The patient has given written informed consent for the publication of her case details.

The skin and ocular surface share a close relationship, with similarities in immunohistology, steroidogenic properties, and allergic mechanisms.[4] Their similarities in composition elucidate the numerous ocular surface comorbidities associated with AD. Atopic keratoconjunctivitis remains a complicated chronic ocular surface disease involving the cornea, which is always associated with atopic conditions and is estimated to be present in 25% to 42% of patients with AD. Numerous parallels have been drawn between AD and AKC, particularly in their immunopathogenesis and compromised innate immune response. Similarities in dysregulation of toll-like receptors, antimicrobial peptides, and immunoglobulin (Ig)A secretions found in these atopic disorders lead to the impairment of their respective surface barriers.[5]

Furthermore, AD is a heterogeneous disease that can be classified into multiple phenotypes, with further endotypes and genotypes. Most widely recognized is the existence of extrinsic (elevated IgE) and intrinsic subtypes (normal IgE), although demarcations have also been explored between adults and children, different ethnicities (European American, Asian, and African American), and cytokine profiles.[6] Because the ocular surface can be considered a derivative of the skin epithelium, multiple phenotypes of AKC may also exist. This could explain the unexpected resolution of the patient's ocular symptoms because she may have presented with an AKC phenotype that could be resolved through the initiation of dupilumab.

It is speculated that the patient has the Asian subtype of AD, which is characterized by Th2/Th17 blended cytokine axes. The AD lesions of Asian patients were found to have significantly higher levels of IL-19, which is induced by IL-4/IL-13 and interleukin-17 (IL-17).[7] If her AD phenotype could be extrapolated to the epithelium of her ocular surface, the inhibition of IL-4 and IL-13 with dupilumab could elucidate the resolution of her AKC. Tear IL-4 levels were found to be substantially elevated in patients with AKC, along with goblet cell hyperplasia induced by IL-13.[8,9] Inhibition of these 2 interleukins would remedy these key biomarkers found in AKC. The Th17 cytokine axis in AD is thought to be unique in Asian patients and may act as a protective factor for this subset of patients. Given IL-17 remains uninhibited, it can continue to induce IL-19. This in turn, amplifies IL-17A effects on keratinocytes, including the induction of β-defensins.[10]

Despite the adverse ocular surface effects of dupilumab, there exists a subset of patients who may experience relief. Evaluating the close connection between skin and ocular surface and its associated atopic phenotypes may shed light in the identification of these groups.

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References

1. Gooderham MJ, Hong HC, Eshtiaghi P, Papp KA. Dupilumab: a review of its use in the treatment of atopic dermatitis. *J Am Acad Dermatol*. 2018;78(3 suppl 1):S28–S36.
2. Akinlade B, Guttman-Yassky E, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ, et al. Conjunctivitis in dupilumab clinical trials. *Br J Dermatol*. 2019;181(3):459–473.
3. Park S, Lee JH, Park JH, Park SH, Park SY, Jung YW, et al. Ocular surface disorders associated with the use of dupilumab based on WHO VigiBase. *Sci Rep*. 2021;11(1):14293.
4. Valentine L, Norris MR, Bielory L. Comparison of structural components and functional mechanisms within the skin vs. the conjunctival surface. *Curr Opin Allergy Clin Immunol*. 2021;21(5):472–479.
5. Bielory B, Bielory L. Atopic dermatitis and keratoconjunctivitis. *Immunol Allergy Clin North Am*. 2010;30(3):323–336.
6. Tokura Y, Hayano S. Subtypes of atopic dermatitis: from phenotype to endotype. *Allergol Int*. 2022;71(1):14–24.
7. Noda S, Suárez-Fariñas M, Ungar B, Kim SJ, de Guzman Strong C, Xu H, et al. The Asian atopic dermatitis phenotype combines features of atopic dermatitis and psoriasis with increased TH17 polarization. *J Allergy Clin Immunol*. 2015;136(5):1254–1264.
8. Hagan S, Martin E, Enríquez-de-Salamanca A. Tear fluid biomarkers in ocular and systemic disease: potential use for predictive, preventive and personalised medicine. *EPMA J*. 2016;7(1):15.
9. Alam J, de Paiva CS, Pflugfelder SC. Immune - Goblet cell interaction in the conjunctiva. *Ocul Surf*. 2020;18(2):326–334.
10. Monin L, Gaffen SL. Interleukin 17 family cytokines: signaling mechanisms, biological activities, and therapeutic implications. *Cold Spring Harb Perspect Biol*. 2018;10(4): a028522.

Phenotyping older adults with asthma by means of cluster analysis

Check for updates

Whereas a number of publications have identified asthma phenotypes in adults,[1] few have focused only on older adults.[2,3] As a component of a randomized controlled trial of older adults (≥50 years old) with persistent asthma, Baptist et al,[3] identified 4 phenotypic clusters. The purpose of this study was to compare findings from the Baptist et al[3] study with cluster analysis findings from a cohort of older adults with asthma participating in a longitudinal observational study.

Disclosures: Dr Folz reports receiving clinical research funding from AstraZeneca AB, Genentech, Regeneron, Celgene, Insmed, Boehringer Ingelheim, National Institutes of Health (NIH), and Patient-Centered Outcomes Research Institute. The authors have no conflicts of interest to report.
Funding: Research reported in this article was supported by the NIH National Institute on Aging under award number R01AG047297. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Specifics concerning measures and data collection of our study are published elsewhere.[4] Briefly, participants were 60 years old and older, had exhibited bronchodilator response with a 12% or greater increase in forced expiratory volume in 1 second (FEV1) or forced vital capacity (FVC) and a 200-mL increase of lung volume in either measure after bronchodilator administration or had a methacholine challenge test finding of provocation concentration causing a 20% fall in FEV1 less than or equal to 16 mg/mL. We excluded current smokers, those with a 20-pack year or greater history of smoking, diagnosis of other chronic pulmonary disease, and those living in a skilled nursing facility. Data were collected between 2015 and 2019. The study was approved by the University of Louisville Institutional Review Board.

Self-reported demographic data are noted in Table 1. Participants completed the Asthma Control Test (ACT) and the Mini Asthma

Table 1
Cluster Analysis of Older Adults With Asthma (N = 187)

Variables	Total N = 187	Cluster 1 N = 36 (19.3%)	Cluster 2 N = 38 (20.3%)	Cluster 3 N = 113(60.4%)	*P* value
Categorical variables	n (%)	n (%)	n (%)	n (%)	
Male sex[a]	50 (26.7)	2 (5.6)	18 (47.4)	30 (26.5)	<.001
Age at diagnosis >40 y[b]	106 (56.7)	22 (61.1)	11 (28.9)	73 (64.6)	.001
Self-reported race[b]					
African American	37 (19.8)	34 (94.4)	2 (5.3)	1 (0.9)	<.001
White	148 (79.1)	0	36 (94.7)	112 (99.1)	<.001
Other race	11 (5.9)	5 (13.9)	0	6 (5.3)	.04
Atopic sensitization[b]	143 (76.5)	30 (83.3)	35 (92.1)	78 (69.0)	.008
Asthma exacerbation	53 (28.3)	11 (30.6)	14 (36.8)	28 (24.8)	.34
Self-reported history of hay fever[c]	126 (67.4)	22 (61.1)	24 (63.2)	80 (70.8)	.46
Fixed airway obstruction[b]	47 (25.1)	5 (13.9)	38 (100)	4 (3.5)	<.001
Continuous variables	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age, y	68.2 (6.2)	68.4 (7.1)	68.5 (6.0)	67.9 (6.0)	.85
Body mass index[b]	32.5 (8.2)	38.0 (9.9)	29.6 (7.7)	31.7 (6.9)	<.001
Asthma duration[b], y	26.8 (23.8)	26.7 (22.4)	42.1 (25.5)	21.7 (21.5)	<.001
Education[b,d]	3.2 (0.9)	2.4 (1.1)	3.4 (0.7)	3.4 (0.7)	<.001
Mental health[e]	51.3 (10.4)	48.5 (10.5)	54.3 (9.7)	51.3 (10.4)	.055
Tobacco pack-y	5.9 (6.2)	5.3 (5.7)	5.4 (6.2)	6.2 (6.4)	.88
Lifetime nonsmokers, n (%)	114 (61.0)	23 (63.9)	24 (63.2)	67 (59.3)	.84
Asthma medications, n (%)	4.2 (2.1)	4.1 (1.9)	4.6 (2.0)	4.1 (2.2)	.38
Bronchodilators (long and short acting β agonists, antimuscarinics)	171 (91.4)	35 (97.2)	37 (97.4)	99 (87.6)	.07
Anti-inflammatory agents (inhaled corticosteroids, oral steroids)	145 (77.5)	27 (75.0)	32 (84.2)	86 (76.1)	.54
Histaminic antagonists	103 (55.1)	17 (47.2)	21 (55.3)	65 (57.5)	.56
Leukotriene receptor antagonist	84 (44.9)	13 (36.1)	18 (47.4)	53 (46.9)	.50
Biologic (anti-IgE)	1 (0.5)	0	1 (2.6)	0	
Number comorbidities[c]	1.2 (0.9)	1.4 (0.8)	1.1 (0.9)	1.1 (0.9)	.15
Asthma control test[b]	18.2 (4.2)	15.2 (4.7)	18.6 (3.8)	19.0 (3.8)	<.001
Asthma quality of life[b]	4.9 (1.3)	4.0 (1.4)	5.0 (1.2)	5.1 (1.1)	<.001
FEV1/FVC ratio[b], pretreatment	0.72 (0.1)	0.77 (.09)	0.59 (.07)	0.75 (.06)	<.001
FEV1/FVC ratio[b], posttreatment	0.75 (.09)	0.79 (.08)	0.61 (.07)	0.78 (.05)	<.001
FEV1 pretreatment[b] % predicted	79.1 (21.5)	86.2 (22.4)	56.1 (15.3)	84.6 (17.6)	<.001
FEV1 posttreatment[b] % predicted	88.1 (20.1)	96.9 (20.2)	66.4 (13.3)	92.6 (16.8)	<.001
FVC pretreatment[b] % predicted	82.6 (17.2)	86.8 (19.6)	71.7 (16.1)	85.0 (15.3)	<.001
FVC posttreatment[b] % predicted	88.9 (17.0)	95.8 (23.2)	81.5 (14.0)	89.3 (14.7)	.001

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E.
[a]Significant only in current study.
[b]Significant in current study and Baptist et al[3] study.
[c]Significant only in Baptist et al[3] study.
[d]Education: 1 means high school; 2 means high school/equivalent; 3 means some college/technical school; 4 means college graduate.
[e]Lower scores indicate greater mental health issues.

Quality of Life Questionnaire (QoL). As per Baptist et al,[3] comorbidities were considered as the sum of self-reported heart condition, high blood pressure, stroke, or cancer. Mental health was assessed using the Short Form–12 Mental Health Composite Score.[4] Pre and postbronchodilator treatment FEV1, FVC, and FEV1/FVC was measured by means of spirometry per the American Thoracic Society guidelines. Fixed airway obstruction (FAO) was defined as FEV1/FVC less than 0.7 postbronchodilator. Participants were considered atopic when either the skin prick testing or specific immunoglobulin E was positive for any of 14 common local aeroallergens. Body mass index (BMI) was calculated on the basis of measured height and weight. Asthma exacerbation was defined as a self-reported hospitalization, emergency department visit, or unscheduled provider visit for asthma. Asthma medication use was calculated as the total number of reported bronchodilators, anti-inflammatory agents, histaminic antagonists, leukotriene receptor antagonist, and biologics.

The two-step cluster analysis procedure in Statistical Package for the Social Sciences version 27 identified the natural clusters.[5] This procedure allows the optimal number of clusters to be created using both categorical and continuous variables.[6] Preclustering initially occurs by building a cluster feature tree with cluster centers followed by a clustering stage using an agglomerative hierarchical method to define the number of clusters. The distance among clusters was calculated using log-likelihood distance. Differences among the final identified clusters were analyzed using the analysis of variance for continuous variables and the χ^2 test for categorical variables.

There were 187 out of the 189 study participants with no missing data. Most participants (73.3%) were women, 19.8% self-identified as African American, 47.6% were college-educated, the mean age was 68.2 (±6.2) years, and the mean duration of asthma was 26.8 (±23.8) years with 56.7% of the participants diagnosed at 40 years or older. The two-step cluster analysis identified 3 unique clusters (Table 1).

Cluster 1 included 36 (19.3%) participants with most having a high school or less education (52%) and diagnosed with asthma after the age of 40 years (61.1%). All participants in cluster 1 self-identified as African American or other race and most were women (94.4%). Those in cluster 1 had significantly greater BMIs (38.0 ± 9.9; P <.001), significantly lower ACT (15.2 ± 4.7; P < .001), and QoL scores (4.0 ± 1.4; P < .001) indicating worse asthma control and QoL.

Cluster 2 included 38 (20.3%) participants. This cluster included significantly more men (47.4%; P < .001), 92.1% had atopic sensitization, 100% had a positive FAO pattern, and had the longest duration of asthma (42.1 ± 25.5 years). The pretreatment FEV1 percent predicted was significantly lower (56.1%; P <.001) for those in cluster 2 and only rose to 66.4% postbronchodilator treatment. Similarly, the pretreatment FEV1/FVC ratio and the FVC pretreatment percent predicted were significantly lower for those in cluster 2 (P <.001).

Cluster 3 was the largest cluster with 113 (60.4%) participants. Those in cluster 3 were primarily women (73.3%), White (99.1%), significantly fewer had atopic sensitization (69.0%), and only 3.5% had FAO.

Although the Baptist et al[3] study identified 4 clusters and we identified 3 clusters, 64% of the variables differentiated clusters in both studies, whereas 5 (20%) of the variables in both studies were not significantly different among clusters. A potential difference among the studies that may account for the different number of clusters was

that we required American Thoracic Society bronchodilator reversibility testing as entry criteria, whereas the Baptist et al[3] study did not. Of note, of those excluded from our study after the methacholine challenge test, only 1 (4.5%) was identified as having FAO.

We found that 95.2% of our participants could be classified correctly on the basis of the variables Black race and FAO. Both studies noted that African Americans were categorized predominately in 1 cluster and similarly had significantly lower ACT and QoL scores, lower education levels, and higher BMIs than those in other clusters. It is important to note that the race variable is incorporated in our study as a contextual variable indicative of the social determinants of health. As stated by Jones, the race variable describes social classification in a race-conscious society.[7] Cremer et al[8] also identified that social determinants differentiated older African American and Hispanic adults with asthma. Further exploration of our data found that, compared with the remainder of the participants, significantly more participants in cluster 1 rented their homes (57.1% vs 10.6%; $P < .001$), and fewer were employed for wages (11.1% vs 33.3%; $P = .009$) providing additional support for social determinants as key contributors to differences by race.

This study adds to the previous sparse data available specifically describing asthma phenotypes among older adults. Limitations include the regional data collection and the cross-sectional approach, which limit generalizability and the discussion of causation. A primary strength of the study is the validation of key variables that differentiate cluster groups. Such an approach may be useful in the future design of clinical trials, which incorporate a phenotype-based stratification to identify differential treatment responses in older adults with difficult-to-control asthma.

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References

1. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med*. 2008;178(3):218–224.
2. Hanania NA, King MJ, Braman SS, Saltoun C, Wise RA, Enright P, et al. Asthma in the elderly: current understanding and future research needs—a report of a National Institute on Aging (NIA) workshop. *J Allergy Clin Immunol*. 2011;128(3):S4–24.
3. Baptist AP, Hao W, Karamched KR, Kaur B, Carpenter L, Song PX. Distinct asthma phenotypes among older adults with asthma. *J Allergy Clin Immunol Prac*. 2018;6(1):244–249.
4. Polivka BJ, Folz R, Myers J, Barnett R, Antimisiaris D, Jorayeva A, et al. Identifying phenotypes and factors impacting outcomes in older adults with asthma: a research protocol and recruitment results. *Res Nurs Health*. 2018;41(4):336–345.
5. SPSS I. TwoStep cluster analysis. 2021. Available at: https://www.ibm.com/docs/en/spss-statistics/27.0.0?topic=edition-twostep-cluster-analysis. Accessed March 10, 2022.
6. Şchiopu D. Applying TwoStep cluster analysis for identifying bank customers' profile. *Buletinul*. 2010;62(3):66–75.
7. Jones CP. Invited commentary: "race," racism, and the practice of epidemiology. *Am J Epidemiol*. 2001;154(4):299–304.
8. Cremer NM, Baptist AP. Race and asthma outcomes in older adults: results from the National Asthma Survey. *J Allergy Clin Immunol Prac*. 2020;8(4):1294–1301.

Cross-sectional study of urinary biomarkers of environmental tobacco and e-cigarette exposure and asthma morbidity

Check for updates

Exposure to environmental tobacco smoke or e-cigarette exposure (ETS) is common and may have a significant impact on asthma control.[1] We leveraged the School Inner-City Asthma Study to establish whether urinary cotinine and total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) levels (hereafter referred to as tobacco biomarkers), are independently associated with asthma morbidity. Furthermore, we studied the interaction between tobacco biomarkers and asthma morbidity by allergen sensitization, as an effect modifier.

This study included a subset of children in the School Inner-City Asthma Study. Detailed methods and prespecified primary and secondary outcomes have been previously published.[2] Students with active asthma were identified by validated school screening surveys[3] and completed a baseline clinical assessment, including surveys, aeroallergen sensitization assessment by allergy skin testing (MultiTest device, Lincoln Diagnostic, Decatur, Illinois) or serum-specific immunoglobulin (Ig)E testing (ImmunoCAP, Phadia AB, Uppsala, Sweden), and urine collection. Allergen sensitization was defined as any sensitization by skin prick test wheal size ≥ 3 mm than negative

Disclosures: Dr Phipatanakul discloses advisory consulting for Genentech, Novartis, Regeneron, and Sanofi for asthma therapeutics not directly related to the study and receiving reagents for allergy testing from Alk Abello and support from Thermo Fisher for the study. The other authors have no example of conflict of interests to disclose.
Funding: Research supported by the National Institute of Environmental Health Sciences Children's Health Exposure Analysis Resource (1U2CES026555 and 1U2CES026561), T32AI007512, K23ES031663, P30ES000002, K24AI106822, U01AI110397.
Role of funder: The National Institutes of Health and industry supporters had no role in the design and conduct of the study.
Clinical Trial Registration: This study was registered on ClinicalTrials.gov (identifier: NCT02291302; https://clinicaltrials.gov/ct2/show/NCT02291302).