The Burden of Childhood Atopic Dermatitis in the Primary Care Setting- A report from the Meta-LARC Consortium

Jinan Al-naqeeb, MD MPH[1], Sankirtana Danner, MA, CCRP[2], Lyle J. Fagnan, MD[2], Katrina Ramsey, MPH[3], LeAnn Michaels[2], Julie Mitchell[4], Kelsey Branca, MPH[2], Cynthia Morris, PhD, MPH,[4] Donald E. Nease, Jr., MD[5], Linda Zittleman, MSPH[5], Barcey Levy, MD,PhD[6], Jeanette Daly, RN, PhD[6], David Hahn, MD, MS[7], Rowena J. Dolor, MD, MHS[8], Hywel C. Williams, DSc, FMedSci, [9] Joanne R Chalmers, PhD, BSc[9] , Jon Hanifin, MD[1], Susan Tofte, RN, FNP[1], Katharine E. Zuckerman, MD, MPH[3,10], Karen Hansis, Mollie Gundersen, Julie Block, Francie Karr, Sandra Dunbrasky, MD, Kathy Siebe, CPNP, Kristen Dillon[2], MD, Ricardo Cibotti, PhD, Jodi Lapidus, PhD[3] and Eric L. Simpson, MD, MCR[1]

[1]Department of Dermatology, Oregon Health and Science University, Portland Oregon

[2]Oregon Rural Practice-based Research Network, Oregon Health and Science University, Portland Oregon

[3]Public Health and Preventive Medicine, Oregon Health and Science University, Portland Oregon

[4]Oregon Clinical and Translational Research Institute, Oregon Health & Science University, Portland Oregon

[5]High Plains Research Network, University of Colorado

[6]Iowa Research Network, University of Iowa

[7]Wisconsin Research and Education Network, University of Wisconsin

[8]Primary Care Research Consortium, Duke University

[9]Centre of Evidence-Based Dermatology, University of Nottingham, England

[10]Division of General Pediatrics, Oregon Health and Science University, Portland, Oregon

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Study concept and design: Simpson, Danner
Acquisition, analysis, and interpretation of data: Simpson, Danner, Daly, Al-naqeeb.
Drafting of the manuscript: Al-naqeeb, Simpson.
Critical revision of the manuscript for important intellectual content: all authors
Statistical analysis: Al-naqeeb, Ramsey
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Address for Correspondence:
Eric Simpson
OHSU Department of Dermatology
3303 SW Bond Avenue, CHH 16D
Portland OR 97239
Phone: 503-494-2121
Email: simpsone@ohsu.edu

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Abstract

Background: Little is known about the burden of AD encountered in U.S. primary care practices and the frequency and type of skin care practices routinely used in children.

Objectives: To estimate the prevalence of AD and allergic comorbidities in children 0-5 years attending primary care practices in the U.S. and to describe routine skin care practices used in this population.

Design: A cross-sectional survey study of a convenience sample of children under the age of 5 attending primary care practices for any reason.

Setting: Ten primary care practices in five U.S. states

Results: Amongst 652 children attending primary care practices, the estimated prevalence of ever having AD was 24 % (95% CI= 21-28) ranging from 15% among those under the age of one to 38% among those aged 4- 5 years. The prevalence of comorbid asthma was higher among AD participants compared to those with no AD, 12% and 4%, respectively ($p<0.001$). Moisturizers with high water:oil ratios were most commonly used (i.e., lotions) in the non-AD population, whereas moisturizers with low water:oil content (i.e. ointments) were most common when AD was present.

Conclusions: Our study found a large burden of AD in the primary care practice setting in the U.S. The majority of households reported skin care practices in children without AD that may be detrimental to the skin barrier such as frequent bathing and the routine use of moisturizers with high water: oil ratios. Clinical trials are needed to identify which skin care practices are optimal for reducing the significant risk of AD in the community.

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Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin condition that usually starts in early childhood but can develop at any age.[1-3] AD represents a substantial disability burden on a global scale.[4] Large international studies reveal a wide range of prevalence rates in industrialized countries ranging between 10-30%, with rates varying greatly by geographic area.[5-7] U.S.-specific studies find similar high rates of disease prevalence and similar geographic variability in prevalence.[8,9] Most of our understanding of AD prevalence in the U.S. stems from a limited number of national population-based surveys which are now over ten years old.[2,8,9] While they provide a reasonable estimate of population prevalence, population-based studies do not always accurately reflect the burden of a disease encountered in community healthcare settings - an important consideration for resource allocation by decision makers.[10,11] A better understanding of the burden of AD and the associated allergic comorbidities encountered in primary care practices helps to plan disease prevention strategies appropriate to this setting. Prevention strategies that prevent AD development may also reduce allergic comorbidities that often follow AD development such as allergic asthma.

Epidemiological studies identify several risk factors for AD development including climatic factors,[12] cat ownership, [13]proximity to traffic,[14] early allergen sensitization, family history of atopic diseases, and a FLG gene mutation (a gene important for proper skin barrier function).[15] In a large unselected cohort from the U.K., skin barrier dysfunction as measured by transepidermal water loss at 2 days and 2 months of age was the strongest risk factor for AD development at 12 months of age- more so than a FLG mutation or family history of atopy.[15]

Because of the role early skin barrier dysfunction may play in AD development, our group and others have been interested in how skin care practices and moisturizer use may modify AD disease risk. Currently, there are no data to support the need for routine emollient use in healthy newborns.[16] However, three pilot trials suggest daily moisturizer therapy in high-risk populations may reduce the risk of developing AD by as much as 50%.[17-19] The optimal type of moisturizer that protects against AD in not clear, although moisturizers with higher oil content are thought to enhance skin barrier function more so than lower oil content moisturizers.[20] Because plain water and fragrances can be an irritant to skin, fragranced moisturizers with high water content may, in theory, be detrimental to skin barrier function. Some authors postulate that the increased use of fragranced lotions early in life may explain the rising epidemic of AD although no studies have shown this association in a rigorous manner.[21]

In order to develop and study novel skin care interventions as a prevention strategy for AD, data are needed regarding the routine skin practices currently used by U.S. families. In preparation for a large community-based trial evaluating moisturizers for the prevention of AD, we sought to determine the prevalence of AD in children attending primary care settings using a convenience sample of children under the age of five and aimed to describe current skin care practices utilized by parents on their children both with and without AD.

Methods

Study Design, Population and Setting

This study, named the Community-based Assessment of Skin Care, Allergies and Eczema (CASCADE) study, was a cross sectional survey study conducted in five U.S. states. CASCADE was a planning study to determine the feasibility of conducting a large, five-year, community-based pragmatic randomized controlled clinical trial to test the hypothesis that certain skin care practices can prevent or delay AD and allergic comorbidities. Study participants were dyads of parents or guardian and children 0-5 years old attending one of ten community-based pediatric (n=6) and family medicine (n=4) clinics located in Oregon, Wisconsin, Colorado, North Carolina, and Iowa. These clinics were all members of a practice-based research network (PBRN) within their respective state and were a mix of rural and suburban practices. All participating PBRNs collaborate via the Meta-network Learning and Research Center (Meta-LARC) consortium, an administrative structure funded by the Agency for Healthcare Research and Quality encompassing almost 1000 primary care practices and 7000 clinicians (https://www.ohsu.edu/xd/outreach/oregon-rural-practice-based-research-network/meta-larc/index.cfm, accessed April, 2018). PBRNs serve as essential partners in translating academic research advances into real-world health improvements in the general ambulatory care population.[22] The study was approved by the institutional review board (IRB#11116) of Oregon Health and Science University and recruited participants from April 2015 through January 2016.

Inclusion required being a parent or legal guardian, aged ≥18 years, of a child between the ages of 0 and 5 years who was a current patient at the participating clinic; respondents also needed to be able to read and write in either English or Spanish. Potential respondents were excluded if unable to complete the questionnaire due to mental or cognitive capacity, if they or another of

the child's parents had already completed the questionnaire (ascertained by self-report), or if the child had been born preterm at less than 25 weeks of pregnancy.

Recruitment

The Iowa PBRN recruited participants by mail only whereas all other PRBNs used a combination of the following methods to capture as wide a sample as possible: in clinic while waiting for their appointments, mailed surveys, and electronic surveys via Research Electronic Data Capture (REDCap) hosted by OHSU. This flexibility in recruitment methods allowed for a minimal impact on clinic workflow that is critical to performing research in this setting. Clinic staff were instructed to broadly distribute the surveys to all eligible patients attending the clinic during the enrollment period, without selecting for any demographic or medical history in order to minimize selection bias. Due to the nature of the survey distribution in a busy practice setting, refusals were not recorded, thus we are unable to report a participation rate.

Instrument

The questionnaire was completed by the child's caregiver and included questions about AD history, symptoms, age of onset, presence of other atopic disorders, medications use, and skin care and bathing practices (Supplemental Figure 1.) The questionnaire was adapted from previous childhood AD surveys that have been used and validated in a community setting to measure the prevalence of AD. [2,9,23]

AD and severity assessment

A history of AD was determined by a positive response to the question "Have you ever been told by a health care provider that your child has eczema or atopic dermatitis?" A similar question has been shown to have adequate sensitivity and specificity to estimate the prevalence of AD in the US. [24-26] We assessed the effect of AD on the child's sleep by asking how many nights in the past week the child's sleep had been disturbed because of a red rash or eczema. AD severity was assessed by asking respondents to rate the rash or eczema as mild, moderate, or severe. This question has been used previously in epidemiological studies to assess severity and found to be a good indicator of childhood AD burden. [2,9,27]

Comorbidities and Family History

A history of asthma and wheezing were measured using the questions "Has your child ever been diagnosed with asthma by a healthcare provider?" and "Has your child ever had wheezing?" Food allergies were measured by asking "Has your child ever been diagnosed with a food allergy by a healthcare provider?" Family history of any atopic condition was assessed by asking the question "Has at least one of your child's parents or older brothers or sisters (related by blood) ever had any of the following conditions: eczema, asthma, or hay fever/spring-time allergies". Parental history of asthma was considered positive if at least one of the parents had asthma. The questions were adapted from previously validated questions used in epidemiological studies which measured comorbidities.[28,29]

Skin Care and Bathing

Moisturizer use was assessed by answering the question “do you use a moisturizer/lotion/ oil on your child’s skin.” An affirmative response to the above question was followed by secondary questions about the type of moisturizer and the application site-all over the body or just on dry areas. Moisturizer type was assessed by asking the following question: “Which moisturizer(s) did you use on your child”. The answer choices included the most commonly used commercial moisturizers brands.; CeraVe cream, Cetaphil cream, Vaseline/ petroleum jelly, Sunflower seed oil, Aveeno, Aquaphor, Vanicream and Johnson’s baby lotion. If the moisturizer that had been used was not listed in the answer choices that were given, the parents were instructed to check “other” and write what they were using. For a better understanding of current trends in moisturizer use, more than one answer was acceptable for this question. We stratified moisturizers based on their content: lotion, cream, ointment or liquid oil. If the parents did not specify the type (i.e. lotion, ointment, cream or liquid oil), and the brand product could represent more than one type of moisturizer, the answer was excluded from analysis.

Moisturizer frequency and bathing or shower frequency was measured using the following questions: “Over the past 3 months, on average how many days per week was a moisturizer/ lotion/oil applied to your child’s skin” and “Over the past 3 months, on average how many days per week did your child receive either a bath or shower?” Moisturizer frequency was asked only in those participants who were using moisturizers, while bathing frequency was asked of the whole sample. We categorized frequency of moisturizer use and bathing into two categories: < 4 and 4 days or more per week. Since the biological effect of most moisturizers lasts more than twenty-four hours, we considered 4 days a week or more to be frequent use.

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223 Sample Size and Statistical Analysis

224 A sample size of approximately 250 was estimated to provide a reasonably precise sample of
225 disease prevalence from age 0-5 years with a 95% confidence interval within 5 percentage
226 points. Our actual sample was significantly larger in order to obtain an adequate sample from all
227 age groups and study sites. We excluded 9 respondents who failed to provide the child's age
228 (n=5) and history of provider diagnosis of AD (n=3), or both (n=1); our final dataset included
229 652 children.

230

231 We calculated simple descriptive statistics overall and for AD and non-AD groups and tested
232 differences with Chi square (χ^2) tests. To estimate age-specific characteristics of AD, we used
233 predictive margins from a logistic regression model with clustered standard errors to account for
234 correlation between respondents from the same clinic. Similarly, estimates of comorbid
235 conditions and skin care practices resulted from logistic or log-binomial (relative risk) models
236 with clustered standard errors and including age, in months, as a covariate to adjust for this
237 effect. All analyses were performed using Stata SE for windows version 14 (Stata Corp, College
238 Station, Texas).

239

240 **Results**

241 A total of 652 caregivers with children aged between 0-5 years participated in the study with 24
242 % (95% CI 21-28) overall parent-reported prevalence of AD. The mean ± standard deviation of

age of participants was 22.5 ±19.4 months, and the mean age at which AD first appeared was 9±10.4 months. Those with AD were far more likely to experience dry skin than those in the non-AD group (63% vs 17%, p <0.001).There were no significant differences between those with AD compared to the non-AD group in regards to sex, parent language, race/ethnicity, or geographic distribution. Participants' characteristics are summarized in Table 1.

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AD prevalence and severity

As expected, AD prevalence steadily increased with age, ranging from 14.5 % among children less than 1 year old to 38 % among children 4-5 years old (p<0.001). Overall, 58% of children with AD had mild symptoms, 39% had moderate and only 3% (4 children) had severe disease. Among the same children with AD, 21 % had reported AD-related sleep disturbance in the previous week. Although we did not detect trends in severity or AD- related sleep disturbance by age, prescriptions for eczema medications were common overall (75% of children with AD) and increased with age. 67% and 69 % of children less than 1 year of age and 1-2 years-olds, respectively were prescribed medication compared to higher percents, 75% and 86%, for older age groups (2-3 years, and 4-5 years, respectively; p = 0.019), see Table 2.

Comorbidities and Family History

Children with AD in this study had a higher reported prevalence of certain comorbidities with known or suspected links to AD. Age adjusted prevalence of asthma was about three times as high in the AD group compared to non-AD group (prevalence ratio (PR) 3.0, p<0.001). History

of wheezing, including wheezing without a cold, were higher among the AD population compared to the non-AD group (PR 1.4 and 1.8, $p< 0.05$). Food allergies were 3.7 times more common among those with AD ($p=0.005$). Family history of any atopic condition—a known risk factor for AD—was also significantly higher in the AD group (PR 1.3, $p< 0.001$). (Table 3)

Skin Care and Bathing

Use of moisturizer (at any frequency) was common in the whole sample; however it was found to be significantly higher among the AD group (90%) compared to the non-AD group (74%, $p <0.001$). For children *without* AD, parents most commonly used lotions (64%) on their children, whereas parents of children *with* established AD most commonly used oil-rich moisturizers such as cream or ointment (65%) possibly in response to guideline-driven recommendations for AD treatment by their health practitioners. The mean number of days used per week for the overall sample was 4.3 and the mean number of daily bath/showers per week was 4.6. Among those who used moisturizer, the majority (65%) applied it 4 or more days per week and there was no significant difference in moisturizer frequency application when stratified by age. Those with AD applied moisturizers more days per week than those in the non-AD group (4 or more days a week = 75% vs. 60%, $P =0.001$). Overall 41% of the children received a bath/shower less than 4 days/week, while 59% received a bath/shower 4 or more days per week. There was no significant difference in bathing frequency between those with AD compared to those without AD. When bathing frequency was examined by age, those who were under the age of one received less bath/

shower per week compared with the older participants regardless of AD status, $P < 0.001$. Summaries of skin care practices appear in Tables 4 and 5.

Discussion

We estimated the prevalence of AD among children age 0-5 attending community based primary care practices to be approximately 24%, with a mean age of AD onset in the first year of life. Parent reported AD severity was mild in more than half of participating children, and 20% of those with AD, had their sleep disturbed at least once a week as a result of their AD. As anticipated, a higher prevalence of AD-associated comorbidities and a family history of atopic conditions were found among those with AD. The majority of parents were using some kind of moisturizer on their child's skin on a regular basis; children with AD were more likely to receive creamy and oily moisturizers while children without AD were receiving lotions primarily. This large community based study is the first study to describe the pediatric AD burden within community-based primary care practices and provides important insight into skin care practices that may be modifiable in future disease prevention studies.

A higher prevalence of AD (24%) was found in children under the age of five in our study compared to U.S. population-based studies using data from the National Survey of Children Health (NSCH). Shaw found prevalence rates ranging between 13.12 % - 14.73% among those under the age of four.[8] Similar to our findings, previous studies of chronic illnesses found a higher prevalence rate in the primary care setting compared to the population setting.[10,11] Measuring the prevalence of AD in children attending primary care clinics reflects the disease burden in these community clinics, while population-based studies provide estimates for a

general population that may or may not be accessing the healthcare system.[10] Understanding the disease burden is important from both perspectives to provide information to investigators, clinicians, patients and resource allocation stakeholders.

Similar to population-based studies, our study confirmed that allergic comorbidities are also common in children with AD attending community-based primary care clinics. The consistency of our data with other national surveys of allergic diseases lends support that our sample population adequately represents the U.S. AD population. For example, the overall prevalence of asthma found in our sample population of 0-5 year olds of 7% closely mirrors the Centers for Disease Control and Prevention (CDC) statistics from the Behavioral Risk Factor Surveillance System (BRFSS) 2013 data which measured the life time prevalence of asthma in the general U.S. population to be 7.3% among children under the age of five.[30] We also confirmed the higher rate of asthma among those with AD (16%) compared to non-AD children (4%) consistent with many previous studies.[31-33] Patients with AD also had a higher prevalence of a family history of allergic disease in our study confirming that a family history of atopy represents an important risk factor for AD development.

This study provides insight into skin care practices used in the very young- a subject of relatively limited study especially given our new understanding of the importance of the skin barrier in the development of AD. Kelleher and colleagues found skin barrier function in the first 2 months of life to be the strongest predictors of AD development.[34] Thus, skin care practices that have the potential to alter skin barrier function may represent important determinants or modifiers of AD

development. In this present study, the majority of caregivers applied some kind of moisturizer on their child's skin, even among children without reported AD diagnosed by a healthcare provider. As expected, children with AD reported more frequent use of thick moisturizers (i.e. creams and ointments) than those without AD, as this is the most common first-line treatment for mild AD. Thus, children with AD appear to receive appropriate education regarding moisturizer use supported by published treatment guidelines.[35] In those without AD, we found the majority of parents used more water-based moisturizers (i.e. lotions) on the skin, as opposed to thicker moisturizers, with the majority of usage more than 4 days per week. These skin care practices are similar to those described in a single-center study in Oregon and confirm findings from a market-based study showing a very high use of water-based moisturizers (lotions) in babies on a regular basis.[36,37] This high use of moisturizers are likely a result of cultural preferences or marketing as skin care guidelines for neonates do not recommend routine use of mositurizers. The U.S. Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN) released updated guidelines for neonate and infant skin care that state it is unclear whether the routine use of moisturizers benefits infant health.[16] Certain moisturizers could potentially even harm the skin barrier with frequent use such as those with irritants, fragrances or high water content,[38-41] thus potentially provoking AD in genetically-susceptible neonates. There is no clinical evidence, however, that the use of fragranced lotions in neonates promotes AD. The guidelines do recommend moisturizer use for dry or cracking skin and routine use for AD and infantile seborrheic dermatitis. Published guidelines from a European roundtable meeting on best practice for infants recommend routine moisturizer/ moisturized cleanser use during and after bathing for infants who are at high risk of developing AD if its needed based on their skin condition.[42] It is

unclear what influence the frequency and type of moisturizer used has on the development of AD. Further studies are needed to inform best practices in the general population.

Similar to moisturizer use, the type and frequency of bathing is an understudied area in newborn health. Several studies found that exposure to water alone can be detrimental to the skin barrier,[43] although no studies have evaluated the clinical effects of various methods of bathing or frequency on AD development. We found that more than half of the participants received baths/showers on 4 or more days per week. These results are in agreement with a previous case-control study that found the mean frequency of baths children received was 4-5 per week.[37] The current AWHONN guidelines for neonates and infants recommended bathing infants every few days and no more than every other day.[16] Additionally, AWHONN concluded that there were no clear benefits from daily bathing however they left the decision about frequency of bathing to be based on individual neonate's needs considering the family beliefs and culture.[16] Similar recommendations were published in 2009 by the European roundtable meeting on best practice for infants which recommend bathing 2-3 times a week using a mild cleanser and conclude that bathing does not harm the baby.[42]

The strengths of our study include the use of primary care-based sampling to better understand AD burden in the primary care clinical setting, the use of clinics that are members of practice-based research networks experienced in executing research protocols, and the inclusion of questions regarding skin care practices that are usually overlooked in AD surveys. Limitations of the study are that we cannot exclude the potential for selection bias that could yield artificially

inflated prevalence rates. Because of regional variation in AD prevalence, the prevalence data from the states included in this study may not be generalizable to all states in the U.S. In addition, the diagnosis of AD was made by parental report of a healthcare provider diagnosis rather than direct examination by a provider. Last, possible failure to complete the survey existed for children with more complex healthcare visits such as those with chronic health conditions.

In conclusion, our study found a large burden of AD in the primary care practice setting in the U.S. The majority of households use skincare practices that may be detrimental to the skin barrier of children not diagnosed with AD such as frequent bathing and the use of watery lotions frequently. Clinical trials will allow us to identify which skin care practices are optimal for reducing the significant burden of AD in the community.

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