7-5-2024

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Citation Details

Han, E. J., Liu, C. M., Fischer, J. L., Mace, J. C., Markarian, K., Alt, J. A., Bodner, T. E., Chowdhury, N. I., Eshaghian, P. H., Gao, Y. A., Getz, A. E., Hwang, P. H., Khanwalkar, A., Kimple, A. J., Lee, J. T., Li, D. A., Norris, M., Nayak, J. V., Owens, C., … Beswick, D. M. (2024). Impact of sociodemographic status and sex on chronic rhinosinusitis and olfaction in people with cystic fibrosis. International Forum of Allergy & Rhinology. Portico.

Received: 27 May 2024 | Revised: 19 June 2024 | Accepted: 23 June 2024

DOI: 10.1002/alr.23402

IFAR: International Forum of Allergy & Rhinology

ORIGINAL ARTICLE

Impact of sociodemographic status and sex on chronic rhinosinusitis and olfaction in people with cystic fibrosis

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Abstract

Background: Sociodemographic status (SDS) including race/ethnicity and socioeconomic status as approximated by education, income, and insurance status impact pulmonary disease in people with cystic fibrosis (PwCF). The relationship between SDS and chronic rhinosinusitis (CRS) remains understudied.

Funding information
Cystic Fibrosis Foundation, Grant/Award Numbers: BESWIC20A0, BESWIC22Y5; National Institute on Deafness and Other Communication Disorders of the National Institutes of Health, Grant/Award Number: R25DC020151

Methods: In a prospective, multi-institutional study, adult PwCF completed the 22-Question SinoNasal Outcome Test (SNOT-22), Smell Identification Test (SIT), Questionnaire of Olfactory Disorder Negative Statements (QOD-NS), and Cystic Fibrosis Questionnaire-Revised (CFQ-R). Lund–Kennedy scores, sinus computed tomography, and clinical data were collected. Data were analyzed across race/ethnicity, sex, and socioeconomic factors using multivariate regression.

Results: Seventy-three PwCF participated with a mean age of 34.7 ± 10.9 years and 49 (67.1%) were female. Linear regression identified that elexacaftor/tezacaftor/ivacaftor (ETI) use (β = −4.09, 95% confidence interval [CI] [−6.08, −2.11], $p < 0.001$), female sex (β = −2.14, 95% CI [−4.11, −0.17], $p = 0.034$), and increasing age (β = −0.14, 95% CI [−0.22, −0.05], $p = 0.003$) were associated with lower/better endoscopy scores. Private health insurance ($\beta = 17.76$, 95% CI [5.20, 30.32], $p = 0.006$) and >16 educational years (β = 13.50, 95% CI [2.21, 24.80], $p = 0.020$) were associated with higher baseline percent predicted forced expiratory volume in one second ($ppFEV_1$). Medicaid/Medicare insurance was associated with worse endoscopy scores, CFQ-R respiratory scores, and $ppFEV_1$ (all $p < 0.017$), and Hispanic/Latino ethnicity was associated with worse SNOT-22 scores ($p = 0.047$), prior to adjustment for other cofactors. No other SDS factors were associated with SNOT-22, QOD-NS, or SIT scores.

Conclusions: Differences in objective measures of CRS severity exist among PwCF related to sex, age, and ETI use. Variant status and race did not influence patient-reported CRS severity measures or olfaction in this study. Understanding how these factors impact response to treatment may improve care disparities among PwCF.

Clinical Trials: NCT04469439

KEYWORDS
chronic rhinosinusitis, cystic fibrosis, patient symptoms, socioeconomic status

1 | INTRODUCTION

Chronic rhinosinusitis (CRS) is highly prevalent among people with cystic fibrosis (PwCF) and significantly decreases quality of life (QOL).[1] Disparities in socioeconomic status (SES) and sociodemographic status (SDS), including sex and race/ethnicity as proxies for racism, have been associated with increased mortality, decreased pulmonary function, and poor nutritional outcomes in PwCF.[2] Some of these disparities may begin to manifest as early as in utero and are believed to exert lasting effects into later life, setting a course toward compromised health.[2,3] However, the relationship between SDS and sinonasal disease severity in PwCF remains unclear. CRS is particularly significant among PwCF, as untreated CRS can serve as a reservoir for pathogenic organisms and contribute to pulmonary exacerbations and worse lung function in PwCF.[4] Thus, differences in CRS severity, which may be related to SDS factors, may lead to downstream consequences for pulmonary function and potentially mortality.

Prior research in CRS patients, without a diagnosis of cystic fibrosis (CF), found that SES disparities may contribute to delayed access to rhinologic care and greater loss to follow-up, potentially contributing to worse CRS treatment outcomes.[5,6] Additionally, living in disadvantaged neighborhoods with greater airborne pollutant exposure may also precipitate sinonasal inflammation and reduce treatment response.[7,8] These effects may be magnified in PwCF given their predisposition to airway disease and underlying mucociliary dysfunction.

Elexacaftor/tezacaftor/ivacaftor (ETI) has improved both sinonasal function and QOL in many PwCF, possibly reducing rhinologic care utilization and the need for sinus surgery in this population.[9,10] However, availability of ETI to PwCF is not solely dependent on cystic fibrosis transmembrane conductance regulator (CFTR) variant

but also on insurance status, region/country, and capacity to pay for this expensive medication. Based on the fact that variants assessed for CFTR modulator responsiveness were initially investigated in variants common in those of European ancestry, PwCF from minoritized groups are also less likely to possess an eligible variant for ETI and be prescribed ETI in the presence of an eligible variant, further potentiating disparities in CF care.[11–13]

There is a need to better understand which sociodemographic factors may affect sinonasal disease severity in PwCF, especially as new therapies emerge. The aim of this study was to evaluate the impact of SDS factors on objective and patient-reported measures of CRS and pulmonary disease severity in PwCF.

2 | METHODS

2.1 | Study design

Study participants were prospectively enrolled into a multi-institutional, observational study between 2018 and 2023, as previously described.[9,14] Study sites were CF Foundation-accredited Care Centers and included: University of California, Los Angeles (UCLA, Los Angeles, CA), Medical University of South Carolina (Charleston, SC), National Jewish Health (Denver, CO), Oregon Health and Science University (Portland, OR), University of Colorado (Aurora, CO), University of Utah (Salt Lake City, UT), University of North Carolina at Chapel Hill (Chapel Hill, NC), and Stanford University (Palo Alto, CA). All participating sites received local Institutional Review Board approval, and written, informed consent was secured from all study participants.

2.2 | Study population, inclusion, and exclusion criteria

As previously described, individuals were considered for study inclusion if they were of adult age (≥18 years), carried a diagnosis of CF based on sweat chloride or genetic testing, and were diagnosed with comorbid CRS as per multidisciplinary guidelines and international consensus statements.[9,15,16] Participants in this observational study self-elected to either undergo endoscopic sinus surgery (ESS) or continued appropriate medical therapy under the guidance of their clinical care team. Participants who underwent ESS within 12 months of enrollment or initiated or changed CFTR modulator therapy within 3 months of enrollment were excluded to avoid potential confounding effects.

2.3 | Measures of sociodemographic status

Enrolled participants provided comprehensive sociodemographic information during baseline screening and enrollment visits including: age, sex (male/female), race, ethnicity, annual household income, educational attainment, health insurance status, and marital status. Annual household income was stratified into categories of: $0–25,000, $25,000–100,000, and $100,000+ based on a modified Thompson–Hickley model.[17] Educational attainment was measured by the total years of education completed and was evaluated both continuously and categorically separated into: 0–11 years (less than high school), 12–15 years (high school ± some college), and 16+ years (college graduate and above). Additionally, as PwCF who identify as Black, Indigenous, or People of Color are less likely to be eligible for ETI based on CFTR variant, outcomes were analyzed based on ETI eligibility status. Participants were categorized as ETI-eligible or ETI-ineligible based on underlying CFTR variant and a known list of responsive variants from the drug manufacturer (Vertex Pharmaceuticals).[11,12,18]

2.4 | Patient-reported and objective measures of disease severity

Participants completed each of the following patient-reported outcome measures upon enrollment: the 22-question Sinonasal Outcome Test (SNOT-22; 2006; Washington University), Cystic Fibrosis Questionnaire-Revised (CFQ-R), Questionnaire of Olfactory Disorder Negative Statements (QOD-NS), and the 40-Question Smell Identification Test (SIT; Sensonics International, Inc.) upon enrollment.[9] The SNOT-22 is used to evaluate sinonasal symptom severity in CRS patients across several subdomains, with higher scores indicating worse sinonasal QOL (range: 0–110).[19,20] The CFQ-R is a validated questionnaire that evaluates CF disease burden on various QOL domains (e.g., respiratory, weight, emotion; range: 0–100); higher scores signify better health in that domain.[21] Olfactory-specific QOL was measured using the QOD-NS, with higher scores indicating worse olfactory QOL (range: 0–51).[22] Total SIT summary scores were classified into olfactory diagnoses (total score range: 0–40; normosmia: male 34–40, female 35–40; hyposmia/microsmia: male 19–33, female 19–34; anosmia: 6–18) with higher scores corresponding to better olfactory function.[23,24]

Objective clinical measures of disease severity were also evaluated through sinonasal endoscopy and sinus computed tomography (CT) scanning. Nasal endoscopy

was scored using the Lund–Kennedy (LK) staging system (score range: 0–20), and sinus CT scans were scored according to Lund–Mackay (LM) staging (score range: 0–24) by the treating rhinologist.[25,26] Higher bilateral nasal endoscopy and sinus CT scores indicate more severe disease. The most recent set of pulmonary function test results, including percent predicted forced expiratory volume in one second ($ppFEV_1$), at the time of study enrollment were extracted from clinical records.

2.5 | Biostatistical analysis

Study data were collected and managed using a secure, web-based electronic data capture platform centrally hosted by UCLA (REDCap; Vanderbilt University). Descriptive analyses were completed for participant-level data including: participant sociodemographic factors, including self-reported race and/or ethnicity, comorbidities, clinical characteristics, CFTR gene variants and associated ETI eligibility, and PROM using SPSS software (version 29.0; IBM Corporation). Assumptions of univariate data normality were evaluated using Shapiro–Wilk testing and normal Q–Q plotting for all scaled data. Bivariate and multivariate comparisons of mean values were evaluated using either independent sample, two-tailed *t*-testing or one-way analysis of variance (ANOVA) for parametric data. Mann–Whitney *U* or Kruskal–Wallis testing was used for similar between-group comparisons for nonparametric data. Type-I error probabilities (*p*-value) are reported for each association of interest. When omnibus testing identified likely significant variability within stratified groups, post hoc, multiple comparisons testing was used with adjusted type-I error rates (adj. *p*-values) using Bonferroni corrections. Spearman's rank correlation (Rs) was used to evaluate bivariate relationships between continuous/scaled data variables without adjustment.

Exploratory linear regression modeling was used to investigate multivariate associations between measures of SES and each clinical or patient-report outcome measure of disease severity. Participant characteristics were screened for univariate significance ($p < 0.20$) for likely model inclusion. Variations associated with enrollment site and ETI use were manually controlled while preliminary models were built using manual forward inclusion and stepwise, backwards elimination ($p < 0.05$) of screened covariates with consideration for maximizing data variance using coefficient of multiple determination (R^2) and impact to overall data fit and modeling accuracy (*F*-test). Modeling validity was confirmed via standardized residual analysis while multicollinearity between all modeling covariates was evaluated using variance inflation factors (VIFs) to identify potential increases in effect estimate variance due to collinear socioeconomic or nonsocioeconomic factors. Any VIF greater than 5.0 was considered the threshold by which final model restructuring would be warranted.[27]

3 | RESULTS

A total of 73 PwCF + CRS were included in this study. Participant sociodemographic factors and clinical characteristics are described in Table 1, and clinical and patient-reported outcome measures are reported in Table 2. The mean age was 34.7 (standard deviation [SD] ±10.9) years and 49 (67.1%) participants were female. The mean $ppFEV_1$ was 76.0% (SD ±24.4%), and 50.7% ($n = 37$) of the cohort was on active ETI therapy, compared to the 89.0% ($n = 65$) who possessed ETI-eligible CFTR variant(s). Over three-quarters ($n = 56$, 76.7%) of PwCF reported a history of previous ESS. Most participants ($n = 69$, 94.5%) identified as White, and over half ($n = 37$, 50.7%) had completed a college degree. The majority ($n = 51$, 69.9%) had employer-provided or private health insurance, while 30.2% ($n = 22$) had either Medicare or Medicaid as their primary health insurer. High prevalence of depression ($n = 34$, 46.6%) and anxiety ($n = 44$, 60.3%) were reported among PwCF. Of the 59 (80.0%) participants who completed SIT testing, over half (31/59, 52.5%) met the diagnostic criteria for hyposmia/microsmia, and 12/59 (20.3%) were diagnosed with anosmia.

3.1 | Patient-reported outcome measures and olfactory scores

All participants completed the SNOT-22, QOD-NS, and CFQ-R questionnaires and 59 (80.8%) PwCF completed SIT testing. Having Medicaid as primary health insurance was significantly associated with worse CFQ-R Respiratory and Digestion subdomain symptom scores compared to employer-provided/private and Medicare insurances (all $p < 0.05$). Hispanic/Latino ethnicity was associated with increased sinonasal symptom burden as measured by SNOT-22 total scores ($p = 0.047$). Age, sex, race, educational attainment, income, or health insurance provision were not associated with differences in SNOT-22 total and subdomain scores, QOD-NS scores, or SIT scores (Table 3).

3.2 | Objective measures of disease severity

Objective measures of disease severity were compared across participant SDS factors (Table 4). PwCF + CRS

TABLE 1 Patient demographics and clinical characteristics of study participants.

Patient characteristics ($n = 73$)	*N* (%)	Mean [±SD]	Range: LL, UL	Median (*Q*1, *Q*3)
Age (years)	73 (100.0%)	34.7 [±10.9]	20.0, 63.0	33.0 (26.0, 39.0)
Sex				
Male	24 (32.9%)	–	–	–
Female	49 (67.1%)	–	–	–
Race				
White	69 (94.5%)	–	–	–
Black	1 (1.4%)	–	–	–
More than one race	3 (4.2%)	–	–	–
Ethnicity				
Hispanic/Latino	3 (4.1%)	–	–	–
Annual household income				
$0–$25,000	19 (26.0%)	–	–	–
$26,000–$100,000	20 (27.4%)	–	–	–
Over $100,000	17 (23.3%)	–	–	–
Unknown or declined to answer	17 (23.3%)	–	–	–
Highest education attainment				
Continuous years	68 (93.2%)	15.8 [±2.4]	10.0, 24.0	15.0 (14.0, 17.0)
12–15 years (categorical)	36 (49.3%)	–	–	–
16+ years (categorical)	37 (50.7%)	–	–	–
Primary health insurer				
Employer provided/private	51 (69.9%)	–	–	–
Medicare	11 (15.1%)	–	–	–
Medicaid	11 (15.1%)	–	–	–
Marital status				
Married/remarried/partnership	40 (54.8%)	–	–	–
Single/never married	29 (39.7%)	–	–	–
Divorced/separated/widowed	4 (5.5%)	–	–	–
Management				
ESS	25 (34.2%)	–	–	–
CAMT	48 (65.8%)	–	–	–
Nasal polyposis	35 (47.9%)	–	–	–
Septal deviation	24 (32.9%)	–	–	–
History of prior ESS	56 (76.7%)	–	–	–
Variant				
F508del homozygous	26 (35.6%)	–	–	–
F508del heterozygous	32 (43.8%)	–	–	–
Other (no F508del allele)	15 (20.5%)	–	–	–
BMI	72 (98.6%)	24.5 [±4.6]	16.1, 40.6	24.1 (20.7, 26.5)
Prior lung transplant	8 (11.0%)	–	–	–
Headache	49 (67.1%)	–	–	–
Depression	34 (46.6%)	–	–	–
Anxiety	44 (60.3%)	–	–	–
Current/former smoking/tobacco use	2 (2.8%)	–	–	–
Current/former alcohol use	23 (31.5%)	–	–	–
History of pseudomonas positivity	55 (75.3%)	–	–	–
History of pancreatic insufficiency	62 (84.9%)	–	–	–

(Continues)

TABLE 1 (Continued)

Patient characteristics ($n = 73$)	N (%)	Mean [±SD]	Range: LL, UL	Median ($Q1$, $Q3$)
History of CF-related DM	29 (39.7%)	–	–	–
ETI-eligible based on CFTR variant	65 (89.0%)	–	–	–
Active CFTR modulator therapy	47 (64.4%)	–	–	–
ETI	37 (50.7%)	–	–	–
Ivacaftor	3 (4.1%)	–	–	–
Tezacaftor/Ivacaftor	7 (9.6%)	–	–	–

Abbreviations: BMI, body mass index; CAMT, continued appropriate medical therapy; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; DM, diabetes mellitus; ESS, endoscopic sinus surgery; ETI, elexacaftor/tezacaftor/ivacaftor; IQR, interquartile range; LL, lower limit; N, sample size; $Q1$, first quartile; $Q3$, third quartile; SD, standard deviation; UL, upper limit.

with an annual household income of $0–$25,000 had lower $ppFEV_1$ compared to those with an annual income of $26,000–$100,000 (63.6% vs. 86.3%, adj. $p = 0.025$). Having Medicare primary health insurance was also associated with lower average $ppFEV_1$ compared to employer-provided/private insurance (58.0% vs. 82.6%, adj. $p = 0.012$). PwCF and Medicaid insurance were found to have clinically meaningful, but not statistically, lower average $ppFEV_1$ compared to employer-provided/private insurance, although this difference was non-significant (63.6% vs. 82.6%, adj. $p = 0.069$). There was also a moderate positive correlation between continuous years of educational attainment and $ppFEV_1$ (Rs = 0.397; $p = 0.001$).

Multivariate linear regression modeling identified that, after manual adjustment for both enrollment site variation and current ETI use, having employer-provided/private health insurance ($\beta = 17.76$, 95% CI [5.20, 30.32], $p = 0.006$), annual household income of $26,000–$100,000 ($\beta = 13.07$, 95% CI [1.27, 24.87], $p = 0.031$), and educational attainment of 16+ years ($\beta = 13.50$, 95% CI [2.21, 24.80], $p = 0.020$) were associated with higher baseline $ppFEV_1$ (Table 5). Final modeling for $ppFEV_1$ outcomes had adequate modeling fit ($F = 5.95$, $p < 0.001$) without evidence of multicollinearity (all VIFs < 1.28) or violations of modeling assumptions, while explaining 33.1% of outcome data variation.

Differences in sinonasal-specific measures of disease severity were also observed among sociodemographic groups. Female PwCF + CRS had significantly lower LM sinus CT scores and LK nasal endoscopy scores than male participants on average (Table 4). Having Medicaid primary health insurance was also associated with worse LK endoscopy scores compared to employer-provided/private insurance (adj. $p = 0.012$). There was a weak negative correlation between age and LK score (Rs = −0.300, $p = 0.025$).

Multivariate linear regression modeling identified that, after adjustment for enrollment site variation, current ETI use ($\beta = -4.09$, 95% CI [−6.08, −2.11], $p < 0.001$), female sex ($\beta = -2.14$, 95% CI [−4.11, −0.17], $p = 0.034$), and increasing age ($\beta = -0.14$, 95% CI [−0.22, −0.05], $p = 0.003$) were associated with lower LK endoscopy scores (Table 5). Final modeling for LK endoscopy scoring had adequate modeling fit ($F = 10.24$, $p < 0.001$) without evidence of multicollinearity (all VIFs < 1.19) or violations of modeling assumptions, while explaining 44.5% of outcome data variation.

The final models presented in Table 5 were rebuilt using forward inclusion of all separate SDS cofactors while comparing VIFs for covariate within each separate model. None of the SDS cofactors excluded during univariate screening were found to be significantly collinear (all VIFs < 2.50) with those covariates retained in the final model for either $ppFEV_1$ or LK nasal endoscopy scores as dependent outcomes. Additional screening of covariate interaction between SDS cofactors and prevalence of ETI-eligible CFTR variant(s) found no significant independent association between ETI-eligible participants with either $ppFEV_1$ ($p = 0.774$) or LK nasal endoscopy scores ($p = 0.737$). There was also no evidence of significant confounding effects against any SDS covariate estimates retained in those models.

4 | DISCUSSION

The impact of SES on CRS severity and olfactory dysfunction in PwCF is understudied yet important to consider in this population to optimize clinical care. This study examined the relationship between multiple components of SDS—age, sex, race, income, and educational attainment—with patient-reported and objective measures of CF-specific QOL, CRS severity, olfaction, and pulmonary function. We found that various SDS factors were associated with differences in sinonasal and pulmonary disease severity, whereas there was minimal impact of SDS factors on patient-reported sinonasal disease severity. This study is the first to evaluate the impact of SDS factors in CF-CRS using both objective and patient-reported outcome measures of disease severity. Findings are aligned with prior work on SDS and lung function.[2,28,29]

TABLE 2 Clinical and patient-reported outcome measure results for study participants.

Characteristics	Mean [±SD]	Range: LL, UL	Median (*Q1*, *Q3*)
Lund–Kennedy nasal endoscopy score ($n = 56$, 76.7%)	6.9 [±4.5]	0.0, 18.0	6.0 (3.3, 10.0)
Lund–Mackay CT score ($n = 44$, 60.3%)	12.1 [±7.1]	0.0, 24.0	12.0 (7.3, 18.0)
FEV_1 (%) predicted ($n = 66$, 90.4%)	76.0% [±24.4]	28.1%, 180.0%	78.0 (51.6, 94.5)
SIT total score ($n = 59$, 80.8%)	27.6 [±9.1]	8.0, 39.0	31.0 (19.0, 35.0)
Anosmia ($n = 12$, 20.3%)	12.4 [±3.9]	8.0, 18.0	11.0 (9.0, 16.8)
Hyposmia/microsmia ($n = 31$, 52.5%)	28.8 [±4.2]	19.0, 33.0	30.0 (26.0, 32.0)
Normosmia ($n = 16$, 27.1%)	36.6 [±1.1]	35.0, 39.0	37.0 (36.0, 37.0)
SNOT-22 total score ($n = 73$, 100%)	37.1 [±19.7]	5.0, 80.0	35.0 (23.0, 52.0)
Rhinologic symptom domain	11.3 [±6.3]	0.0, 26.0	11.0 (7.0, 16.0)
Extra-nasal rhinologic symptom domain	6.0 [±3.6]	0.0, 15.0	6.0 (3.5, 8.0)
Ear/facial symptom domain	6.9 [±4.3]	0.0, 18.0	6.0 (4.0, 9.5)
Psychological dysfunction domain	11.3 [±7.9]	0.0, 27.0	11.0 (4.0, 16.5)
Sleep dysfunction domain	9.4 [±6.5]	0.0, 23.0	10.0 (3.0, 15.0)
QOD-NS total score ($n = 73$, 100%)	7.5 [±8.8]	0.0, 33.0	4.0 (1.0, 11.0)
CFQ-R domain scores			
Physical domain ($n = 73$, 100%)	65.6 [±29.3]	4.2, 100.0	75.0 (37.5, 91.7)
Vitality domain ($n = 73$, 100%)	49.5 [±22.6]	8.3, 91.7	50.0 (33.3, 66.7)
Emotion domain ($n = 73$, 100%)	71.8 [±20.6]	20.0, 100.0	73.3 (60.0, 86.7)
Eating domain ($n = 73$, 100%)	83.9 [±20.3]	44.4, 100.0	100.0 (66.7, 100.0)
Treatment burden domain ($n = 73$, 100%)	61.5 [±23.6]	11.1, 100.0	55.6 (44.4, 77.8)
Health perceptions domain ($n = 73$, 100%)	62.6 [±24.6]	0.0, 100.0	66.7 (44.4, 77.8)
Social domain ($n = 73$, 100%)	66.0 [±21.6]	22.2, 100.0	66.7 (50.0, 83.3)
Body image domain ($n = 73$, 100%)	70.0 [±28.0]	0.0, 100.0	77.8 (55.6, 100.0)
Role/school domain ($n = 72$, 98.6%)	72.8 [±24.5]	8.3, 100.0	79.2 (58.3, 91.7)
Weight symptom scale ($n = 72$, 98.6%)	75.9 [±36.4]	0.0, 100.0	100.0 (33.3, 100.0)
Respiratory symptom scale ($n = 72$, 98.6%)	67.0 [±24.2]	11.1, 100.0	66.7 (50.0, 83.3)
Digestion symptom scale ($n = 71$, 97.3%)	70.0 [±21.1]	11.1, 100.0	66.7 (55.6, 88.9)

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire-Revised; CT, computed tomography; FEV, forced expiratory volume; IQR, interquartile range; LL, lower limit; *N*, sample size; *Q1*, first quartile; *Q3*, third quartile; QOD-NS, Questionnaire of Olfactory Disorders-Negative Statements; SD, standard deviation; SIT, Smell Identification Test (Sensonics International, Inc.); SNOT-22, 22-item SinoNasal Outcome Test survey; UL, upper limit.

Female sex was associated with less severe CRS on sinus CT and nasal endoscopy on average. This largely aligns the non-CF CRS literature, which has found that female patients have lower objective sinonasal disease burden compared to males.[30–32] The pathophysiologic mechanism behind this difference is relatively unknown—evidence suggests that sex hormone levels and genetic variations may play a role, but these studies had limited power, and their findings have yet to be corroborated.[33–35] It is also well-established that non-CF females with CRS report worse sinonasal symptom burden on the SNOT-22 despite less severe CRS on objective examination, a finding which we did not observe in this cohort of PwCF.[31,33,36] We hypothesize that the differences between this study's findings and prior research examining individuals without CF may be explained by the systemic nature of CF and overall treatment needs. Self-reporting may be influenced by the responding individual's expectations, coping mechanisms, and perceptions of disease.[14] CF can drastically impair pulmonary, gastrointestinal, and metabolic function, placing significant lifetime symptom burden onto PwCF. Thus, PwCF may have a higher threshold for what constitutes significant symptom severity compared to non-CF individuals. These results suggest that the CF population is a unique subset of individuals with CRS, emphasizing the need for further investigation into the interplay between the two diseases.

We also found that increasing age was correlated with less severe CRS on endoscopy. While it is generally accepted that CRS is more prevalent with older age, the impact of age on CRS severity is unclear.[37,38] Studies in non-CF individuals with CRS have identified alterations in the nasal microbiome and inflammatory cytokine profile with increasing age, which may account for this observed

TABLE 3 Associations of patient-reported outcome measures and socioeconomic factors.

Characteristics	SNOT-22 total, mean [±SD]	*p*-Value	QOD-NS, mean [±SD]	*p*-Value	CFQ-R digestion, mean [±SD]	*p*-Value	CFQ-R respiratory, mean [±SD]	*p*-Value	SIT total, mean [±SD]	*p*-Value
Age (years)[a]	37.1 [±19.7]	0.658	7.5 [±8.8]	0.687	70.0 [±21.1]	0.199	67.0 [±24.2]	0.088	27.6 [±9.1]	0.172
Sex										
Male	39.6 [±16.7]	0.398	7.5 [±9.3]	0.394	69.9 [±18.1]	0.362	62.5 [±27.5]	0.362	24.4 [±10.3]	0.049
Female	35.9 [±21.1]		7.5 [±7.9]		70.0 [±22.7]		69.2 [±22.3]		29.5 [±7.9]	
Race										
White	37.1 [±19.9]	0.818	7.5 [±8.8]	0.916	69.5 [±21.4]	0.885	66.9 [±24.8]	0.885	27.6 [±9.4]	0.511
Black	28.0 [–]		5.0 [–]		66.7 [–]		77.8 [–]		–	
More than one race	41.3 [±21.2]		8.0 [±12.2]		81.5 [±17.0]		64.8 [±11.6]		27.7 [±3.8]	
Ethnicity										
Hispanic/Latino	59.3 [±11.9]	**0.047**	9.0 [±8.2]	0.664	51.9 [±28.0]	0.186	48.1 [±26.3]	0.186	32.0 [–]	0.847
Non-Hispanic/Latino	36.2 [±19.4]		7.4 [±8.9]		70.8 [±20.7]		67.8 [±23.9]		27.5 [±9.2]	
Annual household income										
$0–$25,000	40.9 [±16.7]	0.308	6.4 [±7.1]	0.183	70.4 [±23.2]	0.360	60.2 [±27.9]	0.360	26.4 [±9.9]	0.116
$26,000–$100,000	35.5 [±17.9]		7.7 [±8.1]		71.1 [±21.1]		70.3 [±21.0]		26.8 [±9.7]	
$101,000+	30.8 [±20.0]		4.2 [±7.0]		72.9 [±19.9]		73.5 [±24.3]		32.1 [±7.5]	
Unknown, declined	41.1 [±23.9]		11.8 [±11.5]		65.4 [±21.1]		63.7 [±23.0]		25.2 [±8.6]	
Educational attainment										
Continuous years[a]	37.1 [±19.7]	0.230	7.5 [±8.8]	0.910	70.0 [±21.1]	0.449	67.0 [±24.2]	0.242	27.4 [±9.3]	0.684
12–15 years	39.4 [±20.9]	0.297	7.1 [±8.9]	0.541	68.9 [±21.9]	0.120	62.1 [±26.1]	0.120	27.7 [±8.9]	0.772
16+ years	34.9 [±18.4]		7.9 [±8.8]		71.0 [±20.6]		71.6 [±21.5]		27.5 [±9.5]	
Primary health insurer										
Employer provided/private	35.9 [±21.0]	0.535	7.4 [±8.6]	0.957	72.0 [±20.8]	**0.005**	68.7 [±22.5]	**0.005**	28.3 [±8.6]	0.643
Medicare	38.3 [±17.0]		8.6 [±12.1]		70.0 [±22.3]		81.1 [±16.0]		24.4 [±11.1]	
Medicaid	41.6 [±16.2]		6.6 [±6.0]		60.6 [±20.7]		46.0 [±26.1]		27.4 [±10.4]	
Marital status										
Married/remarried/partnership	37.3 [±20.0]	0.813	7.7 [±9.0]	0.996	67.5 [±22.0]	0.522	69.6 [±24.0]	0.522	28.3 [±9.0]	0.439
Single/never married	36.3 [±20.2]		7.4 [±9.0]		73.8 [±18.2]		63.7 [±24.9]		27.3 [±9.9]	
Divorced/separated/widowed	40.8 [±16.1]		6.0 [±6.7]		66.7 [±32.7]		63.9 [±23.4]		23.7 [±4.2]	

Note: Symbol "–" denotes insufficient number of participants to perform statistics. Bolded values indicate a significance level of p<0.05.

Abbreviations: CFQ-R, Cystic Fibrosis Questionnaire-Revised; *N*, sample size; QOD-NS, Questionnaire of Olfactory Disorders-Negative Statements; SD, standard deviation; SIT, Smell Identification Test (Sensonics International, Inc.); SNOT-22, 22-item SinoNasal Outcome Test survey.

[a]Reported *p*-values using Spearman's rank correlation coefficient.

TABLE 4 Omnibus associations of clinical measures of disease severity with socioeconomic factors of interest.

Characteristics	LK endoscopy score, mean [±SD]	*p*-Value	LM CT score, mean [±SD]	*p*-Value	$ppFEV_1$, mean [±SD]	*p*-Value
Age (years)[a]	6.9 [±4.5]	**0.025**	12.1 [±7.1]	0.374	76.0 [±24.4]	0.216
Sex						
Male	8.3 [±3.8]	**0.032**	16.3 [±6.3]	**0.001**	72.3 [±24.4]	0.467
Female	6.1 [±4.7]		9.2 [±6.1]		77.8 [±24.5]	
Race						
White	6.9 [±4.6]	0.738	11.9 [±7.1]	0.519	76.9 [±24.5]	0.491
Black	6.0 [–]		12.0 [–]		58.1 [–]	
More than one race	8.5 [±2.1]		20.0 [–]		61.7 [±23.2]	
Ethnicity						
Hispanic/Latino	6.5 [±0.7]	0.947	–	–	71.3 [±35.2]	0.885
Non-Hispanic/Latino	6.9 [±4.6]		12.1 [±7.1]		76.2 [±24.2]	
Annual household income						
$0–$25,000	7.4 [±4.7]	0.501	13.1 [±6.5]	0.266	63.6 [±23.6]	**0.038**
$26,000–$100,000	7.1 [±3.9]		15.0 [±8.5]		86.3 [±21.6]	
$101,000+	5.6 [±4.3]		9.9 [±6.3]		75.9 [±25.7]	
Unknown, declined	7.9 [±5.4]		10.1 [±6.4]		78.6 [±22.7]	
Educational attainment						
Continuous years[a]	6.9 [±4.5]	0.783	12.1 [±7.1]	0.366	76.0 [±24.4]	**0.001**
12–15 years	7.8 [±4.8]	0.214	12.9 [±6.3]	0.540	66.3 [±24.3]	**0.002**
16+ years	6.1 [±4.1]		11.4 [±7.7]		85.1 [±21.1]	
Primary health insurer						
Employer provided/private	6.1 [±4.2]	**0.016**	10.9 [±6.9]	0.167	82.6 [±23.3]	**0.003**
Medicare	6.9 [±3.8]		16.5 [±8.1]		58.0 [±17.6]	
Medicaid	11.3 [±4.3]		13.6 [±5.9]		63.6 [±23.0]	
Marital status						
Married/remarried/partnership	6.7 [±4.5]	0.756	11.2 [±7.2]	0.295	80.5 [±21.4]	0.226
Single/never married	7.3 [±4.3]		13.9 [±6.7]		69.7 [±25.4]	
Divorced/separated/widowed	6.0 [±7.2]		7.0 [±7.1]		72.5 [±40.8]	

Note: Symbol "–" denotes insufficient number of participants to perform statistics. Bolded values indicate a significance level of $p<0.05$.

Abbreviations: CT, computed tomography; LK, Lund–Kennedy; LM, Lund–Mackay; SD, standard deviation.

[a]Reported *p*-values using Spearman's rank correlation coefficient.

decrease in severity.[37,39,40] Additionally, allergic reactivity and immune responsiveness tend to decrease with age, reducing their contribution to disease state.[41] However, since nasal microbial diversity and cytokine profiles differ in PwCF + CRS compared to their non-CF counterparts, further research is warranted to clarify the relationship between age and disease severity.[42,43]

PwCF with Medicaid insurance had worse inflammation on nasal endoscopy compared to those with employer or private insurance prior to adjustment for other significant cofactors. Individuals with Medicaid insurance coverage often face difficulty accessing specialized care, resulting in delays to initial presentation and more severe disease at presentation.[44,45] Thus, PwCF with Medicaid insurance coverage may have worse nasal inflammation on clinical examination. It is also possible that environmental factors related to low SES contribute to worsened CRS disease severity, although this was not directly assessed in this study. While geographic differences were not evaluated in this analysis, living in disadvantaged neighborhoods is associated with increased air pollutant exposure, which increases sinonasal inflammation and has been linked to increased incidence of CRS in non-CF populations.[6,8] These effects may be further magnified in PwCF, who have pre-existing mucociliary dysfunction and airway disease. The association between Medicaid insurance and worsened LK endoscopy scores was ultimately eliminated in the multivariate analysis, likely due to a small sample size within that subgroup. Nonetheless, given the connection between the upper and lower airway, optimization of CRS

TABLE 5 Multivariate linear regression modeling of socioeconomic factors associated with differences in both Lund–Kennedy nasal endoscopy scores and percent predicted forced expiratory volume in one second ($ppFEV_1$).

	Effect estimates (*B*)	95% CI	SE	*t*-Test	*p*-Value
$ppFEV_1$					
Constant term	63.11	51.41, 74.81	5.85	10.79	**<0.001**
Enrollment site	−1.98	−4.30, 0.34	1.16	−1.71	0.093
Current ETI use	−6.99	−17.58, 3.61	5.30	−1.32	0.192
Primary health insurer: employer provided/private	17.76	5.20, 30.32	6.28	2.83	**0.006**
Educational attainment: 16+ years	13.50	2.21, 24.80	5.65	2.39	**0.020**
Annual household income: $26,000–$100,000	13.07	1.27, 24.87	5.90	2.22	**0.031**
Lund–Kennedy nasal endoscopy score					
Constant term	15.95	12.36, 19.55	1.79	8.92	**<0.001**
Enrollment site	−0.29	−0.74, 0.16	0.22	−1.29	0.204
Current ETI use	−4.09	−6.08, −2.11	0.99	−4.13	**<0.001**
Age (years)	−0.14	−0.22, −0.05	0.04	−3.18	**0.003**
Sex (referent—male)	−2.14	−4.11, −0.17	0.98	−2.18	**0.034**

Note: Bolded values indicate a significance level of $p<0.05$.

Abbreviations: CI, confidence interval; ETI, elexacaftor/tezacaftor/ivacaftor; SE, standard error.

management is of critical importance to PwCF, especially since pulmonary function is closely tied to mortality in CF.[46]

Our findings also showed that PwCF with Medicaid or Medicare health insurance, lower annual household income, and fewer years of educational attainment have lower baseline $ppFEV_1$ on average. These findings align with previous reports that socioeconomically disadvantaged PwCF tend to have worse lung function compared to their peers when using income, education, and health insurance type as proxies for SES.[2,28,29] The multifactorial nature of health outcomes in PwCF involves not only the complexity of medical care but also the accessibility and adherence to that care. Limited financial resources or inadequate insurance coverage may impede access to care, resulting in worsened pulmonary function. Additionally, higher educational attainment has been associated with improved adherence to CF airway therapy regimens, contributing to improved pulmonary outcomes.[47]

Hispanic/Latino ethnicity was associated with higher SNOT-22 scores prior to adjustment for other cofactors; however, other SDS factors were not associated with differences in SNOT-22, QOD-NS, or SIT scores. These findings partially contrast with previous studies in non-CF CRS patients, which found that low-income, non-White, and Medicare patients reported worse sinonasal symptom severity.[48,49] Of note, only 4 individuals in our study identified as Black or more than one race, so this study may have been underpowered to detect differences for this subgroup. Alternatively, similar to our findings of sex differences, this finding may reflect a differential between the symptom-reporting threshold of PwCF + CRS versus CRS patients without CF. On the other hand, Medicaid insurance provision was significantly associated with worse CFQ-R Respiratory and Digestion subdomain scores on average, which aligns with our findings of more severe pulmonary disease and other reports on the impact of SES on patient-reported outcomes in CF.[50]

Although our cohort was not designed to be powered to evaluate the impact of ETI treatment across different subgroups, regression analysis demonstrated that current ETI use was significantly associated with reduced sinonasal inflammation on endoscopy. This result is consistent with findings that ETI decreases endoscopic sinus inflammation and CT opacification.[51,52] Previous work from our group also indicates that ETI improves sinonasal QOL and may reduce the need for sinus surgery.[9] We also investigated the effect of ETI eligibility on measures of disease severity, as PwCF who identify as Black, Indigenous, or People of Color are less likely to possess a CFTR gene variant responsive to ETI. The percentage of study participants eligible for ETI in this study (89%) is similar to national data from the CF Foundation Patient Registry.[53] Within our cohort, ETI eligibility did not independently associate with any disease severity measures or was there evidence of confounding effects of SDS cofactors on multivariate modeling. Ultimately, given the financial cost but substantial impact of ETI on sinonasal and pulmonary disease, future investigations should examine how SES factors may influence patterns in ETI usage.

The strengths of this study include a multicenter prospective design and inclusion of multiple factors that serve as components of SDS, in addition to a broad set of patient-reported and objective measures of disease

severity. There are several potential limitations to our study. Most participants had employer-provided/private health insurance, high educational attainment, and identified as White, while other groups were underrepresented. Our demographic distribution of race is modestly different than that published in the CF Foundation Patient Registry and suggests the need for further study and ongoing enrollment.[53] Our study may have been underpowered to detect certain differences across SDS factors, including ETI-eligibility based on CFTR variant status, resulting in the possibility of type II error. Additionally, this study only included PwCF seen at CF Foundation-accredited care centers, while the majority of CF care in the United States takes place at these centers, overall findings may not be representative of the CF population who receive care at non-CF centers.

5 | CONCLUSIONS

Sex, age, and use of highly effective modulator therapy were associated with differences in objective sinonasal disease severity. Hispanic/Latino ethnicity was associated with worse SNOT-22 scores before adjustment for other cofactors. There were no differences in patient-reported sinonasal symptom severity or olfaction based on other components of SDS. Primary health insurance type, annual household income, and educational attainment were associated with differences in pulmonary disease. Further understanding how SDS barriers affect treatment of CRS in PwCF will be necessary to improve care equity and outcomes in this population.

ACKNOWLEDGMENTS

This work was supported by the Cystic Fibrosis Foundation (BESWIC20A0 and BESWIC22Y5). This foundation provided support for the planning and execution of this work but did not have specific involvement in the study design, data collection, analysis, or interpretation, or decision to submit the article for publication. Research reported in this publication was supported by the National Institute on Deafness and Other Communication Disorders of the National Institutes of Health under award number R25DC020151. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

CONFLICT OF INTEREST STATEMENT

Ethan J. Han, Jakob L. Fischer, Anne E. Getz, Jivianne T. Lee, Meghan Norris, Cameran Owens, and Timothy L. Smith: None to disclose. Christine M. Liu: NIDCD grant related to work. Jess C. Mace: Received grant support from CF Foundation related to this work in the past 36 months (BESWIC20AO). Jeremiah A. Alt: Consultant for OptiNose and Medtronic. Speaker panel GSK. GlycoMira board and equity holder. Grant support from CF Foundation related to this work BESWIC20A0. Todd E. Bodner: Received grant support from CF Foundation related to this work in the past 36 months (BESWIC-ZOAD). Naweed I. Chowdhury: Unrelated to this work, N.I.C. has received grant support from the Burroughs Wellcome Fund, American Rhinologic Society, and the National Cancer Institute. Peter H. Hwang: Consultant for Stryker, Medtronic, Slate Therapeutics. Equity ownership in Sound Health Systems. Ashoke Khanwalkar: Advisory Board for Sound Health Systems. Adam J. Kimple: Consultant for Acclarent. Douglas A. Li: In the last 36 months, D.A.L. has received grant support from the CF Foundation unrelated to this work. Jayakar V. Nayak: Consultant with Aerin Medical. Equity/Patent with SpirAir LLC. Grant support from the National Institutes of Health. No conflicts of interest related to this work. Zara M. Patel: Consultant/Advisory Board for Optinose, Medtronic, Dianesis, Wyndly, Third Wave Therapeutics, Regeneron/Sanofi, Mediflix, ConsumerMedical. Equity in Olfera Therapeutics. Rodney J. Schlosser: Consultant for OptiNose, Medtronic, Stryker, Cyrano. Medical Directory for Healthy Humming. Kristine A. Smith: In the last 24 months, consultant for SanofiGenzyme. Zachary M. Soler: Consultant for OptiNose, Regeneron, SanofiGenzyme, and Lyra. Medical Directory for Healthy Humming. Grant A. Turner: In the last 36 months, GAT has received grants from the CF Foundation unrelated to this work. Marilene B. Wang: None related to this work. Jennifer L. Taylor-Cousar: In the last 36 months, JLT-C has received grants from the CF Foundation related to this work as well as for work unrelated to the manuscript. Unrelated to this work, she has received grants to her institution from Vertex Pharmaceuticals Incorporated, Eloxx, and 4DMT; has received fees to her institution from Vertex Pharmaceuticals Incorporated and 4DMT related to consultation on clinical research design. She served on a DMC for AbbVie. She serves as the adult patient care representative to the CFF Board of Trustees, and on the CF Foundation's Clinical Research Executive Committee, Clinical Research Advisory Board, Racial Justice Working Group and as immediate past chair of the CF TDN's Sexual Health, Reproduction and Gender Research Working Group, on the scientific advisory board for Emily's Entourage, and as the ATS International Conference Committee Chair Elect. She previously served on the ATS Respiratory Health Awards, Scientific Grant Review and Clinical Problems Assembly Programming Committees. Milene T. Saavedra: Received funding from CFF unrelated to this work. Daniel M. Beswick: In the last 36 months, DMB has received grant support from CF Foundation, International

Society of Inflammation and Allergy of the Nose and the American Rhinologic Society CORE/Sue Ann and John L. Weinberg Foundation; honoraria from multiple sources including from National Jewish Health; consulting fees from Amgen, on medicolegal cases and from Garner Health (equity). The remaining authors did not respond with any financial disclosures.

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How to cite this article: Han EJ, Liu CM, Fischer JL, et al. Impact of sociodemographic status and sex on chronic rhinosinusitis and olfaction in people with cystic fibrosis. *Int Forum Allergy Rhinol*. 2024;1-14. https://doi.org/10.1002/alr.23402