.[14]

FIGURE 1.1 – Prevalence of AD in the United States, by State

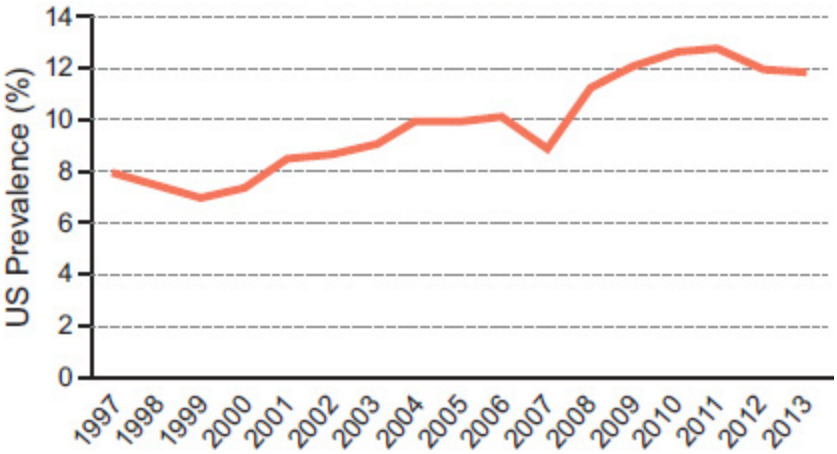


Tertile 1		Tertile 2		Tertile 3	
State	%	State	%	State	%
AR	10.3	AK	12.3	CT	14.9
AZ	10.9	AL	12.9	DC	19.8
CA	7.7	CO	12.6	GA	14.0
IA	11.9	DE	13.1	IL	13.4
IN	10.5	FL	12.3	KY	13.2
KS	11.4	HI	12.2	LA	14.7
MN	10.3	ID	12.1	MA	13.7
MO	11.8	ME	12.5	MD	13.9
MT	11.9	NC	12.7	MI	14.5
ND	11.0	NE	12.6	MS	14.1
NM	10.1	NH	12.4	NJ	14.9
OR	11.9	NV	12.7	NY	16.6
SD	8.3	OK	12.9	OH	14.2
TN	11.8	RI	12.7	PA	13.6
TX	10.8	SC	12.7	UT	13.4
WI	11.7	VA	12.5	WA	13.4
WV	9.9	VT	12.2	WY	13.8

Data from the 2007 National Survey of Children's Health divided into tertiles.

Adapted and modified from Silverberg JI. *Dermatol Clin*. 2017;35(3):283-289.

FIGURE 1.2 — Increasing Prevalence of Childhood AD in the United States Between 1997 and 2013



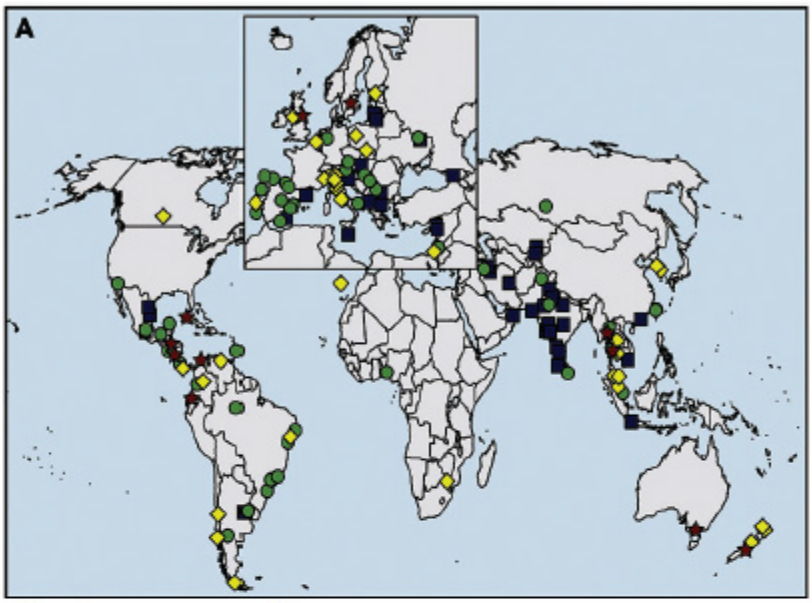
Data from the National Health Interview Survey.

Silverberg JI. *Dermatol Clin*. 2017;35(3):283-289.

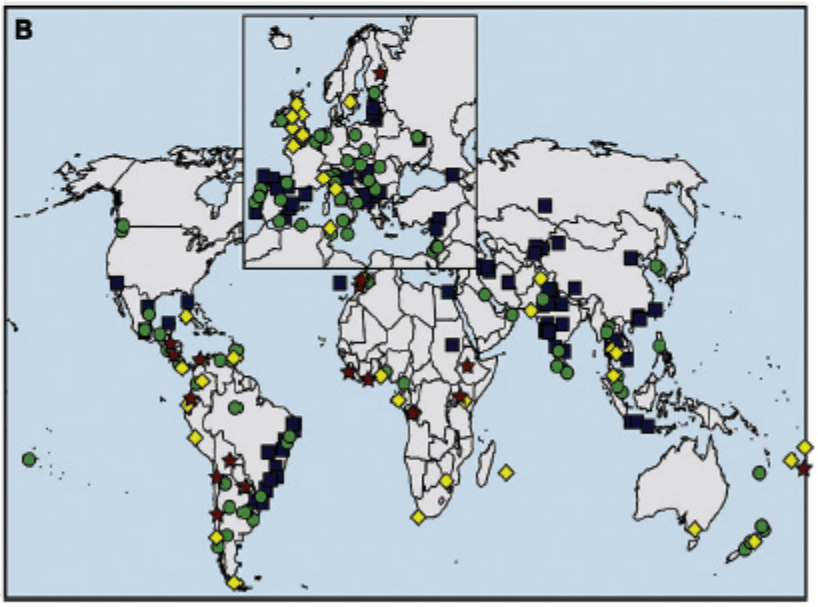
Most textbooks cite a statistic that 50% of AD cases begin in the first year of life and 85% by age 5 years.[15] However, those studies were limited to younger children and did not study adolescents and adults. In fact, multiple epidemiological studies and clinical trials found high rates of self-reported adult-onset AD (16.8% to 54%).[16-18] A meta-analysis of 17 studies on adult-onset AD (reported age of onset >16 years) found a pooled proportion of adult-onset AD of 26.1%.[19] The issue of adult-onset AD is somewhat controversial, as some of these patients may have forgotten they had childhood disease. However, adult-onset AD presents with a distinct set of characteristics (see *Chapter* 4), and likely represents a separate phenomenon from adult-recurrence AD. Regardless of whether such cases are adult-onset per se or adult-recurrence, there appears to be a large proportion of patients with adult flares of AD.

FIGURE 1.3 — World Map Showing Prevalence of Current Symptoms of Eczema for the Age Groups of 6 to 7 Years and 13 to 14 Years

Age Group 6 to 7 Years



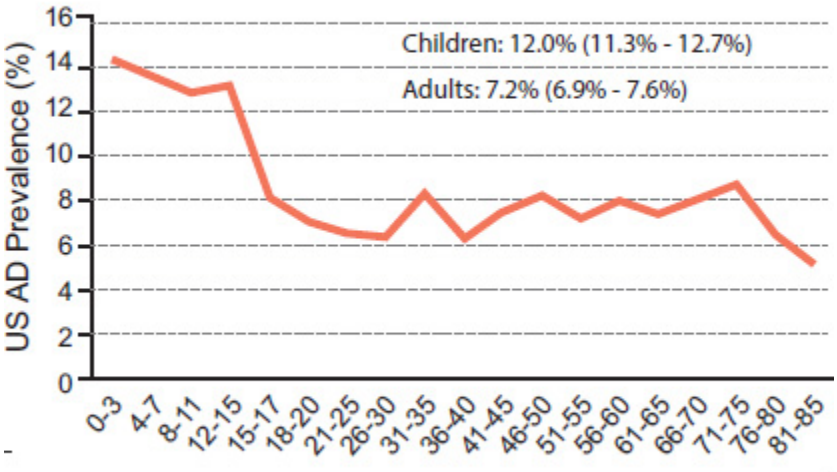
Age Group 13 to 14 Years



Blue squares indicate prevalence of <5%, green circles indicate prevalence of 5% to <10%, yellow diamonds indicate prevalence of 10% to <15%, and red stars indicate prevalence of 15% or more.

Adapted from Odhiambo JA, et al. *J Allergy Clin Immunol*. 2009;124(6):1251-1258.e23.

FIGURE 1.4 — Prevalence of AD in the United States, by Age



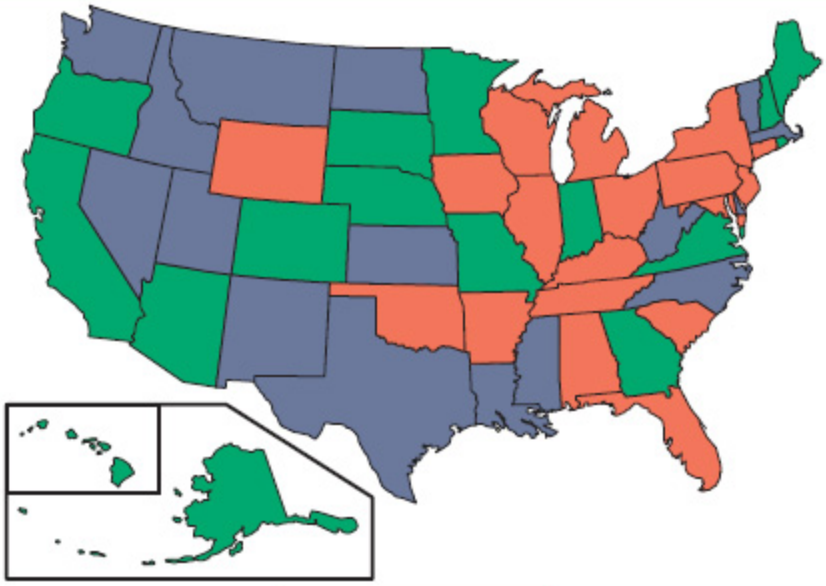
Data from the National Health Interview Survey.

Silverberg JI. *Dermatol Clin*. 2017l;35(3):283-289.

AD Severity

AD severity assessments reflect a combination of symptoms (eg, itch, sleep disturbance), lesional severity (eg, redness, thickness, lichenification, scaling, etc) and/or the extent of disease, and quality of life impairment. A US population-based study (NSCH 2007-2008) found that 67.0% of children had reportedly mild disease, 26.0% moderate, and 7.0% severe disease overall, amounting to 2.98 million children with moderate-severe disease.[5,20] The distribution of severe childhood AD in the United States is shown in **Figure 1.5**. The proportion of moderate-severe AD was even higher in adolescents than younger children (37.5% vs. 31.4%). AD severity was also found to be worse in African-Americans/Blacks and Hispanics.[5,20] A population-based study of 1760 children living around Nottingham, England found that 84% had mild, 14% moderate, and 2% severe disease as judged by a dermatologist.[21] In an international, survey-based study of more than 65,000 children and adolescents, the proportion of mild AD ranged from 43.4% (Israel) to 72.3% (Saudi Arabia and Japan), moderate AD from 24.0% (Saudi Arabia) to 47.5% (Russia), and severe AD from 2.2% (Japan) to 18.1% (Israel).[9]

FIGURE 1.5 – Prevalence of Severe AD in the United States, by State



Tertile 1		Tertile 2		Tertile 3	
State	%	State	%	State	%
AK	0.4	DE	0.7	AL	1.6
AZ	0.3	ID	0.7	AR	1.2
CA	0.5	KS	0.7	CT	1.3
CO	0.6	LA	0.8	DC	1.2
GA	0.5	MA	0.7	FL	0.9
HI	0.6	MS	0.7	IA	1
IN	0.6	MT	0.7	IL	0.9
MO	0.5	NC	0.7	MI	1.8
NE	0.3	ND	0.8	NJ	1.2
MN	0.5	NM	0.7	MD	1.1
ME	0.4	NV	0.8	KY	1.1
NH	0.6	TX	0.8	NY	1.3
OR	0.6	UT	0.7	OH	1.1
RI	0.5	VT	0.8	OK	1.5
SD	0.4	WA	0.8	PA	1.5
VA	0.6	WV	0.7	SC	1.6
				TN	1.1
				WI	0.9
				WY	0.9

Data from the 2007 National Survey of Children's Health divided into tertiles.

Adapted and modified from Silverberg JI. *Dermatol Clin*. 2017;35(3):283-289.

A cross-sectional, population-based study of 602 adults with AD found that 53.1% reported having mild AD, 38.8% moderate AD, and 8.1% severe AD.[12] AD severity was found to correlate with lower overall health, mental health, and life satisfaction, while itch, excessive dryness/scaling and red/inflamed skin were reported as the most burdensome symptoms (see *Chapter 4*).

Socio-Demographic Risk Factors

Several socio-demographic groups appear to be at higher risk for childhood AD in the United States. There appear to be racial/ethnic disparities in AD. Compared with white children, African-American/black children had higher prevalence of AD in the United States,[5,20] and London-born black children of Caribbean descent had a higher prevalence of AD in the United Kingdom.[22] African American/black children may be prone to more severe AD[23,24] and increased healthcare utilization for AD[25] compared with Caucasians/whites. One study of urban children in 20 large US cities found an overall AD prevalence of 14.5-15.1%, and an increased odds of AD among black and female children.[26] Conflicting results have been found with respect to whether AD prevalence is higher in females.[4,27-30]

Several studies have suggested that AD may be more common in higher socioeconomic groups. That is, higher household incomes and family education level, smaller family sizes, and urban and metropolitan living were all associated with higher AD prevalence in US children.[4] Similarly, international studies found higher AD prevalence in wealthier, developed nations compared with poorer, developing nations[4,6,27,28, 31-37] and higher AD prevalence in advantaged socioeconomic groups.[38,39] However, some data suggests that AD may be more prevalent among disadvantaged children. An analysis of the 2007-2008 National Survey of Children's Health data found increased prevalence and severity of AD among urban children living in unsafe, unsupportive, or underdeveloped neighborhoods, and lower AD severity among children from neighborhoods possessing a library or a bookmobile.[40] Adverse childhood experiences (ACEs),

including household dysfunction and physical, emotional, and sexual abuse, are also associated with childhood AD. One analysis of data from the Fragile Families and Child Wellbeing Study found that children who experienced at least one ACE had an increased odds of AD at age 5, and children who experienced three or more ACEs also had an increased odds of AD at age 9.[41]

In addition to demographic factors, genetic, epigenetic, and environmental factors, including seasonal variation in weather conditions, may influence AD prevalence. One study of healthcare registry data from Denmark found that healthcare utilization by AD patients (clinic/hospital visits and drug prescriptions) was highest in winter and spring, and that healthcare utilization was negatively correlated with temperature, regardless of season.[42] One large meta-analysis found significantly increased odds of AD in children of parents with history of AD or other atopic disease, which likely reflects both the influence of genetic factors and environmental hazard clustering.[43]

Cost of AD

Although AD is nonfatal, it is associated with substantial disease-related morbidity and disability. It affects patient health and well-being on a physical, financial, and occupational level. Along with prevalence rates, the healthcare costs required to treat this condition have increased in recent decades.[44,45] AD-related outpatient healthcare utilization also increased, with the frequency of visits to a healthcare provider more than doubling between 1996-1999 and 2012-2015 in the US, a change driven primarily by increased visits to primary care physicians, since visits to dermatologists actually decreased between the two time periods.[46] One population-based study found that outpatient utilization ranged from 29.3%-34.7% in patients with mild AD to 36.2%-49.8% and 50.6%-86.6% in patients with moderate and severe AD, respectively.[47] A relatively high proportion of patients with AD or eczema required urgent care (8.2%), emergency department (ED) care (9.6%), and hospitalization (6.7%). An analysis of the 2002-2012 National Impatient Sample (NIS) data found that nonwhite race or ethnicity, lowest-quartile annual household income, and Medicaid or no health insurance were predictors of hospitalization for AD or eczema, prolonged

length of stay, and increased cost of care.[48] The inpatient financial burden of AD is considerable, with another analysis of the 2002-2012 NIS data estimating AD-related hospitalization costs of at least $127 million.[49] Analysis of the 2006-2012 National Emergency Department Sample data revealed that the prevalence of AD-related ED visits increased significantly over this period, with total ED visit costs rising from $127.3 million in 2006 to $265.5 million in 2012.[50] Out-of-pocket (OOP) expenses also represent a significant burden on children and adults with AD, with one survey-based study reporting a median annual OOP cost of $600, with 42% and 8.5% of respondents reporting an annual OOP cost of >$1000 or >$5000, respectively.[51]

Although there are no recent direct estimates of the overall costs of AD in the United States, a 2002 study estimates direct payer costs of AD to be approximately $3.8 billion per year.[44] However, this likely underestimates the cost for several reasons. First, the population has increased since then, as has the prevalence of AD. Second, the estimate does not include costs associated with comorbid conditions, as patients with AD are more likely to have certain comorbidities, including asthma and allergic rhinitis,[5,52] insomnia and sleep disruption,[9] obesity,[53,54] and others. Third, it does not include indirect costs, such as the impact of symptoms on mental health[55-57] and activities of daily living,[58] or patient and/or caregiver costs of AD secondary to increased health utilization, missed work, transportation, copays, or costs of over-the-counter emollients and medications. One US population study found excess out-of-pocket costs related to health care utilization alone of $371 to $489 per person-year in adults with AD.[59] Thus, the economic burden of AD is likely much greater than previously reported.

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