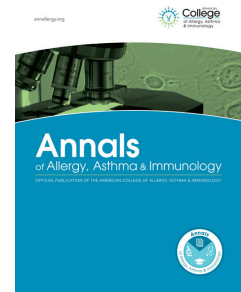


Journal Pre-proof

Childhood Atopic Dermatitis is Associated with Cognitive Dysfunction A NHIS study from 2008-2018

LaDonya Jackson-Cowan, PhD, MSc, Emily F. Cole, MD, MPH, Jonathan I. Silverberg, MD, PhD, MPH, Leslie P. Lawley, MD



PII: S1081-1206(20)31170-4

DOI: <https://doi.org/10.1016/j.anai.2020.11.008>

Reference: ANAI 3423

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 5 October 2020

Revised Date: 3 November 2020

Accepted Date: 9 November 2020

Please cite this article as: Jackson-Cowan L, Cole EF, Silverberg JI, Lawley LP, Childhood Atopic Dermatitis is Associated with Cognitive Dysfunction A NHIS study from 2008-2018, *Annals of Allergy, Asthma and Immunology* (2020), doi: <https://doi.org/10.1016/j.anai.2020.11.008>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. 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.

© 2020 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Article type: Original article

Childhood Atopic Dermatitis is Associated with Cognitive Dysfunction

A NHIS study from 2008-2018

LaDonya Jackson-Cowan, PhD, MSc¹, Emily F.Cole, MD, MPH², Jonathan I. Silverberg, MD, PhD, MPH³, Leslie P. Lawley, MD²

¹The Medical College of Georgia at Augusta University, AU/UGA Medical Partnership, Athens, GA; ²Department of Dermatology, Emory University School of Medicine, Atlanta, GA; ³Department of Dermatology, George Washington University School of Medicine and Health Sciences, Washington, DC

Corresponding Author:

LaDonya Jackson-Cowan The Medical College of Georgia at Augusta University, AU/UGA Medical Partnership, Athens, GA

Tel: 404-778-3794

Fax: 404-712-4920

Email: Ladonyajackson@gmail.com

Funding sources: The study was supported by Medical College of Georgia Medical Scholars program.

Conflicts of interest: No conflicts of interest.

Keywords: Atopic dermatitis, inflammation, cognitive dysfunction, learning and memory

Abbreviations: Atopic dermatitis (AD), attention deficit hyperactivity disorder (ADHD), National Health Interview Survey (NHIS), brain-derived growth factor (BDNF), odds ratio (OR), adjusted odds ratio (aOR)

Tables: 5

Figures: none

Abstract word count: 221

Manuscript word count: 2159

20-10-0653R1

Background: Atopic dermatitis (AD) is a common inflammatory skin disease in children and adults. Little is known about the association of childhood AD with cognitive dysfunction.

Objective: To examine the association of AD and cognitive dysfunction, including memory impairment and developmental delays, in US children (age <18 years). **Methods:** Data were analyzed from the National Health Interview Survey (NHIS) 2008-2018 for children. The NHIS utilizes a multistage, clustered, cross-sectional design.

Results: The prevalences of cognitive dysfunction, such as memory impairment (0.87% vs. 0.42%), developmental delays (6.96% vs. 3.87%) and attention deficit (hyperactivity) disorder (ADD/ADHD) (10.78% vs. 8.10%) were higher in children with versus without AD. In multivariable logistic regression models adjusting for age, sex, race, region, socioeconomic factors, allergic conditions and mental health childhood AD was associated with higher odds of memory impairment (adjusted odds ratio [95% confidence interval]: 1.84 [1.34-2.51]), developmental delays (1.54 [1.40-1.70]) and ADD/ADHD (1.31 [1.20-1.42]) compared to children without AD. Childhood atopic disease (defined as comorbid AD, asthma, allergic rhinitis and food allergies) further increased the prevalence of developmental delays to 13.44% (2.10 [1.20-3.70]) in male but not in female children.

Conclusion: In a nationally representative sample of the US population, a significant positive association between childhood AD and atopic disease with cognitive dysfunction was identified. Furthermore, a dimorphic relationship with developmental delays was identified between sexes.

1 Introduction

Atopic dermatitis (AD) is a common inflammatory skin disease in both children and adults.¹ The pathophysiology is characterized by aberrant immune activation in the skin and blood of both children and adults.^{2,3} Multiple studies have reported increased peripheral inflammation (systemic inflammation outside of the central nervous system) and neurotrophins in children and adults with AD.²⁻⁷ The peripheral inflammation in AD is also illustrated by the increased risk of developing other immune-mediated inflammatory diseases.¹

Immune dysregulation has been implicated in the pathophysiology of many forms of cognitive dysfunction.⁸⁻¹¹ Increased peripheral inflammation can influence central inflammation in areas of the brain, e.g. hippocampus, to alter neurodevelopmental processes in children and cognitive function in adults.⁸⁻¹²

A recent prospective study using the Patient-Reported Outcomes Measurement Information System (PROMIS) 8-item Cognitive Function survey in adult AD patients identified a positive correlation between cognitive dysfunction and multiple domains of AD severity. It was the first to examine the impact of AD severity on cognitive measures such as memory and mental acuity in adults.¹³ Whether this association exists in children is still unknown. The vast majority of studies investigating cognitive dysfunction in childhood AD focuses solely on the association with attention deficit (hyperactivity) disorder (ADD/ADHD), leaving the impact of AD on memory impairment and other developmental processes that contribute to mental acuity in childhood unexplored.^{14,15}

The objective of this study was to evaluate the association between AD and cognitive dysfunction defined as self-reported memory impairment, developmental delays and/or ADD/ADHD in children.

Methods

Procedures

This study used data from the National Health Interview Survey (NHIS), a national health survey of the United States (US) population.¹⁶ The NHIS is a continuously enrolling survey administered to a representative sample of US households used to monitor the health status of the US population. It uses a multistage, clustered, cross-sectional design.¹⁶ For each household in the NHIS that includes children, one child is randomly selected and detailed information is collected about their health from an adult caregiver. Data from the 2008-2018 NHIS were used in this study for the US child population. The NHIS has an annual response rate of approximately 70%. Participants responding anything other than “Yes” or “No” to cognitive dysfunction and AD were excluded from the study. This resulted in a sample size of 109,842 included children (150,964 excluded). Atopic Disease was defined as comorbid AD, asthma, allergic rhinitis (AR) and food allergies (FA). Race/ethnicity was separated into Hispanic and non-Hispanic groups. Non-Hispanics were further divided into White, Black, Asian, Native American or other. Data was compiled and combined using Integrated Public Use Microdata Series (IPMS).¹⁷

Ascertainment of Variables

All variables examined are detailed in **Table 1**. Due to the survey design self-reporting biases may exist.

Statistical Analyses

Multivariable logistic regression models were constructed to examine the association of AD (predictor) with memory impairment, developmental delay or ADD/ADHD (outcomes). Models adjusted for the following covariates: age, sex, race, region, socioeconomic factors, allergic comorbidities and mental health. Socioeconomic factors included whether the household reported their annual income as above or below the poverty line, and the level of parental education. Allergic comorbidities included asthma, allergic rhinitis (AR) and food allergies (FA). Mental health included depression and anxiety. Adjusted odds ratios (aORs) and 95% confidence intervals (CI) were estimated. Interactions were tested by adding their multiplicative interaction terms in the multivariable models. Interactions were evaluated for the contribution of sex and allergic conditions.

Similarly, aOR and CI were computed to analyze the association between atopic disease and developmental delays, with atopic disease being defined as comorbid AD, asthma, AR and FA.

All data analyses were conducted using survey procedures of SPSS (IBM, Version 26.0.

Armonk, NY). ** indicates a $p < 0.01$, *** indicates a $p < 0.001$

Results

Study Population

The study included 109,482 children (ages 2-17 years) **Table 2**. The study population consisted of 59.20% of children between the ages of 2-11, 51.48% male, 48.44% non-hispanic white and 36.21% residing in the south. 18.37% of the study population reported living below the poverty line, 43.09% of mothers and 41.54% of fathers obtained a college degree. 9.93% of the children reported asthma, 11.66% allergic rhinitis (AR) and 5.69% food allergies (FA). 4.25% of the population reported symptoms of anxiety and 2.20% reported symptoms of depression.

The overall prevalence of AD across 2008-2018 was 12.24% in children, including 13.68% in younger children, 10.11% in older children, 11.73% in males, and 12.78% in females. Black children had the highest prevalence of AD (17.26%) and Hispanic children had the lowest (9.77%). The prevalence of AD in children who also reported allergic conditions was 25.31%, 25.69%, 35.21% for asthma, AR and FA respectively.

AD is Associated with Cognitive Dysfunction

In multivariable logistic regression models childhood AD was associated with highest odds of self-reported memory impairment (prevalence: 0.87% vs. 0.42%; aOR [95% CI] 1.84 [1.34-2.51]; $p<0.001$), followed by developmental delay (6.96% vs. 3.87%; 1.54 [1.40-1.70]; $p<0.001$), and ADD/ADHD (10.78% vs. 8.10%; 1.31 [1.20-1.42]; $p<0.001$) **Table 3**. Upon further analysis an interaction existed between sexes with childhood AD as a predictor of developmental delays.

Male children displayed an increased occurrence of AD associated developmental delays (9.45% vs. 4.52%; $p=0.043$) **Table 4**.

Atopic Disease is Associated with Cognitive Dysfunction

The contribution of other allergic conditions to the relationship between AD and cognitive dysfunction was initially explored by evaluating existing interactions within asthmatic, AR and FA children. Asthmatic children displayed a slightly increased occurrence of ADD/ADHD (16.47 vs. 15.61%; $p<0.001$) **Table 4**. Children with AR displayed an increased occurrence of developmental delays (9.27% vs. 6.20%; $p=0.001$). Children with FA displayed increased occurrences of memory impairment, developmental delays and ADD/ADHD (1.14% vs. 0.82%; $p=0.022$ memory impairment, 8.70% vs. 6.56%; $p=0.002$ developmental delays, 11.55 vs. 10.59%; $p=0.003$).

The abundant interactions observed with comorbid allergic conditions, as well as the interaction of sex differences led us to further evaluate the association between atopic disease (AD, asthma, AR and FA) and developmental delays separately in males and females. Atopic disease was dimorphically associated with an increased occurrence of developmental delays in male but not female children (13.44% vs. 5.43%; 2.10 [1.20-3.70]; $p<0.01$) (**Table 4**).

Discussion

In a nationally representative sample, we found a significant association between AD and self-reported memory impairment developmental delays, and as ADD/ADHD in children. The

association persisted after adjustment for age, sex, race, region, socioeconomic factors, allergic comorbidities and mental health.

We report that childhood AD is associated with developmental delays. This coincides with two previous studies. One utilizing the National Survey of Children's Health and the 2007-2013 NHIS reported an association between AD and moderate and severe speech disorders in children (OR 2.35 & 2.28).¹⁸ A second 2015 Eurasian study reported that 36% of children with developmental delays demonstrated co-morbid AD.¹⁹

The observation that the association between atopic disease (defined as AD, asthma, AR and FA) and cognitive dysfunction may differ between sexes is intriguing. AD is dimorphically associated with amplified odds of reporting developmental delays in male children. In agreement with this finding, a previous study reported that young females were less likely to develop asthma with early onset AD when compared to young males.³⁵ This builds upon the wealth of studies investigating sex differences in immune responses to peripheral challenges. Future clinical studies should take sex differences into account when evaluating the implications of AD and atopic disease.

ADD/ADHD is the most common learning disability, making it easier to identify in smaller sample sizes.^{14,20} Similar to our reported findings a vast majority of studies have shown an association between ADHD and AD.²⁰ Pruritus, scratching behavior, pain, and sleep disturbances are all important potential mediators to this particular pathology.^{20,21} Symptoms of AD, including scratching, may be mistaken for the hyperactivity seen in ADHD, resulting in a tendency to

overdiagnose ADD/ADHD in these patients. Due to this overlap one must be cautious in deducing a formal relationship between the two.

This study expands upon the clinical association between AD and memory impairment recently evaluated in adults.¹³ We report that AD is associated with an increased prevalence of memory impairment in children. Although the overall prevalence is low in children the prevalence of memory impairment is known to increase with aging. When taken into consideration with previous studies reporting the correlation between adulthood AD with memory impairment the underlying mechanisms contributing to the pathophysiology of such a crippling disorder as memory impairment is warranted.

The findings within this study substantiates previous studies indicating that the developing brain is particularly sensitive to peripheral inflammation and that these conditions may alter neural synapses both acutely and long-term. AD, asthma, AR and FA are all associated with Th2 over-expression. In animal models early life over-exposure to IL-4 is reported to reduce myelination and lead to cognitive impairment and developmental delays.^{23,24} The acute impact of this Th2 over-expression may underly the cognitive dysfunction observed in childhood AD and may also contribute beyond childhood into adulthood.

The hippocampus is a key structure for learning and memory. Previous reports illustrated the detrimental influence that exaggerated immune cell responses triggered by peripheral challenges can exert on learning and memory.^{9,12,25} An increased pro-inflammatory axis and diminished anti-inflammatory axis in the hippocampus are key initiators of cognitive decline in murine

models.⁸⁻¹⁰ Th2 mediated conditions such as AD and atopic disease, are reported to modulate immune activation in the hippocampus.²⁶ An imbalanced pro-inflammatory/anti-inflammatory axis can alter neural processes (such as synaptic plasticity and neurogenesis) essential for memory and may contribute to the association with cognitive dysfunction we observed in childhood AD.²⁷

In adulthood chronic inflammatory conditions have been reported to elicit the development of cognitive impairment via the same mechanism in specific areas such as the hippocampus.⁸ Immune mediated- disorders such as diabetes, hypertension, multiple sclerosis and rheumatic arthritis all display a similar upregulated pro-inflammatory axis and are also associated with cognitive dysfunction.^{8,28} In addition to the acute effects, long-term the exposure to peripheral inflammation also allows for modulation of future responses to subsequent immune challenges in adulthood via either prolonged or exaggerated pro-inflammatory cytokine production and/or decreased anti-inflammatory regulation long-term.¹² This suggests that the impact of childhood AD may extend into adulthood with modulation of the immune response similar to that observed in other immune mediated disorders. The impact of childhood AD on the adult brain, and adult onset AD on the adult brain warrants delineation in future investigations.

The potential contributors to the association between AD and cognitive dysfunction may be multifactorial. AD patients exhibit altered inputs entering the CNS. AD has been shown to alter intraepidermal nerve fiber density and to have abnormal expression of axonal guidance molecules, such as nerve growth factor (NGF).²⁹ This could result in altered communication axes between the CNS and PNS. Additionally, children and adults with AD display increased serum

185 levels of brain-derived growth factor (BDNF).^{4,5,7,30,31} Blood BDNF levels are correlated to CNS
186 BDNF levels.³² Although most research suggests that increases in BDNF can be protective,
187 excess BDNF has also been linked to learning and memory deficits.³³ BDNF levels are reported
188 to increase with intensity of itch.³⁴ Chronic itch may induce alterations in the pleasure/reward
189 center related to scratching behavior modulated through dopaminergic pathways including the
190 ventral tegmental areas (VTA).³⁵ These altered CNS feedback loops due to chronic itch may also
191 interfere with learning and memory. Clinical trials are warranted to evaluate the specificity and
192 sensitivity of BDNF, ESR, CRP and/or itch severity as biomarkers for cognitive dysfunction in
193 children.

194
195 Several limitations exist in this study. The survey question of AD was broadly posed as “had
196 eczema, or other skin allergy” and could also be interpreted to include other inflammatory
197 conditions such as: acute urticaria, or contact dermatitis as skin allergy. The NHIS data are self-
198 reported, preventing confirmation of AD or any comorbid conditions with standardized disease
199 scoring criteria. Similarly, specifics of AD including severity and phenotype could not be
200 assessed. This may have resulted in a smaller odds ratio, as it would allow participants not
201 meeting the clinical threshold of AD to be included within the analyses. In addition, given the
202 lack of data on therapeutics we were unable to control for sedating medications such as anti-
203 histamines and neuroleptics, which likely play a role in cognitive dysfunction. However,
204 previous studies have suggested that these therapies do not impact the association between AD
205 and cognitive dysfunction.¹³ Possible prematurity was not controlled for within this study. Lastly
206 limitations exist in cross-sectional designs, as the simultaneous assessment of exposure and
207 outcome limits the assessment of directionality as well as the grading of severity.

208

209 In conclusion, we report that AD is significantly and positively associated with memory
210 impairment, developmental delays and ADD/ADHD in children, and that atopic disease is
211 positively associated with developmental delays in male children. Clinical studies should be
212 conducted to assess the applicability of this association. Additional clinical studies utilizing AD
213 diagnostic and severity guidelines are needed to confirm the true magnitude of this association.
214 Laboratory studies are needed to fully elucidate the mechanism underlying this association as
215 well as potential methods to prevent or mitigate cognitive dysfunction in patients with AD.

216

217

References

1. Weidinger S, Novak N. Atopic dermatitis. *Lancet*. 2016;387(10023):1109-1122.
2. Batmaz SB. Simple Markers for Systemic Inflammation in Pediatric Atopic Dermatitis Patients. *Indian J Dermatol*. 2018;63(4):305-310.
3. Brunner PM, Suarez-Farinas M, He H, et al. The atopic dermatitis blood signature is characterized by increases in inflammatory and cardiovascular risk proteins. *Sci Rep*. 2017;7(1):8707.
4. Namura K, Hasegawa G, Egawa M, et al. Relationship of serum brain-derived neurotrophic factor level with other markers of disease severity in patients with atopic dermatitis. *Clin Immunol*. 2007;122(2):181-186.
5. Raap U, Werfel T, Goltz C, et al. Circulating levels of brain-derived neurotrophic factor correlate with disease severity in the intrinsic type of atopic dermatitis. *Allergy*. 2006;61(12):1416-1418.
6. Hon KL, Ching GK, Wong KY, Leung TF, Leung AK. A pilot study to explore the usefulness of antibody array in childhood atopic dermatitis. *J Natl Med Assoc*. 2008;100(5):500-504.
7. Folster-Holst R, Papakonstantinou E, Rudrich U, et al. Childhood atopic dermatitis-Brain-derived neurotrophic factor correlates with serum eosinophil cationic protein and disease severity. *Allergy*. 2016;71(7):1062-1065.
8. Jackson L, Dong G, Althomali W, et al. Delayed Administration of Angiotensin II Type 2 Receptor (AT2R) Agonist Compound 21 Prevents the Development of Post-stroke Cognitive Impairment in Diabetes Through the Modulation of Microglia Polarization. *Transl Stroke Res*. 2019.
9. Jackson L, Dumanli S, Johnson MH, Fagan SC, Ergul A. Microglia knockdown reduces inflammation and preserves cognition in diabetic animals after experimental stroke. *J Neuroinflammation*. 2020;17(1):137.
10. Jackson L, Eldahshan W, Fagan SC, Ergul A. Within the Brain: The Renin Angiotensin System. *Int J Mol Sci*. 2018;19(3).
11. Jackson L, Li W, Abdul Y, Dong G, Baban B, Ergul A. Diabetic Stroke Promotes a Sexually Dimorphic Expansion of T Cells. *Neuromolecular Med*. 2019;21(4):445-453.
12. Bilbo SD, Schwarz JM. The immune system and developmental programming of brain and behavior. *Front Neuroendocrinol*. 2012;33(3):267-286.
13. Silverberg JI, Lei D, Yousaf M, et al. Association of atopic dermatitis severity with cognitive function in adults. *J Am Acad Dermatol*. 2020.
14. Strom MA, Fishbein AB, Paller AS, Silverberg JI. Association between atopic dermatitis and attention deficit hyperactivity disorder in U.S. children and adults. *Br J Dermatol*. 2016;175(5):920-929.
15. Mikhael NW, Hamed AM, Mansour AI, Abdelrahman ES. Serum levels of brain-derived neurotrophic factor in patients with acne vulgaris. *J Cosmet Dermatol*. 2019;18(6):1998-2003.
16. Parsons VL, Moriarity C, Jonas K, Moore TF, Davis KE, Tompkins L. Design and estimation for the national health interview survey, 2006-2015. *Vital Health Stat 2*. 2014(165):1-53.

17. Lynn A. Blewett JARD, Miriam L. King and Kari C.W. Williams. IPUMS Health Surveys: National Health Interview Survey, Version 6.4 [dataset]. Minneapolis, MN: IPUMS, 2019. , <https://doi.org/10.18128/D070.V6.4>.
18. Strom MA, Silverberg JI. Eczema Is Associated with Childhood Speech Disorder: A Retrospective Analysis from the National Survey of Children's Health and the National Health Interview Survey. *J Pediatr*. 2016;168:185-192 e184.
19. Kandelaki E, Kavlashvili N, Kherkheulidze M, Chkhaidze I. Prevalence of Atopic Dermatitis Symptoms in Children with Developmental and Behavioral Problems. *Georgian Med News*. 2015(243):29-33.
20. L LK, Cices A, Fishbein AB, Paller AS. Neurocognitive function in moderate-severe pediatric atopic dermatitis: A case-control study. *Pediatr Dermatol*. 2019;36(1):110-114.
21. Atefi N, Rohaninasab M, Shooshtari M, et al. The Association between Attention-Deficit/Hyperactivity Disorder and Atopic Dermatitis: A Study among Iranian Children. *Indian J Dermatol*. 2019;64(6):451-455.
22. Wang X, Yang J, Xing Z, et al. IL-4 mediates the delayed neurobehavioral impairments induced by neonatal hepatitis B vaccination that involves the down-regulation of the IL-4 receptor in the hippocampus. *Cytokine*. 2018;110:137-149.
23. Zanno AE, Romer MA, Fox L, et al. Reducing Th2 inflammation through neutralizing IL-4 antibody rescues myelination in IUGR rat brain. *J Neurodev Disord*. 2019;11(1):34.
24. Ward R, Valenzuela JP, Li W, Dong G, Fagan SC, Ergul A. Poststroke cognitive impairment and hippocampal neurovascular remodeling: the impact of diabetes and sex. *Am J Physiol Heart Circ Physiol*. 2018;315(5):H1402-H1413.
25. Klein B, Mrowetz H, Thalhamer J, Scheiblhofer S, Weiss R, Aigner L. Allergy Enhances Neurogenesis and Modulates Microglial Activation in the Hippocampus. *Front Cell Neurosci*. 2016;10:169.
26. Traiffort E, Kassoussi A, Zahaf A, Laouarem Y. Astrocytes and Microglia as Major Players of Myelin Production in Normal and Pathological Conditions. *Front Cell Neurosci*. 2020;14:79.
27. Newcombe EA, Camats-Perna J, Silva ML, Valmas N, Huat TJ, Medeiros R. Inflammation: the link between comorbidities, genetics, and Alzheimer's disease. *J Neuroinflammation*. 2018;15(1):276.
28. Tominaga M, Tengara S, Kamo A, Ogawa H, Takamori K. Psoralen-ultraviolet A therapy alters epidermal Sema3A and NGF levels and modulates epidermal innervation in atopic dermatitis. *J Dermatol Sci*. 2009;55(1):40-46.
29. Raap U, Goltz C, Deneka N, et al. Brain-derived neurotrophic factor is increased in atopic dermatitis and modulates eosinophil functions compared with that seen in nonatopic subjects. *J Allergy Clin Immunol*. 2005;115(6):1268-1275.
30. Guseva D, Rudrich U, Kotnik N, et al. Neuronal branching of sensory neurons is associated with BDNF-positive eosinophils in atopic dermatitis. *Clin Exp Allergy*. 2020;50(5):577-584.
31. Klein AB, Williamson R, Santini MA, et al. Blood BDNF concentrations reflect brain-tissue BDNF levels across species. *Int J Neuropsychopharmacol*. 2011;14(3):347-353.

- 84 32. Cunha C, Angelucci A, D'Antoni A, et al. Brain-derived neurotrophic factor (BDNF)
85 overexpression in the forebrain results in learning and memory impairments. *Neurobiol*
86 *Dis.* 2009;33(3):358-368.
- 87 33. Hon KL, Lam MC, Wong KY, Leung TF, Ng PC. Pathophysiology of nocturnal scratching in
88 childhood atopic dermatitis: the role of brain-derived neurotrophic factor and substance
89 P. *Br J Dermatol.* 2007;157(5):922-925.
- 90 34. Ishiuchi Y. Addiction and the itch-scratch cycle. What do they have in common? *Exp*
91 *Dermatol.* 2019;28(12):1448-1454.
92

Table 1: Ascertainment of Variables

	Variable	Question
Atopic Dermatitis	Atopic Dermatitis	Had eczema, or other skin allergy in the past 12 months
Cognitive Dysfunction	Self- Reported Memory Impairment	Activities limited by difficulty remembering
	Developmental Delay	Doctor or health professional ever diagnosed with a developmental delay other than intellectual disability, formally known as mental retardation, or ADD/ADHD
	ADD/ADHD	Doctor or health professional ever diagnosed with ADD or ADHD
Allergic Conditions	Asthma	Still have asthma
	Allergic Rhinitis (AR)	Had respiratory allergy in the past 12 months
	Food Allergies (FA)	Had food allergy in the past 12 months
Mental Health	Anxiety	Often seems worried in the past 6 months
	Depression	Often unhappy, depressed, or tearful in the past 6 months

Table 2 Demographic and Atopic Dermatitis (AD) Prevalence in 109,482 Children

	Pediattic Age			Sex		
	2-11	12-17	M	F		
% of Full Sample	59.50%	40.50%	51.48%	48.52%		
% AD Prevalence	13.68%	10.11%	11.73%	12.78%		
	Race					
	White	Black	Hispanic	Asian	Native American	Other
% of Full Sample	48.44%	15.38%	27.86%	6.06%	0.97%	1.29%
% AD Prevalence	11.99%	17.26%	9.77%	12.08%	11.88%	16.08%
	Region					
	Northeast		North Central/ Midwest	South	West	
% of Full Sample	15.73%		20.27%	36.21%	27.78%	
% AD Prevalence	12.20%		12.14%	12.56%	11.90%	
	Socioeconomic Status					
	Socioeconomic Status (% below poverty line)		% Mothers with a College Degree	% Fathers with a College Degree		
% of Full Sample	18.37%		43.09%	41.54%		
% AD Prevalence	12.98%		15.32%	13.96%		
	Comorbidities					
	Asthma		Allergic Rhinitis		Food Allergies	
% of Full Sample	9.93%		11.66%		5.69%	
% AD Prevalence	25.31%		25.69%		35.21%	
	Mood Disorders					
	% Reporting Anxiety			% Reporting Depression		
% of Full Sample	4.25%			2.20%		
% AD Prevalence	18.13%			13.84%		
Overall AD prevalence	12.24%					

Table 3 Atopic Dermatitis (AD) is Associated with Cognitive Dysfunction

^aData are expressed as prevalence of each form of cognitive dysfunction among children with or without AD. ^bModel adjusts for age, sex, race, region, socioeconomic factors, allergic conditions and mental health.

Pediatric Cognitive Dysfunction				
Total No.= 109,482	Children with AD, % (No.) ^a <i>n</i> =13,398	Children without AD, % (No.) ^a <i>n</i> =96,084	OR (95% CI)	aOR (95% CI) ^b
Self-Reported Memory Impairment	0.87% (117)	0.42% (400)	2.11 (1.71-2.60) ***	1.84 (1.34-2.51) ***
Developmental Delay	6.96% (932)	3.87% (3,718)	1.86 (1.73-2.00) ***	1.54 (1.40-1.70) ***
ADD/ADHD	10.78% (1,444)	8.10% (7,77)	1.37 (1.29-1.46) ***	1.31 (1.20-1.42) ***

Table 4 Analysis of Interactions: Male Sex and Allergic Comorbidities Increase the Risk of Cognitive Dysfunction in AD

	Sex		Asthma		Allergic Rhinitis		Food Allergies	
	M	F	YES	NO	YES	NO	YES	NO
Memory Impairment								
Interaction	N.S		N.S		N.S		0.022	
% within AD	-		-		-		1.14%	0.82%
Developmental Delay								
Interaction	0.043		N.S		0.001		0.002	
% within AD	9.45%	4.52%	-		9.27%	6.20%	8.70%	6.56%
ADD/ADHD								
Interaction	N.S		<0.001		N.S		0.003	
% within AD	-		16.47%	15.61%	-		11.66%	10.59%

Table 5 Atopic Disease (comorbid Atopic Dermatitis, Asthma, Allergic Rhinitis and Food allergies) is Associated with Developmental Delays in Male but not Female Children

^cModel adjusts for age, sex, race, region, socioeconomic factors, and mental health.

Pediatric Atopic Disease				
Developmental Delays	Children with AD, Asthma, AR and FA % (No.)	Children without AD, Asthma, AR or FA % (No.) ^a	OR (95% CI)	OR (95% CI) ^c
Male	13.44% (34)	5.43% (154)	2.70 (1.82-4.02)***	2.10 (1.20-3.70)**
Female	5.70% (11)	3.15% (53)	N.S	N.S