

Accepted Manuscript

Health utility scores of atopic dermatitis in US adults

Jonathan I. Silverberg, MD, PHD, MPH, Joel M. Gelfand, MD, MSCE, David J. Margolis, MD, PHD, Mark Boguniewicz, MD, Luz Fonacier, MD, Mitchell H. Grayson, MD, Peck Y. Ong, MD, Zelma Chiesa Fuxench, MD, Eric L. Simpson, MD, MCR



PII: S2213-2198(18)30817-1

DOI: <https://doi.org/10.1016/j.jaip.2018.11.043>

Reference: JAIP 1907

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 24 October 2018

Revised Date: 13 November 2018

Accepted Date: 20 November 2018

Please cite this article as: Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, Ong PY, Fuxench ZC, Simpson EL, Health utility scores of atopic dermatitis in US adults, *The Journal of Allergy and Clinical Immunology: In Practice* (2019), doi: <https://doi.org/10.1016/j.jaip.2018.11.043>.

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Title: Health utility scores of atopic dermatitis in US adults.

Running Header: Utilities in AD.

Jonathan I Silverberg, MD, PHD, MPH¹, Joel M Gelfand, MD, MSCE², David J Margolis, MD, PHD², Mark Boguniewicz, MD³, Luz Fonacier, MD⁴, Mitchell H Grayson, MD⁵, Peck Y Ong, MD⁶, Zelma Chiesa Fuxench, MD², Eric L Simpson, MD, MCR⁷

1. Northwestern University Feinberg School of Medicine, Chicago, IL
2. University of Pennsylvania Perelman School of Medicine, Philadelphia, PA
3. National Jewish Health and University of Colorado School of Medicine, Denver, CO
4. NYU Winthrop Hospital, Mineola, NY
5. Nationwide Children's Hospital–The Ohio State University College of Medicine, Columbus, OH
6. Children's Hospital Los Angeles, University of Southern California, Keck School of Medicine, Los Angeles, CA
7. Oregon Health & Science University, Portland, OR

Word count: 2633 **Abstract word count:** 241

Figures: 4 **Tables:** 1 **Supplemental Figures:** 1

Abbreviations used: AD=atopic dermatitis; MH=mental health; CI=confidence interval; OR=odds ratio; aOR=adjusted odds ratio; DLQI = Dermatology Life Quality Index; POEM = Patient-Oriented Eczema Measure; PO-SCORAD = Patient-Oriented Scoring Atopic Dermatitis; HADS = Hospital Anxiety and Depression Scale; HADS-A = Hospital Anxiety and Depression Scale – Anxiety score; HADS-D = Hospital Anxiety and Depression Scale – Depression score; UKWP = United Kingdom Working Party

Keywords: Atopic dermatitis; eczema; epidemiology; health related quality of life; patient-burden; utility; quality of life adjusted years

Corresponding author:

Jonathan I. Silverberg, MD, PhD, MPH
Northwestern University Feinberg School of Medicine
Department of Dermatology
Suite 1600
676 N. St Clair St.
Chicago, IL 60611
Telephone: (312) 503-4985
Fax: (312) 695-0664
JonathanISilverberg@Gmail.com

Acknowledgements:

JI Silverberg had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.
Study concept and design: JI Silverberg

Acquisition of Data: Silverberg JI, Gelfand JM, Margolis D, Fonacier L, Boguniewicz M, Schwartz LB, Grayson MH, Ong P, Chiesa Fuxench Z

Analysis and interpretation of data: Silverberg JI, Gelfand JM, Margolis D, Fonacier L, Boguniewicz M, Schwartz LB, Grayson MH, Ong P, Chiesa Fuxench Z

Drafting of the manuscript: JI Silverberg

Critical revision of the manuscript for important intellectual content: Silverberg JI, Gelfand JM, Margolis D, Fonacier L, Boguniewicz M, Schwartz LB, Grayson MH, Ong P, Chiesa Fuxench Z

Statistical analysis: JI Silverberg

Administrative technical or material support: None

Study supervision: Allergy and Asthma Foundation of America

Conflicts of interest:

Dr. Silverberg served as a consultant and/or advisory board member for Abbvie, Asana, Eli Lilly, Galderma, GlaxoSmithKline, Glenmark, Kiniksa, Leo, Menlo, Pfizer, Regeneron-Sanofi, Realm, Roivant receiving honoraria; speaker for Regeneron-Sanofi; and received research grants from GlaxoSmithKline and Regeneron-Sanofi. Dr. Silverberg is supported by the Dermatology Foundation.

Dr. Gelfand served as a consultant for BMS, Boehringer Ingelheim, GSK, Janssen Biologics, Menlo Therapeutics, Novartis Corp, Regeneron, Dr Reddy's labs, UCB (DSMB), Sanofi and Pfizer Inc., receiving honoraria; and receives research grants (to the Trustees of the University of Pennsylvania) from Abbvie, Janssen, Novartis Corp, Sanofi, Celgene, Ortho Dermatologics, and Pfizer Inc.; and received payment for continuing medical education work related to psoriasis that was supported indirectly by Lilly and Ortho Dermatologics. Dr. Gelfand is a co-patent holder of resiquimod for treatment of cutaneous T cell lymphoma. Dr Gelfand is a Deputy Editor for the Journal of Investigative Dermatology receiving honoraria from the Society for Investigative Dermatology.

Dr. Chiesa Fuxench has served as a consultant for the National Eczema Association and the Asthma and Allergy Foundation, receiving honoraria, and receives or has received research grants (to the Trustees of the University of Pennsylvania) from Regeneron, Sanofi, Tioga and Vanda pharmaceuticals and Realm Therapeutics for work in atopic dermatitis; and has received payment for continuing medical education work related to atopic dermatitis that was supported indirectly by Regeneron and/or Sanofi.

Dr. Margolis is the chair of the data monitoring committee for many Sanofi clinical trials of Dupilumab, and, with respect to atopic dermatitis, has received independent research funding to his institution from the National Institute of Health and Valeant

Dr. Boguniewicz has received research funding from Anacor and Regeneron and consulted for Regeneron, Sanofi-Genzyme and Pfizer.

Dr Fonacier has served as consultant for Regeneron, receiving honoraria; speaker for Regeneron; received research and educational grants from Genentech, Baxter, and Pfizer

Dr Grayson is a board member of AAFA and chair for the AAFA Medical Scientific Council, and has served as a consultant for AstraZeneca.

Dr Simpson has served as a consultant and/or advisory board member for Regeneron-Sanofi.

Dr. Ong is a co-investigator of Atopic Dermatitis Research Network; he has consulted for Pfizer and Theravance, and has received research funding from Regeneron.

Funding Support: Atopic Dermatitis in America Study is an independent research project of the Asthma and Allergy Foundation of America in partnership with the National Eczema Association (NEA) and sponsored by Sanofi Genzyme and Regeneron.

Funding/Sponsor was involved? No

Design and conduct of the study: Yes__ No_X_

Collection, management, analysis and interpretation of data: Yes__ No_X_

Preparation, review, or approval of the manuscript: Yes__ No_X_

Decision to submit the manuscript for publication: Yes__ No_X_

Highlights

What's already known about this topic? Atopic dermatitis is a highly symptomatic disorder that can impact patients' quality of life.

What does this article add to our knowledge? Atopic dermatitis, particularly moderate-severe atopic dermatitis, was associated significantly lower health utility scores that were comparable to other debilitating diseases.

How does this impact current management? These data provide important insight for prioritization of resource allocation and cost-effectiveness research for atopic dermatitis.

Abstract

Background: The impact of atopic dermatitis (AD) on health related quality of life and health utility in the United States adult population is not well-established.

Objectives: To determine the health utilities and quality of life adjusted years (QALYs) lost in adults with vs. without AD among the US population.

Methods: A cross-sectional, population-based study of 3,495 adults was performed. AD was determined using modified UK Diagnostic Criteria for AD. AD severity was assessed using self-reported global AD severity, Patient-Oriented Eczema Measure (POEM), Patient-Oriented Scoring AD (PO-SCORAD), PO-SCORAD-itch and sleep. SF-6D health utility scores and total QALY loss were assessed.

Results: The mean [95% confidence interval] SF-6D score was lower in adults with AD compared to healthy adults (0.69 [0.68-0.70] vs. 0.79 [0.77-0.79]). In particular, moderate-severe AD (mean: 0.53-0.66) had similar or lower SF-6D scores than all other self-reported disorders examined, except autoimmune disorders. Adults with AD and atopic comorbidities had significantly lower SF-6D scores compared to those without atopic comorbidities. Among the 7 disorders examined, AD was associated with higher total QALY loss than autoimmune disorders, diabetes, food allergy, and heart disease in both males and females. The largest QALY loss was for moderate AD in females and mild AD in males.

Conclusion: Moderate-to-severe AD is associated with significant decrements of health utility in the US population. These data illustrate the heavy societal burden of moderate and severe AD and provide important insight for prioritization of resource allocation and cost-effectiveness research.

Introduction

Atopic Dermatitis (AD) is a common inflammatory skin disease of adulthood, affecting approximately 7% of the United States population^{1, 2}. AD is associated with a wide array of health related quality of life (HRQOL) impacts, including itch and skin pain, symptoms of anxiety and depression, impaired physical and social functioning^{1, 3-7}. All of these can have a profound impact on the overall health of AD patients. Various assessments can be used to capture information about HRQOL impacts in order to determine disease-burden and therapeutic response in clinical trials and practice.

HRQOL is an important factor in determining the overall health status of a population. Quality adjusted life years (QALYs) is a measure of health status that incorporates both quantity and quality of life. One QALY is equivalent to one year of life in perfect health. QALYs are fundamental to understanding the population-burden of disease and cost-effectiveness of disease treatment. QALYs are estimated using health utility weights, where one is equivalent to perfect health and zero is the worst possible state of health. However, little is known about the health utilities and QALY of AD in the US population. We hypothesized that AD is associated with significantly lower health utilities and higher QALY loss compared to those without AD. We also hypothesized that AD severity and comorbidities would be associated with even lower health utilities. In the present study, we sought to determine the health utilities and QALY lost in AD in the US population.

Methods

Data Source

Data were obtained from the AD in America survey whose population was sampled from the long-standing GfK Knowledge Panel. The AD in America study was designed to examine multiple facets of the patient-burden, comorbidities and resource utilization of US adults with AD. The GfK Knowledge panel is the largest and oldest probability-based web panel in the US and contains between 40,000 to 50,000 adult panel members at any given time. The GfK web panel was initially constructed from a national address-based sample of households in the US who are recruited to join in and receive small incentives for participating in web surveys on a regular basis. This approach uses a single sampling frame via the Delivery Sequence File of the US Postal Service to provide a statistically valid representation of the US population as well as many difficult-to-survey populations. The GfK web panel also provides internet access to households without existing internet access. This web-based panel has been previously used in other large, epidemiological studies and has been shown to be representative of the US population⁸⁻¹⁰. The survey questionnaire and protocol were approved by the ICF Institutional Review Board.

Study design

This was a cross-sectional study involving a two-stage sampling process. Stage 1 was designed to determine the prevalence of AD in US adults. In this stage, an initial cross-sectional sample of 2,137 adults from the existing GfK Knowledge web panel was invited to participate in the survey. The focus of the survey was not disclosed in the invitation to members of the web

panel to avoid biasing participation based on respondent interest or disinterest in the subject. A total of 1,278 adults completed the survey (completion rate=60.2%). Although this sample provided a precise estimate of the prevalence of AD among the adult population, it did not yield a large enough sample of AD patients to investigate differences between different levels of disease severity. In stage 2, an additional sample of 8,217 adults from the GfK knowledge panel completed screening to identify and interview an additional group of adults with AD; 19.7% met UKWP criteria and were eligible for inclusion (completion rate=59.9%) (Supplemental Figure 1). Using data from the US Census Bureau, sample weights were created that adjusted for age, gender, race, ethnicity, education level, census region, household income, home ownership status and metropolitan area using an iterative proportional fitting procedure. Sample weights were included in all analyses to allow for representative estimates of the US population.

AD, AD severity and atopic comorbidities

An adaptation of the United Kingdom Working Party (UKWP) criteria was selected by the *AD in America* advisory committee as the screening tool for patient eligibility¹¹. This included all aspects of the UKWP criteria (having an itchy skin condition during the past 12 months and 3 or more of the following: [1] history of skin crease involvement; [2] a personal history of asthma or hay fever; [3] a history of general dry skin during the past year; [4] onset under the age of two), except assessment of visible flexural eczema by a clinician was not performed. A sensitivity analysis was also performed using a definition of AD that allowed age of onset <18 years¹². Self-reported lifetime history of asthma or hay fever, and 1-year history of food allergy were assessed.

Self-assessments of AD severity included the previously validated self-reported global AD severity question “Would you describe your atopic dermatitis or eczema as mild, moderate, or severe?”¹³, as well as Patient-Oriented Scoring AD (PO-SCORAD) index [range: 0-103] and PO-SCORAD itch and sleep subscores [range: 0-10]¹⁴, and Patient-Oriented Eczema Measure (POEM) [7 questions; range: 0-28]¹⁵. These patient-reported outcomes were selected *a priori* based on their feasibility, being preferred measures by international consensus of the Harmonizing Outcome Measures in Eczema group^{16, 17} and/or previously being validated^{13, 16-18}. Scores were divided into three categories (clear/almost-clear/mild, moderate, severe/very severe) using previously reported severity strata^{15, 19}.

SF-6D and QALY loss

SF-12 Health Survey version 1.0 was used to assess health status (12 items, 8 domains, 4-week recall period)^{20, 21}. SF-6D is a preference-based single index measure for health that was derived from responses to the SF-12 using the Brazier scoring method and US population-based weights²². SF-6D scores range from 0.0 [worst health] to 1.0 [best health]. The six-point Likert scale for the mental health and vitality questions were converted to a five-point Likert scale using random reallocation of the response ‘a good bit of the time’ to either ‘some of the time’ or ‘most of the time’. SF-6D responses were then given a preference-based utility tariff using the parsimonious consistent model and allows for estimation of quality adjusted life years (QALYs) due to morbidity.

Statistical analyses

All data analyses and statistical processes were performed using SAS version 9.4 (SAS Institute) and included representative sample weights. Baseline respondent characteristics were determined. Weighted mean (95% confidence intervals) SF-6D scores were determined for AD, different strata of AD severity, atopic comorbidities, sex and/or age. Differences of SF-6D scores by the abovementioned groups were assessed using generalized linear models that included sample weights. Spearman correlations were used to compare SF-6D with PO-SCORAD, POEM, PO-SCORAD itch and sleep. Total QALY loss was estimated for mild, moderate and severe AD (determined by PO-SCORAD severity strata) and 6 other self-reported disorders assessed, and stratified by sex. A 2-sided P-value <0.05 was taken to indicate statistical significance for all estimates.

Results

Respondent characteristics

Overall, 3,495 adults were included in this study. Six hundred and two adults met AD criteria, resulting in a prevalence (95% CI) of AD of 7.39% (5.81-8.97%). Subjects with AD were 53.6% female and 71.9% Caucasian/white, with a mean $\pm$ std. dev. age of 52.0 ± 16.3 years. The weighted mean [95% CI] PO-SCORAD was 27.5 [25.7-29.3] and POEM was 7.5 [6.8-8.1].

SF-6D scores in AD

Overall, the mean [95% CI] SF-6D score in adults with AD (0.69 [0.68-0.70]) was numerically lower than healthy adults (0.79 [0.77-0.79]), but higher than all other chronic disorders examined (Figure 1). In particular, moderate-severe AD had the same or lower SF-6D scores than all self-reported disorders, except autoimmune disorders. Among adults with AD, there were no significant differences of SF-6D scores by sex or age-quartile ($P \geq 0.21$).

SF-6D scores in AD and atopic comorbidities

Adults with AD (0.69 [0.68-0.70] vs. 0.74 [0.73-0.75]), lifetime history of asthma (0.69 [0.68-0.70] vs. 0.74 [0.74-0.75]) and 1-year history of food allergy (0.67 [0.65-0.69] vs. 0.73 [0.72-0.74]) had significantly lower weighted mean [95% CI] SF-6D scores compared to those without these disorders ($P < 0.0001$ for all) (Figure 2A). Whereas, SF-6D scores were similar between those with or without a lifetime history of hay fever (0.72 [0.71-0.73] vs. 0.73 [0.71-

0.74], $P=0.58$). AD was associated with significantly lower SF-6D scores in adults both with and without asthma or hay fever, and in those with food allergy, but not in adults without food allergy.

Relationship between AD severity and SF-6D scores

SF-6D scores were moderately inversely correlated with PO-SCORAD (Spearman correlation; $\rho=-0.41$), POEM ($\rho=-0.29$), PO-SCORAD itch ($\rho=-0.28$) and PO-SCORAD sleep ($\rho=-0.42$) ($P<0.0001$ for all). Since AD severity can be defined by different constructs, SF-6D scores were stratified by the lesional severity and extent (PO-SCORAD), frequency of symptoms (POEM) and intensity of itch (PO-SCORAD itch). Moderate-severe (Figure 3A) or severe (Figure 3B) scores for any one of these were associated with significantly lower SF-6D scores ($P<0.0001$). Concurrent moderate-severe or severe PO-SCORAD, POEM and/or PO-SCORAD-itch were associated with even lower SF-6D scores compared with severe scores for only one or two of these assessments ($P<0.0001$).

There were also significant stepwise decreases of mean [95% CI] SF-6D scores severe (0.59 [0.54-0.64]) vs. moderate (0.64 [0.62-0.66]) vs. mild (0.73 [0.72-0.75]) self-reported global AD severity ($P<0.0001$ for all comparisons). Among adults with self-reported moderate-severe AD, there were significantly lower SF-6D scores in females vs. males (0.68 vs. 0.71, $P=0.009$), but no differences by age-quartile ($P=0.16$).

Comorbid asthma or food allergy were associated with lower SF-6D scores at all levels of self-reported global AD severity (Figure 2B). Whereas, comorbid hay fever was only associated with lower SF-6D scores in moderate and severe AD.

273

274 **QALY loss in AD**

275 Among the 7 disorders examined, the largest total QALY loss due to morbidity was for
276 hypertension in males (188,301) and anxiety/depression in females (251,763). When defining
277 AD using a criterion with age of onset <2 years, AD was associated with the second highest total
278 QALY loss in both males (159,774) and females (238,605), which was even higher than self-
279 reported autoimmune disorders, diabetes, food allergy, and heart disease (Figure 4). The largest
280 QALY loss was for moderate AD in females and mild AD in males. In a sensitivity analysis
281 using a definition of AD allowing for age of onset <18 years of age, AD had the highest total
282 QALY loss of all 7 disorders examined in males (201,805) and females (301,551), even higher
283 than high blood pressure, owing to a combination of high burden and higher disease prevalence
284 (9.1% [7.40-10.86%]).

Discussion

Using a US population-based sample, we found that adults with AD, particularly moderate and severe AD, had significantly lower SF-6D health utility scores. SF-6D had stronger correlations with PO-SCORAD and PO-SCORAD sleep than POEM and PO-SCORAD itch. AD and comorbid atopic disease was associated with even lower SF-6D scores compared to those with AD alone. The mean SF-6D scores observed in this study for healthy adults are consistent with estimates from the general US population²³. Further, mean SF-6D scores in respondents with severe AD (range from 0.53-0.66) were similar or lower than previously observed in other debilitating health disorders, e.g. epilepsy (0.67), scleroderma (0.61-0.64)²⁴, systemic lupus erythematosus (0.64)²⁵, moderate-severe psoriasis (0.739), psoriatic arthritis (0.65) and rheumatoid arthritis (0.53)²⁶. These results indicate that moderate-severe AD is associated with substantial decrements of HRQOL and health utility that are comparable or worse than many other chronic health disorders.

In addition, we found that AD was associated with more QALY loss than self-reported autoimmune disorders, diabetes, food allergy, and heart disease, owing to a combination of high prevalence and major HRQOL impact. Severe AD was associated with worse utility scores than mild or moderate AD, which were offset by a lower prevalence. Though, the greatest QALY loss in AD occurred from mild disease in males and moderate disease in males. Thus, mild and moderate AD still pose a societal burden and warrant both effective and cost-effective strategies for their prevention and treatment. Further, AD was associated with substantially lower utility scores among persons with atopic disease, i.e. asthma, hay fever and food allergy. Moreover, comorbid asthma or food allergy were associated with lower utility scores for all levels of AD severity. Interestingly, comorbid hay fever was associated with lower utility scores in persons

with moderate and severe AD, but higher utility scores in those with mild AD for unknown reasons. It may be that adults with mild AD who also have hay fever seek out allergy care and receive earlier treatment for their AD than those without hay fever.

This study builds upon previous reports from the AD in America study that demonstrated significantly poorer skin-related QOL²⁷, mental and physical function¹, and higher rates of anxiety and depression, autoimmune and cardiovascular comorbidities²⁸. This study demonstrates that AD, particularly moderate-severe AD, is associated with dramatically worse overall HRQOL with worse QOL impairment than previously observed in some of the most debilitating and even mortal disorders. The results have particular importance for resource allocation. First, they provide representative US population-based estimates for SF-6D health utility scores that can be used for cost-effectiveness analyses. Further, they indicate that AD poses a major public health burden with very high QALY loss owing to its high prevalence and burden. While most clinicians and epidemiologists are aware of the public health burden and costs of high blood pressure, few recognize the direct and indirect public health impact of AD. It appears that increased prioritization toward the study of AD epidemiology and resource utilization is warranted.

SF-6D is a generic HRQOL assessment that includes seven domains: physical functioning, role participation, social functioning, bodily pain, mental health, and vitality. The marked decreases of SF-6D observed in moderate-severe AD illustrate the multidimensional impact of AD on these HRQOL domains. Many of these HRQOL impacts are secondary to chronic pruritus and may occur in other chronic pruritic disorders²⁹⁻³¹. However, symptoms of pain, anxiety, depression, and limitations of physical and social functioning appear to be modifiable with adequate treatment in AD³²⁻³⁵. Thus, SF-6D may be a useful tool to assess

efficacy and cost-effectiveness of AD treatments. Of note, there are other commonly used health utility scores, including EuroQol EQ-5D and Health Utility Index. In general, all of these utilities have moderate to strong correlations with each other; though, each has its strengths and weaknesses³⁶. The validity of SF-6D and other health utilities in AD has not been established and is the subject of future research.

The strengths of this study include being large-scaled and population-based with a diverse sample and sample weights that allow for generalization of results to the US population, use of multiple and well-validated assessments of AD severity. We used an adaptation of the extensively validated UKWP criteria¹¹ to establish the diagnosis of AD. Thus, we believe that the case-definition of AD is valid. PO-SCORAD, POEM, and self-reported global AD severity have all been studied in AD patients and found to have overall good face validity, construct validity, internal consistency, reliability and/or responsiveness; POEM is the preferred assessment of AD symptoms for clinical trials by the Harmonizing Outcome Measures in Eczema group^{13, 37-52}. However, this study has limitations. Diagnosis and severity classification were not verified by physical exam and may be subject to misclassification. The effects of past and present treatment on HRQOL and health utility were not assessed. While the focus of the survey was not disclosed in the survey invitation, response bias is possible. Unfortunately, data for non-respondents were not recorded to examine this possibility. Future studies are warranted to address these points.

In conclusion, AD, particularly moderate-severe AD, is associated with significant decrements of HRQOL and health utility in the US population. AD was associated with greater total QALY loss than a number of other common chronic illnesses, including autoimmune disease, diabetes, high blood pressure and heart disease. These data illustrate the heavy societal

353 burden of moderate and severe AD and provide important insight for prioritization of resource
354 allocation and cost-effectiveness research.

References

1. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Patient-burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. *Ann Allergy Asthma Immunol* 2018.
2. Hua T, Silverberg JI. Atopic dermatitis in US adults - epidemiology, association with marital status and atopy. *Ann Allergy Asthma Immunol* 2018; In Press.
3. Vakharia PP, Chopra R, Sacotte R, Patel KR, Singam V, Patel N, et al. Burden of skin pain in atopic dermatitis. *Ann Allergy Asthma Immunol* 2017; 119:548-52 e3.
4. Simpson EL, Bieber T, Eckert L, Wu R, Ardeleanu M, Graham NM, et al. Patient burden of moderate to severe atopic dermatitis (AD): Insights from a phase 2b clinical trial of dupilumab in adults. *J Am Acad Dermatol* 2016; 74:491-8.
5. Brunner PM, Silverberg JI, Guttman-Yassky E, Paller AS, Kabashima K, Amagai M, et al. Increasing Comorbidities Suggest that Atopic Dermatitis Is a Systemic Disorder. *J Invest Dermatol* 2017; 137:18-25.
6. Silverberg J, Garg N, Silverberg NB. New developments in comorbidities of atopic dermatitis. *Cutis* 2014; 93:222-4.
7. Silverberg JI, Gelfand JM, Margolis D, Boguniewicz M, Fonacier L, Grayson MH, et al. Association of atopic dermatitis with allergic, autoimmune and cardiovascular comorbidities in US adults. *Annals of Allergy, Asthma & Immunology*.
8. Rowen TS, Gaither TW, Awad MA, Osterberg EC, Shindel AW, Breyer BN. Pubic Hair Grooming Prevalence and Motivation Among Women in the United States. *JAMA Dermatol* 2016; 152:1106-13.
9. Hays RD, Liu H, Kapteyn A. Use of Internet panels to conduct surveys. *Behav Res Methods* 2015; 47:685-90.
10. Heckman CJ, Darlow S, Manne SL, Kashy DA, Munshi T. Correspondence and correlates of couples' skin cancer screening. *JAMA Dermatol* 2013; 149:825-30.
11. Williams HC, Burney PG, Pembroke AC, Hay RJ. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. *Br J Dermatol* 1994; 131:406-16.
12. So how do I define atopic eczema? A practical manual for researchers wishing to define atopic eczema. Nottingham; 2002.] Available from <https://www.nottingham.ac.uk/~mzzfaq/dermatology/eczema/Section5-3.html>.
13. Vakharia PP, Chopra R, Sacotte R, Patel N, Immaneni S, White T, et al. Validation of patient-reported global severity of atopic dermatitis in adults. *Allergy* 2018; 73:451-8.
14. Stalder JF, Barbarot S, Wollenberg A, Holm EA, De Raevé L, Seidenari S, et al. Patient-Oriented SCORAD (PO-SCORAD): a new self-assessment scale in atopic dermatitis validated in Europe. *Allergy* 2011; 66:1114-21.
15. Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. *Br J Dermatol* 2013; 169:1326-32.
16. Spuls PI, Gerbens LA, Simpson E, Apfelbacher CJ, Chalmers JR, Thomas KS, et al. POEM a core instrument to measure symptoms in clinical trials: a HOME statement. *Br J Dermatol* 2016.
17. Chalmers JR, Thomas KS, Apfelbacher C, Williams HC, Prinsen CA, Spuls PI, et al. Report from the fifth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). *Br J Dermatol* 2018; 178:e332-e41.

- 399 18. Silverberg JI, Chiesa Fuxench ZC, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, et al.
400 Validation of a single-item patient-reported outcome for atopic dermatitis severity in US adults.
401 *Ann Allergy Asthma Immunol* 2018; In submission.
- 402 19. Rogers A, DeLong LK, Chen SC. Clinical meaning in skin-specific quality of life instruments: a
403 comparison of the Dermatology Life Quality Index and Skindex banding systems. *Dermatol Clin*
404 2012; 30:333-42, x.
- 405 20. Jenkinson C, Layte R. Development and testing of the UK SF-12 (short form health survey). *J*
406 *Health Serv Res Policy* 1997; 2:14-8.
- 407 21. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales
408 and preliminary tests of reliability and validity. *Med Care* 1996; 34:220-33.
- 409 22. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from
410 the SF-36. *J Health Econ* 2002; 21:271-92.
- 411 23. Hanmer J, Kaplan RM. Update to the Report of Nationally Representative Values for the
412 Noninstitutionalized US Adult Population for Five Health-Related Quality-of-Life Scores. *Value*
413 *Health* 2016; 19:1059-62.
- 414 24. Khanna D, Furst DE, Wong WK, Tsevat J, Clements PJ, Park GS, et al. Reliability, validity, and
415 minimally important differences of the SF-6D in systemic sclerosis. *Qual Life Res* 2007; 16:1083-
416 92.
- 417 25. Aggarwal R, Wilke CT, Pickard AS, Vats V, Mikolaitis R, Fogg L, et al. Psychometric properties of
418 the EuroQol-5D and Short Form-6D in patients with systemic lupus erythematosus. *J Rheumatol*
419 2009; 36:1209-16.
- 420 26. Strand V, Sharp V, Koenig AS, Park G, Shi Y, Wang B, et al. Comparison of health-related quality
421 of life in rheumatoid arthritis, psoriatic arthritis and psoriasis and effects of etanercept
422 treatment. *Ann Rheum Dis* 2012; 71:1143-50.
- 423 27. Chiesa Fuxench Z, Gelfand J, Margolis D, Boguniewicz M, Fonacier L, Grayson M, et al. Atopic
424 Dermatitis in America Study: prevalence and disease burden in the US adult population. *J Invest*
425 *Derm* 2018; In Press.
- 426 28. Silverberg JI, Gelfand JM, Margolis DJ, Boguniewicz M, Fonacier L, Grayson MH, et al. Association
427 of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults.
428 *Ann Allergy Asthma Immunol* 2018; 121:604-12 e3.
- 429 29. Kantor R, Dalal P, Cella D, Silverberg JI. Research letter: Impact of pruritus on quality of life-A
430 systematic review. *J Am Acad Dermatol* 2016; 75:885-6 e4.
- 431 30. Silverberg JI, Hinami K, Trick WE, Cella D. Itch in the General Internal Medicine Setting: A Cross-
432 Sectional Study of Prevalence and Quality-of-Life Effects. *Am J Clin Dermatol* 2016; 17:681-90.
- 433 31. Silverberg JI, Kantor RW, Dalal P, Hickey C, Shaunfield S, Kaiser K, et al. A Comprehensive
434 Conceptual Model of the Experience of Chronic Itch in Adults. *Am J Clin Dermatol* 2018.
- 435 32. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two Phase 3 Trials
436 of Dupilumab versus Placebo in Atopic Dermatitis. *N Engl J Med* 2016; 375:2335-48.
- 437 33. Kataoka YN, S. Is coping of atopic dermatitis patients originated from their own character or
438 secondarily remodeled by disease suffering? Obvious improvement of coping and psychiatric
439 symptoms after ,Ätight eczema control,Ä. *Acta Dermato-Venereologica* 2017; 97:880-1.
- 440 34. Vinnik T, Kirby M, Bairachnaya M, Koman I, Tarkina T, Sadykova G, et al. Seasonality and BDNF
441 polymorphism influences depression outcome in patients with atopic dermatitis and psoriasis.
442 *World Journal of Biological Psychiatry* 2017; 18:604-14.
- 443 35. Kawana S, Kato Y, Omi T. Efficacy of a 5-HT1a receptor agonist in atopic dermatitis. *Clinical and*
444 *Experimental Dermatology* 2010; 35:835-40.

36. Quercioli C, Messina G, Barbini E, Carriero G, Fani M, Nante N. Importance of sociodemographic and morbidity aspects in measuring health-related quality of life: performances of three tools: comparison of three questionnaire scores. *Eur J Health Econ* 2009; 10:389-97.
37. Badia X, Mascaro JM, Lozano R. Measuring health-related quality of life in patients with mild to moderate eczema and psoriasis: clinical validity, reliability and sensitivity to change of the DLQI. The Cavide Research Group. *Br J Dermatol* 1999; 141:698-702.
38. Coutanceau C, Stalder JF. Analysis of correlations between patient-oriented SCORAD (PO-SCORAD) and other assessment scores of atopic dermatitis severity and quality of life. *Dermatology* 2014; 229:248-55.
39. Holm EA, Wulf HC, Stegmann H, Jemec GB. Life quality assessment among patients with atopic eczema. *Br J Dermatol* 2006; 154:719-25.
40. Herd RM, Tidman MJ, Ruta DA, Hunter JA. Measurement of quality of life in atopic dermatitis: correlation and validation of two different methods. *Br J Dermatol* 1997; 136:502-7.
41. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; 19:210-6.
42. Jobanputra R, Bachmann M. The effect of skin diseases on quality of life in patients from different social and ethnic groups in Cape Town, South Africa. *Int J Dermatol* 2000; 39:826-31.
43. Holm EA, Esmann S, Jemec GB. Does visible atopic dermatitis affect quality of life more in women than in men? *Gend Med* 2004; 1:125-30.
44. Twiss J, Meads DM, Preston EP, Crawford SR, McKenna SP. Can we rely on the Dermatology Life Quality Index as a measure of the impact of psoriasis or atopic dermatitis? *J Invest Dermatol* 2012; 132:76-84.
45. Chalmers JR, Schmitt J, Apfelbacher C, Dohil M, Eichenfield LF, Simpson EL, et al. Report from the third international consensus meeting to harmonise core outcome measures for atopic eczema/dermatitis clinical trials (HOME). *Br J Dermatol* 2014; 171:1318-25.
46. Chalmers JR, Simpson E, Apfelbacher CJ, Thomas KS, von Kobyletzki L, Schmitt J, et al. Report from the fourth international consensus meeting to harmonize core outcome measures for atopic eczema/dermatitis clinical trials (HOME initiative). *Br J Dermatol* 2016; 175:69-79.
47. Gerbens LA, Chalmers JR, Rogers NK, Nankervis H, Spuls PI. Reporting of symptoms in randomized controlled trials of atopic eczema treatments: a systematic review. *Br J Dermatol* 2016; 175:678-86.
48. Gerbens LA, Prinsen CA, Chalmers JR, Drucker AM, von Kobyletzki LB, Limpens J, et al. Evaluation of the measurement properties of symptom measurement instruments for atopic eczema: a systematic review. *Allergy* 2017; 72:146-63.
49. Heintz D, Chalmers J, Nankervis H, Apfelbacher CJ. Eczema Trials: Quality of Life Instruments Used and Their Relation to Patient-reported Outcomes. A Systematic Review. *Acta Derm Venereol* 2016; 96:596-601.
50. Heintz D, Prinsen CA, Deckert S, Chalmers JR, Drucker AM, Ofenloch R, et al. Measurement properties of adult quality-of-life measurement instruments for eczema: a systematic review. *Allergy* 2016; 71:358-70.
51. Heintz D, Prinsen CA, Sach T, Drucker AM, Ofenloch R, Flohr C, et al. Measurement properties of quality-of-life measurement instruments for infants, children and adolescents with eczema: a systematic review. *Br J Dermatol* 2016.
52. Schmitt J, Williams H. Harmonising Outcome Measures for Eczema (HOME). Report from the First International Consensus Meeting (HOME 1), 24 July 2010, Munich, Germany. *Br J Dermatol* 2010; 163:1166-8.

ACCEPTED MANUSCRIPT

Figure Legends

Figure 1. Weighted mean (95% confidence intervals) SF-6D utility scores for United States adults with atopic dermatitis and other chronic disorders, and healthy adults without any chronic disorders.

Figure 2. Combined effects of atopic comorbidities with (A) atopic dermatitis and (B) atopic dermatitis severity on weighted mean SF-6D utility scores.

Figure 3. Associations of SF-6D with combined severity of atopic dermatitis signs and symptoms and itch. Combined effects of having no (0), some (1-2) or all (3) (A) moderate-severe or (B) severe scores for AD severity (PO-SCORAD), frequency of symptoms (POEM) and severity of pruritus (PO-SCORAD itch) on SF-6D utility scores. Box-whisker plots and overlaid jitter plots are presented. All subsets of combined AD severity had significantly higher SF-6D scores compared to persons with mild or mild-moderate scores for all three assessments ($P < 0.001$).

Figure 4. Total SF-6D QALY's lost to morbidity among adults with self-reported mild, moderate and severe AD and other chronic disorders. Atopic dermatitis was defined using the United Kingdom Working Party criteria, including having an itchy skin condition during the past 12 months and 3 or more of the following: [1] history of skin crease involvement; [2] a personal history of asthma or hay fever; [3] a history of general dry skin during the past year; [4] onset under the age of two. This is depicted as Atopic Dermatitis (A) in the graph. A sensitivity analysis was also performed using a definition of AD that allowed age of onset < 18 years. This is depicted as Atopic Dermatitis (B).

514

Table 1. Subject characteristics.

Variable	Atopic dermatitis	
	No (n=2291)	Yes (n=602)
Age (yr) – mean $\pm$ std. dev.	52.2 $\pm$ 16.4	51.0 $\pm$ 15.7
Female sex – freq (%)	1202 (52.5%)	349 (58.0%)
Race/ethnicity – freq (%)		
Caucasian/white	1684 (73.5%)	396 (65.8%)
African-American/black	195 (8.5%)	74 (12.3%)
Hispanic	264 (11.5%)	77 (12.8%)
Multiracial/other	148 (6.5%)	55 (9.1%)
Level of education		
Less than high school	140 (6.1%)	48 (8.0%)
High school or equivalent	668 (29.2%)	164 (27.2%)
Some college	703 (30.7%)	186 (30.9%)
Bachelor's degree or higher	780 (34.1%)	204 (33.9%)
Self-reported AD severity		
Mild	–	289 (59.4%)
Moderate	–	172 (34.8%)
Severe	–	34 (6.9%)









