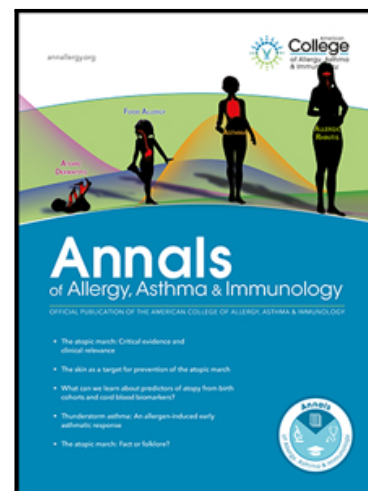


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Socioeconomics of Atopic Dermatitis-Can We Afford New Treatments?

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Title:

Socioeconomics of Atopic Dermatitis-Can We Afford New Treatments?

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To get a grasp of the socioeconomics of atopic dermatitis (AD), we need to understand its prevalence in the population, its burden, co-morbidities, and costs, both direct and indirect. Only then can we extrapolate whether it makes sense for society to cover new, more costly treatments in the management of this condition. AD affects a large percentage of the pediatric and adult population in the United States.¹ Generally, this chronic inflammatory condition of the skin has no mortality, which has to weigh into assessing the socioeconomics of this disorder. Nevertheless, we have to take into consideration the significant morbidity, co-morbidities which could increase mortality, and the poor quality of life for the sufferer, along with the caregiver/parent. It has been difficult to get an exact handle on the prevalence of this disorder in the United States population. For pediatrics, it has been estimated in the range from 6% to almost 13% of children.² Though we tend to think of atopic dermatitis as primarily a disorder of childhood, the number of adults who experience this condition is significant. The 2010 National Health Interview Survey (NHIS) which used a nationally representative sample of 27,157 adults age 18 to 85 years found the prevalence at 10.2%, while the 2012 survey showed a somewhat lower prevalence of 7.2%.³ A more recent international survey on AD using a more stringent criteria found the point prevalence of adult AD in the overall/treated populations was 4.9%/3.9% in the US.⁴ For a condition that is typically thought of as a pediatric disorder, these numbers are eye-opening.

The burden suffered from atopic dermatitis emphasizes the impact of this disorder on the affected population and their parents/caregivers.¹ Why is this important in assessing the socioeconomics of AD? No doubt these burdens add to the cost to the patient, the payer, and society. Using the Children's Life Quality Index, parents of children with AD between 5-16 years rated their child's quality of life poorer than that rated by parents of children with cystic

fibrosis, asthma, and diabetes.⁵ One of the major reasons for the burden of AD is sleep disturbance. A study compared sleep disturbance in children age 6 to 17 years who had moderate-to-severe AD with age- and sex-matched healthy controls. The AD children had significantly higher number of minutes of wake after sleep onset along with a higher frequency of restless sleep, daytime sleepiness, difficulty falling back to sleep at night, and teacher-reported daytime sleepiness.⁶ A study of school aged children (6-16 years) with AD in Australia who had documented sleep impairment showed a 16 point lower full-scale IQ score compared to healthy controls. This neurocognitive impairment could affect entrance to college and future occupation and income.⁷ In focus sessions with parents of young children with AD and 6 expert clinicians, here are some of the adverse effects of AD on the parents mentioned by more than 20% of the attendees: exhaustion/tiredness, sleep deprivation, embarrassment about child's appearance, sadness and depression, strain on relationship with spouse, worry about costs of care, affects decision to work, affects work performance, family stays home more, more housework, reluctant to leave child with others, time-consuming treatments, and vacation restriction.⁸ Silverberg et al used data from the 2012 NHIS and found that AD was associated with higher odds of fatigue, regular daytime sleepiness, and regular insomnia in adults. There were significant interactions between AD and fatigue, sleepiness, and insomnia as predictors of poorer overall health status, number of sick days, and doctor visits.⁹ RAND Europe showed that sleep deprivation in the US had an economic toll of between \$280 billion and \$411 billion in 2015 prices equaling about 2% of the US Gross National Product.¹⁰ A recent literature review from Denmark assessed the impact of AD on work life.¹¹ The review strongly implied that AD affects sick leave, and possibly job choice, change or loss of job and even disability pensions for more severe cases.

The authors found that AD imposes a burden extending beyond personal, emotional, and financial costs.

It is not possible to look at total costs to society for atopic dermatitis without measuring the impact of co-morbidities on the healthcare system. We are all familiar with the atopic march and the development of allergic rhinoconjunctivitis and asthma in patients who have or have had AD. Likewise, there is the high association of food allergy especially in young children with AD. There is now data to suggest that there are co-morbidities in patients with AD that don't have an atopic basis. Epidemiologic surveys suggest that patients with AD may be at an increased risk of cardiovascular diseases, certain malignancies, autoimmune conditions, and neuropsychiatric diseases.¹² Participants from 2005-2006 National Health and Nutrition Examination Survey and the 2012 NHIS were surveyed with questions for history of eczema and depression. Results found that one in three adults with AD met diagnostic criteria for major depressive disorder.¹³ Not surprising is the association of cutaneous infections in patients with atopic dermatitis due to skin-barrier dysfunction. There also appears to be an increased risk of extra-cutaneous infections in the AD population. Evaluation from the 2007 NHIS in children 0 to 17 years and 2012 NHIS in adults found that both groups with AD with or without other atopic disease had higher odds of extracutaneous infections, including strep throat, other sore throat, head or chest cold, influenza/pneumonia, sinus infections, and chickenpox.^{14,15}

Paramount in evaluation of the socioeconomics of atopic dermatitis is understanding the costs associated with this condition. Unfortunately, it is difficult to obtain accurate data, especially as related to indirect costs, comorbidities, and other burdens of disease which add to overall cost. The American Academy of Dermatology produced a national burden of skin disease report using

2013 claims data from private and governmental insurance providers.¹⁶ One of the skin conditions assessed was atopic dermatitis. They found direct costs for AD in 2013 to be \$314 million which only included medical services. A retrospective claim analysis of a private insurer and a state Medicaid program from 1997 and 1998 found the annual costs of AD was similar to emphysema, psoriasis, and epilepsy.¹⁷ In order to assess the financial burden of AD in families, between March 2011 and December 2013, 82 caretakers of children 6 months to 12 years of age with moderate-to-severe AD were asked questions about direct expenses (medical visits, medications, and other products) and indirect expenses (time missed from work, childcare costs) related to AD in the past 4 weeks.¹⁸ The average personal cost of AD in the month before an office visit, including direct costs and indirect costs, was \$274 per patient with \$75 spent on direct costs and \$199 on indirect costs. What was very disturbing in this data was the mean percent of monthly available money spent on AD (income and family-size adjusted cost) was 34.8%. To assess the burden of cost in the adult AD population, healthcare resource utilization was compared in patients who self-reported a diagnosis of AD or psoriasis and adult non-AD controls that were identified from the 2013 US National Health and Wellness Survey.¹⁹ Total direct costs were over \$24,000 for the AD patients vs. almost \$15,000 for the non-AD controls. The difference was largely driven by health care provider visits and associated costs. A retrospective study identified patients with AD from the Truven Health Marketscan Commercial Claims and Encounters database during 2013 and found that AD was associated with higher utilization and costs across inpatient visits, ambulatory visits, outpatient visits, emergency department visits, and prescriptions filled compared to matched controls with an adjusted total incremental annual cost of \$3,302.²⁰ This study found healthcare utilization and costs significantly higher in the more severe AD patients ($p < 0.0001$).

In determining hospital costs related to AD, Narla et al. analyzed data from 2002-2012 National Inpatient Sample, which included 20% representative sample of all hospitalizations in the US.²¹ Their findings showed prevalence of hospitalization with a primary diagnosis of AD increased in adults between 2002 and 2012. In addition, they found total inpatient costs of \$8,288,083 per year for adults and \$3,333,868 per year for children thus demonstrating that there is a substantial inpatient financial burden of AD in the United States.

Getting a handle on medication costs for atopic dermatitis is difficult as patient's cost for prescription medication can vary depending on type of insurance, co-pay, and deductible amounts. Until recently, emollients, topical corticosteroids, topical and oral immunomodulator agents have been the mainstay agents for management of AD patients. CVS Value estimated costs of topical corticosteroids at \$150 per month and topical immunosuppressants at \$500 per month in the care of AD.²² With two new agents approved by the FDA in the last couple of years and many more for AD in the pipeline, costs are likely to rise and access may be restricted depending on the patient's economic situation and insurance coverage, with step therapy and prior authorizations. Will they bring value and make a positive impact on the all the burdens of AD? Just because something is new doesn't prove it is better than the older treatments.

Crisaborole is a topical phosphodiesterase 4 inhibitor for mild-to- moderate atopic dermatitis in adults and children. It has an average wholesale price of \$580 for a 60-gram (2 ounce) tube. When looking at costs alone, topical corticosteroids make the most economic sense, with crisaborole and topical calcineurin inhibitors available for patients that fail these agents or develop side effects. The Institute for Clinical and Economic Review (ICER) is an independent

non-profit research organization in the United States that evaluates medical evidence to assess cost-effectiveness of different treatments. They recently evaluated crisaborole.²³ Their comparative clinical effectiveness summary pointed out that there are not studies to compare crisaborole's efficacy to other topical agents for mild to moderate AD. It seems to cause less application site burning/pain than topical calcineurin inhibitors and no evidence of skin changes as may be seen with topical corticosteroids. A recent critical analysis states that it is essential that crisaborole testing now rapidly progress from vehicle-controlled studies to studies using active comparators and long-term studies of drug safety.²⁴

Of more concern is the cost to the patient, payer, and society of dupilumab, a monoclonal antibody directed against the IL-4 receptor alpha, which blocks the action of IL-4 and IL-13, thus decreasing inflammation in the skin of AD's sufferers. Studies have shown efficacy vs placebo and with concomitant use with topical corticosteroids vs topical corticosteroids alone in adult patients with moderate to severe atopic dermatitis. In health economic analysis as a way to compare costs to society with medical treatments, it is common to calculate the cost for each quality-adjusted life-year (QALY) obtained. A QALY considers both quantity and the quality of life generated by healthcare interventions. This utility measurement has been used as a way to optimize limited health care resources for society and can be beneficial in looking at cost-effectiveness in new treatments for atopic dermatitis. National Institute for Health and Care Excellence (NICE) is the body in the United Kingdom (UK) which examines cost-effectiveness in medical treatment and makes recommendations to the government formulary. In their final guidance on using dupilumab, their most plausible cost-effectiveness estimates for it plus topical

corticosteroids, compared with best supportive care, range from £27,410 (\$36,398) to £28,495 (\$37,839) per quality-adjusted life year gained which meets the range that NICE normally considers an acceptable use of healthcare resources in the UK.²⁵ They recommend to stop the biologic at 16 weeks if there is not clinical improvement by the Eczema Area and Severity Index score and improvement in quality of life by the Dermatology Life Quality Index. Taking in consideration not only clinical improvement but also quality of life is an important step forward in evaluating the worth of a treatment. Kuznik et al used a health economic model using US payer perspective on long-term costs and benefits of dupilumab in AD.²⁶ The annual price of maintenance therapy with dupilumab to be considered cost-effective was estimated for decision thresholds of US \$100,000 and \$150,000 QALY gained. Their findings suggested that this agent was cost-effective at an annual price range of \$29,000 to \$40,000, which is within its current average wholesale price of \$37,000. ICER estimated the cost-effectiveness of dupilumab versus usual care over a lifetime time horizon for adult patients with moderate-to-severe atopic dermatitis. Compared to usual care, the cost per additional QALY for dupilumab was estimated to be approximately \$101,800 with the price of using dupilumab around \$37,000.²³ From US standards, dupilumab shows a supportive cost analysis in moderate-to-severe atopic dermatitis.

When assessing the true socioeconomic burden of AD, it is clear that these new treatments may initially increase direct costs, but hopefully they will lead to a decrease in indirect costs, improvement in quality of life, and a decrease in co-morbidities in our patients. Only in looking at all elements of the effect of AD on the patient can we truthfully say they bring value to the healthcare system. Just because AD is not associated with increased mortality does not mean that society should not cover costs associated with improved outcomes. Each new agent will need to be assessed on its own merit. Ideally, we need head-to-head comparisons between all new

treatments against older proven ones to truly determine whether their cost-effectiveness and safety can be justified to the patient, the payer, and society.

1. Drucker AM, Wang AR, Li W-Q, Sevetson E, Block JK, Qureshi AA. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. *Journal of Investigative Dermatology*. 2017;137(1):26-30.
2. Silverberg JI. Public Health Burden and Epidemiology of Atopic Dermatitis. *Dermatology Clinics*. 2017;35(3):283-289.
3. 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(5):1132-1138.
4. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. *Allergy*. 2018;73(6):1284-1293.
5. Beattie PE, Lewis-Jones MS. A comparative study of impairment of quality of life in children with skin disease and children with other chronic childhood diseases. *Br J Dermatol*. 2006;155(1):145-151. doi:10.1111/j.1365-2133.2006.07185.x.

6. Fishbein AB, Mueller K, Kruse L, et al. Sleep disturbance in children with moderate/severe atopic dermatitis: A case-control study. *Journal of the American Academy of Dermatology*. 2018;78(2):336-341.
7. Camfferman D, Kennedy JD, Gold M, Simpson C, Lushington K. Sleep and neurocognitive functioning in children with eczema. *International Journal of Psychophysiology*. 2013;89(2):265-272.
8. Chamlin SL. Effects of Atopic Dermatitis on Young American Children and Their Families. *Pediatrics*. 2004;114(3):607-611.
9. Silverberg JI, Garg NK, Paller AS, Fishbein AB, Zee PC. Sleep Disturbances in Adults with Eczema Are Associated with Impaired Overall Health: A US Population-Based Study. *Journal of Investigative Dermatology*. 2015;135(1):56-66.
10. Hafner M, Stepanek M, Taylor J, Troxel WM, van Stolk C. Why Sleep Matters—The Economic Costs of Insufficient Sleep: A Cross-Country Comparative Analysis. *Rand Health Quarterly*. 2017;6(4):11.
11. Nørreslet LB, Ebbelhøj NE, Ellekilde Bonde JP, Thomsen SF, Agner T. The impact of atopic dermatitis on work life - a systematic review. *J Eur Acad Dermatol Venerol*. 2017;32(1):23-38.
12. Andersen YMF, Egeberg A, Skov L, Thyssen JP. Comorbidities of Atopic Dermatitis: Beyond Rhinitis and Asthma. *Curr Derm Rep*. March 2017:1-7.
13. Yu SH, Silverberg JI. Association between Atopic Dermatitis and Depression in US Adults. *Journal of Investigative Dermatology*. December 2015:1-4.
14. 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(4):1041-1047.
15. Strom MA, Silverberg JI. Association between atopic dermatitis and extracutaneous infections in US adults. *Br J Dermatol*. 2016;176(2):495-497.
 16. Lim HW, Collins SAB, Resneck JS, et al. The burden of skin disease in the United States. *Journal of American Academy of Dermatology*. 2017;76(5):958–972.
 17. Ellis CN, Drake LA, Prendergast MM, et al. Cost of atopic dermatitis and eczema in the United States. *Journal of the American Academy of Dermatology*. 2002;46(3):361-370.
 18. Filanovsky MG, Pootongkam S, Tamburro JE, Smith MC, Ganocy SJ, Nedorost ST. The Financial and Emotional Impact of Atopic Dermatitis on Children and Their Families. *J Pediatr*. 2016;169:284-290.
 19. Eckert L, Gupta S, Amand C, Gadkari A, Mahajan P, Gelfand JM. The burden of atopic dermatitis in US adults: Health care resource utilization data from the 2013 National Health and Wellness Survey. *Journal of American Academy of Dermatology*. 2018;78(1):54–61.
 20. Drucker AM, Qureshi AA, Amand C, et al. Health Care Resource Utilization and Costs Among Adults with Atopic Dermatitis in the United States: A Claims-Based Analysis. *The Journal of Allergy and Clinical Immunology: In Practice*. 2018;6(4):1342-1348.
 21. Narla S, Hsu DY, Thyssen JP, Silverberg JI. Inpatient Financial Burden of Atopic Dermatitis in the United States. *Journal of Investigative Dermatology*. 2017;137(7):1461-1467. doi:10.1016/j.jid.2017.02.975.

22. Brennan T. New Specialty Drug for Atopic Dermatitis <https://payorsolutions.cvshealth.com/sites/default/files/cvs-health-payor-solutions-insights-feature-new-specialty-drug-for-atopic-dermatitis-october-.pdf>. Published October 18, 2016. Accessed June 20, 2018.
23. Institute for Clinical and Economic Review. Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value. https://icer-review.org/wp-content/uploads/2016/10/MWCEPAC_ATOPIC_FINAL_EVIDENCE_REPORT_060717.pdf. Published June 8, 2017. Accessed June 17, 2018.
24. Ahmed A, Solman L, Williams HC. Magnitude of benefit for topical crisaborole in the treatment of atopic dermatitis in children and adults does not look promising: a critical appraisal. *Br J Dermatol*. 2017;178(3):659-662.
25. National Institute for Health and Care Excellence. Dupilumab for treating moderate to severe atopic dermatitis. <https://www.nice.org.uk/guidance/gid-ta10218/documents/appraisal-consultation-document>. Published March 2, 2018. Accessed June 17, 2018.
26. Kuznik A, Bégo-Le-Bagousse G, Eckert L, et al. Economic Evaluation of Dupilumab for the Treatment of Moderate-to-Severe Atopic Dermatitis in Adults. *Dermatology and Therapy*. 2017;7(4):493-505.