

1 **Article Type:** Research Letter

2
3 **Title:** Association between alopecia areata and atopic dermatitis: a nested case-control study of the All of
4 Us database

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20 **Acknowledgement:** The All of Us Research Program is supported by the National Institutes of Health,
21 Office of the Director: Regional Medical Centers: 1 OT2 OD026549; 1 OT2 OD026554; 1 OT2
22 OD026557; 1 OT2 OD026556; 1 OT2 OD026550; 1 OT2 OD 026552; 1 OT2 OD026553; 1 OT2
23 OD026548; 1 OT2 OD026551; 1 OT2 OD026555; IAA #: AOD 16037; Federally Qualified Health
24 Centers: HHSN 263201600085U; Data and Research Center: 5 U2C OD023196; Biobank: 1 U24
25 OD023121; The Participant Center: U24 OD023176; Participant Technology Systems Center: 1 U24
26 OD023163; Communications and Engagement: 3 OT2 OD023205; 3 OT2 OD023206; and Community
27 Partners: 1 OT2 OD025277; 3 OT2 OD025315; 1 OT2 OD025337; 1 OT2 OD025276. In addition, the
28 All of Us Research Program would not be possible without the partnership of its participants.

29 **Conflict of Interest:** E. Guttman-Yassky has received institutional grants from AbbVie, Celgene,
30 Eli Lilly, Janssen, Dermavant, DS Biopharma, Novartis, Pfizer, Regeneron, Glenmark,
31 Galderma, Asana Biosciences, Innovaderm, Dermira, LEO Pharma, Novan, Kyowa Kirin,
32 Concert, Union Therapeutics, and Ralexar; and is consultant for Sanofi, Regeneron, Celgene,
33 Dermira, Galderma, Glenmark, Novartis, Pfizer, LEO Pharma, AbbVie, Eli Lilly, Kyowa Kirin,
34 Mitsubishi Tanabe, Asana Biosciences, Union Therapeutics, Allergan, Amgen, Concert, DS
35 Biopharma, EMD Serono, Escalier, and Flx Bio. BU is an employee of Mount Sinai and has
36 received research funds (grants paid to the institution) from: Incyte, Rapt Therapeutics, and
37 Pfizer. He is also a consultant for Arcutis Biotherapeutics, Castle Biosciences, Fresenius Kabi,
38 Pfizer, and Sanofi. The other authors have no conflicts of interest.

39 **Financial Disclosure:** None

40
41 **Word Count:** 500 [Max: 500]

42 **References:** 5 [Max: 5]

43 **Number of Tables:** 2

44 **Number of Figures:** 0

45 **Supplemental Material:** <https://data.mendeley.com/datasets/mvykrt4b2z/1>

46
47 **IRB approval:** N/A

48 **Patient Consent:** N/A

49 **Keywords:** alopecia areata; atopic dermatitis; atopy; Th2; case-control; skin of color; All of Us

This is the author's manuscript of the article published in final edited form as:

Diaz, M. J., Haq, Z., Abdi, P., Tran, J. T., Guttman-Yassky, E., & Ungar, B. (2023). Association between alopecia areata and atopic dermatitis: A nested case-control study of the All of Us database. *Journal of the American Academy of Dermatology*. <https://doi.org/10.1016/j.jaad.2023.10.031>

50 *To the Editor,*

51
52 The relationship between alopecia areata (AA) and atopic dermatitis (AD) is increasingly being
53 investigated, with recent evidence implicating a Th2 pathway component in AA's pathogenesis,¹ and a
54 genetic association identified between AD and AA.² Epidemiologic data have also linked the two
55 diseases, but measures of this association in a socioeconomically and racially/ethnically diverse
56 population are lacking.

57
58 The All of Us (AoU) database is an NIH initiative designed to capture populations historically
59 underrepresented in biomedical research. Participants with AA in AoU were identified (SNOMED:
60 68225006) and matched to four controls using nearest neighbor propensity-score matching based on sex,
61 age, and race/ethnicity. AA cases were compared to controls using the Fisher's exact test for categorical
62 variables and the unpaired t-test for continuous variables. Logistic regression models were generated to
63 calculate the odds ratio (OR) of having AD (SNOMED: 43116000) among individuals with AA.
64 Covariates included age, race/ethnicity, sex, income, education, smoking status, body mass index (BMI),
65 and other autoimmune disorders. Significance was set at $P < 0.05$, and Wald-based intervals were
66 developed at 95% confidence.

67
68 A total of 984 AA cases were analyzed (mean age 55.3y [standard deviation: 15.3], 74.1% female) (Table
69 1). Patients were most commonly white (41.5%), reported an income $\geq \$50,000$ (43.2%), and college
70 graduates (44.6%). Black and Hispanic patients comprised 43% of the AA case population. Compared to
71 age, sex, and race/ethnicity matched controls, individuals with AA reported significantly lower income
72 ($P < 0.001$), increased prevalence of higher education, lower BMI ($P < 0.001$), and increased prevalence of
73 AD ($P < 0.001$) and other autoimmune disorders ($P < 0.001$).

74
75 **Table 1.** Sociodemographic and clinical traits of alopecia areata cases/controls in All of Us

Characteristic	Cases No. (%) (n= 984)	Controls No. (%) (n= 3936)	P value
Age, mean (SD)	55.29 (15.32)	55.29 (15.32)	>0.99
Sex			>0.99
Male	230 (23.37)	920 (23.37)	
Female	729 (74.09)	2916 (74.09)	
Other*	25 (2.54)	100 (2.54)	
Race/Ethnicity			>0.99
White	408 (41.46)	1632 (41.46)	
Asian	42 (4.27)	168 (4.27)	
Black	208 (21.14)	832 (21.14)	
Hispanic	215 (21.85)	860 (21.85)	
Other*	111 (11.28)	444 (11.28)	
Annual Income			<0.001
$\geq \$50k$	425 (43.19)	1333 (33.87)	
\$35k- \$50k	76 (7.72)	306 (7.77)	
\$25k- \$35k	59 (6.00)	290 (7.37)	
\$10k- \$25k	111 (11.28)	491 (12.47)	
$\leq \$10k$	103 (10.47)	613 (15.57)	
Other*	210 (21.34)	903 (22.94)	

76

Education			<0.001
College graduate	439 (44.61)	1479 (37.58)	
Attended college	272 (27.64)	1039 (26.40)	
12th Grade	165 (16.77)	822 (20.88)	
No HS degree	75 (7.62)	434 (11.03)	
Other*	33 (3.35)	162 (4.12)	
Ever smoker	412 (41.87)	1622 (41.21)	0.718
BMI, mean (SD)	29.38 (7.29)	30.47 (7.93)	<0.001
Atopic Dermatitis	247 (25.10)	255 (6.48)	<0.001
Autoimmune disease**	221 (22.46)	351 (8.92)	<0.001

77 *No*: Number, *HS*: high school, *BMI*: body mass index

78 *Includes participants with more than one indicated, no matching concept, other, or unknown

79 **Includes systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, celiac
80 disease, type 1 diabetes mellitus, Hashimoto thyroiditis, Grave's disease, and vitiligo

81
82 Compared to matched controls, individuals with AA had significantly increased odds of having an AD
83 diagnosis (OR: 4.84, 95% confidence interval (CI): [3.99-5.86], P<0.001). After adjusting for income,
84 education, smoking status, BMI, and other autoimmune disorders, AA remained significantly associated
85 with AD (OR: 4.42, 95% CI: [3.61, 5.40], P<0.001) (Table 2).

86
87 **Table 2.** Univariable, and multivariable-adjusted odds of atopic dermatitis in patients with alopecia areata

Condition	Univariable OR (95% CI)	P value	Multivariable aOR (95% CI)*	P value
No atopic dermatitis	Ref		Ref	
Atopic dermatitis	4.84 (3.99, 5.86)	<0.001	4.42 (3.61, 5.40)	<0.001

88 *aOR*: multivariable adjusted odds ratio, *CI*: confidence interval

89 * Multivariable regression analysis controlled for age, race, ethnicity, sex, income, education, smoking
90 status, BMI, and autoimmune disease

91
92 To test for bidirectionality, we assessed the reverse relationship (AD with AA) (Table S1, S2). After
93 adjusting for covariates, we found that individuals with AD also had significantly increased odds of
94 having AA (OR: 5.08, 95% CI: [4.17-6.21], P<0.001). Univariable regression revealed similar insights.

95
96 In an Israeli AA cohort (n=51,561), Kridin and colleagues similarly reported significantly increased risk
97 of AD (OR: 1.55, 95% CI: [1.44-1.66], P<0.001).³ Continuing, an England population-based study
98 revealed that patients with AA had a higher prevalence and incidence of AD across all subgroups of sex,
99 age, socioeconomic status, and ethnicity compared to matched controls.⁴ The association between AA and
100 AD is further reinforced by a meta-analysis that found individuals with AD (n=184,401) also have a
101 higher prevalence of AA (relative risk: 5.78, 95% CI: [3.82-8.73]).⁵

102
103 This effort, assessing the bidirectional relationship between AA and AD in a diverse United States cohort,
104 provides additional support for the hypothesis of contribution of type 2 inflammation in AA. Potential
105 study limitations include the sample size and the use of All of Us electronic health records, which may
106 contain inaccuracies and incomplete data. Additional research is warranted to establish temporal and
107 causal aspects of this association.

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