

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

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71 **Abstract**

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

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

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

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

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

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



93 **Introduction**

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

108

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



115

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

127

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

## 134 **Methods**

### 135 Study Design, Population and Setting

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

153

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

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

160

### 161 Recruitment

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

### 171 Instrument

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

177

### 178 AD and severity assessment

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

187

#### 188 Comorbidities and Family History

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

198

#### 199 Skin Care and Bathing

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

213

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

222

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 ( $\chi^2$ ) 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  $\pm$  standard deviation of

243 age of participants was  $22.5 \pm 19.4$  months, and the mean age at which AD first appeared was  
244  $9 \pm 10.4$  months. Those with AD were far more likely to experience dry skin than those in the  
245 non-AD group (63% vs 17%,  $p < 0.001$ ). There were no significant differences between those  
246 with AD compared to the non-AD group in regards to sex, parent language, race/ethnicity, or  
247 geographic distribution. Participants' characteristics are summarized in Table 1.

248 .

### 249 AD prevalence and severity

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

259

### 260 Comorbidities and Family History

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

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

268

269

#### 270 Skin Care and Bathing

271 Use of moisturizer (at any frequency) was common in the whole sample; however it was found  
272 to be significantly higher among the AD group (90%) compared to the non-AD group (74%,  $p$   
273  $< 0.001$ ). For children *without* AD, parents most commonly used lotions (64%) on their children,  
274 whereas parents of children *with* established AD most commonly used oil-rich moisturizers such  
275 as cream or ointment (65%) possibly in response to guideline-driven recommendations for AD  
276 treatment by their health practitioners. The mean number of days used per week for the overall  
277 sample was 4.3 and the mean number of daily bath/showers per week was 4.6. Among those who  
278 used moisturizer, the majority (65%) applied it 4 or more days per week and there was no  
279 significant difference in moisturizer frequency application when stratified by age. Those with  
280 AD applied moisturizers more days per week than those in the non-AD group (4 or more days a  
281 week = 75% vs. 60%,  $P = 0.001$ ). Overall 41% of the children received a bath/shower less than 4  
282 days/week, while 59% received a bath/shower 4 or more days per week. There was no significant  
283 difference in bathing frequency between those with AD compared to those without AD. When  
284 bathing frequency was examined by age, those who were under the age of one received less bath/



285 shower per week compared with the older participants regardless of AD status,  $P < 0.001$ .

286 Summaries of skin care practices appear in Tables 4 and 5.

## 287 **Discussion**

288 We estimated the prevalence of AD among children age 0-5 attending community based primary  
289 care practices to be approximately 24%, with a mean age of AD onset in the first year of life.

290 Parent reported AD severity was mild in more than half of participating children, and 20% of  
291 those with AD, had their sleep disturbed at least once a week as a result of their AD. As

292 anticipated, a higher prevalence of AD-associated comorbidities and a family history of atopic  
293 conditions were found among those with AD. The majority of parents were using some kind of

294 moisturizer on their child's skin on a regular basis; children with AD were more likely to receive  
295 creamy and oily moisturizers while children without AD were receiving lotions primarily. This

296 large community based study is the first study to describe the pediatric AD burden within

297 community-based primary care practices and provides important insight into skin care practices  
298 that may be modifiable in future disease prevention studies.

299

300 A higher prevalence of AD (24%) was found in children under the age of five in our study

301 compared to U.S. population-based studies using data from the National Survey of Children

302 Health (NSCH). Shaw found prevalence rates ranging between 13.12 % - 14.73% among those

303 under the age of four.<sup>8</sup> Similar to our findings, previous studies of chronic illnesses found a

304 higher prevalence rate in the primary care setting compared to the population setting.<sup>10,11</sup>

305 Measuring the prevalence of AD in children attending primary care clinics reflects the disease

306 burden in these community clinics, while population-based studies provide estimates for a

307 general population that may or may not be accessing the healthcare system.<sup>10</sup> Understanding the  
308 disease burden is important from both perspectives to provide information to investigators,  
309 clinicians, patients and resource allocation stakeholders.

310

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

323

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

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

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

353

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

367

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

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

379

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

385

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