

Identifying an at-risk population for poor asthma outcomes: Data from the American Lung Association Asthma Clinical Trials Registry

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Clinical Implications

- In a large clinical trials registry, patients with asthma who are current smokers have distinct demographic and clinical characteristics in comparison to former and never smokers, raising awareness of a unique asthma phenotype requiring targeted therapeutic strategies to achieve optimal asthma control.

TO THE EDITOR:

Combustible cigarette use is one of the most important public health problems worldwide, and is disappointingly prevalent among patients with asthma. Despite well-known respiratory hazards, in the United States, smoking rates among patients with asthma are greater than rates among patients without asthma (21% vs 17%).¹ Smoking is associated with numerous adverse asthma outcomes, including more frequent respiratory symptoms,² increased health care utilization,³ and faster decline in lung function.⁴ Furthermore, patients with asthma who smoke appear to be relatively insensitive to the primary treatment modality for persistent asthma—inhaled corticosteroids (ICSs).⁵ These findings have generated speculation that patients with asthma who smoke may represent a unique phenotype of airways disease; however, clinical characteristics, presentation, and trajectory of this subgroup are not well understood due to the traditional exclusion of smokers from asthma trials. Further knowledge regarding patients with asthma who smoke is critical to help design targeted public health interventions to reduce asthma morbidity in this subpopulation. In this study, we sought to investigate characteristics of active, former, and never smokers with asthma in a national clinical trials registry.

The Asthma Clinical Trials Registry is a multicenter database comprising adults recruited to potentially participate in clinical trials of the American Lung Association Airways Clinical Research Centers. The registry was approved and monitored by institutional review boards at all participating centers, and all participants provided informed consent to be included. Adult participants older than 18 years with self-report of physician-diagnosed asthma enrolled into the registry between October 2009 and August 2018 were analyzed. Patients carrying a concurrent diagnosis of chronic obstructive pulmonary disease were excluded. Demographic characteristics, smoking history, and pharmacologic therapies were collected at registry entry. The Asthma Control Test (ACT)⁶ was recorded if available; control

was defined as ACT score of more than 19. Descriptive analyses included medians with interquartile ranges (IQRs) and proportions. Comparisons between subgroups classified by smoking status were analyzed using chi-square and Kruskal-Wallis tests for categorical and continuous characteristics, respectively. Analyses were performed using SAS statistical software package (version 9.4, SAS Institute, Inc., Cary, NC).

A total of 2285 adults were included in analyses. Overall, participants had a median (IQR) age of 45 (31-56) years and were predominantly female (68%). Most participants either identified as white (46%) or black (32%) race, and non-Hispanic ethnicity (86%). Sixty-five percent of the population reported use of either ICS alone or in combination with a long-acting β -agonist in the past month. Median (IQR) ACT score was 19 (14-22). Smokers (either current or former) comprised 42% of all participants; 21% were active smokers at time of enrollment. E-cigarette use data were available in a subset of participants (14%), of which a small minority (4%) reported ever having tried, or currently using, nicotine in this form (Table 1).

We found significant differences between subgroups by smoking status. For example, men with asthma were more likely to be current smokers rather than former or never smokers ($P < .001$), and a disproportionate number of current smokers with asthma were male (42%), and of black race (53%), relative to the overall population. Current smokers had poorer asthma control compared with former and never smokers (median ACT score of 16 vs 19 vs 20; $P < .001$). Despite worse asthma control, current smokers were less likely to use single ICS or combination ICS/long-acting β -agonist than nonsmokers (40% vs 71%; $P < .001$), but more likely to use a short-acting bronchodilator agent (84% vs 67%; $P < .001$). After stratifying by race-sex subgroups, black men with asthma had higher proportions of those currently smoking, not taking ICS, and having uncontrolled asthma (Figure 1). Because participants with chronic obstructive pulmonary disease were excluded on the basis of self-report, sensitivity analyses including only registry participants with less than 10 pack tobacco history (eliminating those who may have potentially been misclassified) did not change our findings with regard to ICS use and asthma control, or demographic and asthma characteristics, among never versus current smokers.

This is the first report to describe clinical and demographic characteristics unique to current smokers with asthma enrolled in a large clinical trials registry. Smokers with asthma have consistently been excluded from clinical trials, resulting in a paucity of data. Our results reinforce the concept that smokers with asthma represent a unique phenotype, having distinct demographic characteristics and significantly poorer asthma control compared with never smokers. The epidemiologic characterization of smokers with asthma links to published mechanistic studies that, in parallel, identify unique patterns of immunologic profiles in this subpopulation compared with nonsmokers, thus providing a pathobiologic basis to our work.⁷ Given that smokers with asthma have higher disease burden and relative resistance to corticosteroids, therapeutic strategies, informed by data on the effects of smoking on patient outcomes and tailored specifically for this subgroup, may be needed.

TABLE I. Registry participants, total and by smoking status

Characteristic	Total (N = 2285)	Current (N = 490)	Former (N = 460)	Never (N = 1316)	Missing (N = 19)	P value*
Demographic						
Age at entry (y), median (Q1, Q3)	45 (31, 56)	41 (29, 50)	54 (43, 62)	44 (29, 56)	38 (30, 56)	<.001
Sex, n (%)						
Male	733 (32)	205 (42)	156 (34)	366 (28)	6 (32)	<.001
Female	1551 (68)	285 (58)	303 (66)	950 (72)	13 (68)	
Missing	1 (0)		1 (0)			
Ethnicity, n (%)						
Hispanic	293 (13)	37 (8)	67 (15)	187 (14)	2 (11)	<.001
Non-Hispanic	1973 (86)	451 (92)	392 (85)	1117 (85)	13 (68)	
Missing	19 (1)	2 (0)	1 (0)	12 (1)	4 (21)	
Race, n (%)						
White	1048 (46)	187 (38)	202 (44)	652 (50)	7 (37)	<.001
Black	734 (32)	262 (53)	131 (28)	336 (26)	5 (26)	
Asian	33 (1)	5 (1)	3 (1)	25 (2)		
American Indian	11 (0)	3 (1)	3 (1)	5 (0)		
Hawaiian	7 (0)	3 (1)	1 (0)	3 (0)		
Other	108 (5)	15 (3)	28 (6)	65 (5)		
Missing	344 (15)	15 (3)	92 (20)	230 (17)	7 (37)	
ACT scores†						
Median (Q1, Q3)	19 (14, 22)	16 (12, 19)	19 (14, 22)	20 (16, 22)	13 (11, 21)	<.001
ACT score >19, n (%)	638 (28)	87 (18)	125 (27)	425 (32)	1 (5)	<.001
ACT score ≤19, n (%)	807 (35)	270 (55)	141 (31)	394 (30)	2 (11)	
Missing, n (%)	840 (37)	133 (27)	194 (42)	497 (38)	16 (84)	
Pack years, median (Q1, Q3)	12 (5, 26)	15 (9, 30)	10 (3, 20)			<.001
Missing, n (%)	1416 (62)	32 (7)	49 (11)	1316 (100)	19 (100)	<.001
E-Cigarette use status, n (%)						
Current	3 (0)		3 (1)			<.001
Former	2 (0)	1 (0)	1 (0)			
Tried, but less than 5 times	9 (0)	1 (0)	5 (1)	3 (0)		
Never	300 (13)	8 (2)	74 (16)	218 (17)		
Missing	1971 (86)	480 (98)	377 (82)	1095 (83)	19 (100)	
Treatments in past month, n (%)						
ICS or ICS/LABA	1476 (65)	195 (40)	339 (74)	935 (71)	7 (37)	<.001
Oral corticosteroids	195 (9)	18 (4)	56 (12)	121 (9)		<.001
SABA	1617 (71)	410 (84)	316 (69)	888 (67)	3 (16)	<.001

LABA, Long-acting β -agonist; SABA, short-acting β -agonist.

*P values are based on χ^2 and Kruskal-Wallis tests for categorical and continuous characteristics, respectively.

†Higher scores indicate better health.

A key finding of our study was that current smokers with asthma reported lower rates of controller medication use. Conversely, a higher proportion of current smokers reported rescue medication use, in comparison to former and never smokers. Although relationships between higher asthma morbidity and decreased controller medication use may be intuitive, reasons for disparities between smokers with asthma and nonsmokers with asthma are unclear and likely involve various biologic, social, and behavioral mechanisms. For example, biologically driven poor responses to standard therapies may result in reluctance of clinicians to prescribe these treatments, or of patients to adhere to these regimens, thereby increasing dependence on symptomatic approaches. Alternatively, smokers with asthma may have limited access to maintenance health care, opting instead for emergency settings.⁸ Finally, poor control among smokers with asthma may be

influenced by psychosocial factors associated with smoking such as mental health disease (eg, depression), risk-taking behaviors, and lack of self-efficacy, resulting in suboptimal therapy.⁹

Limitations of our study include that registry participants were recruited for various asthma clinical trials, and findings may therefore not be generalizable to a general population of patients with asthma. However, our large cohort had broad, diverse geographic representation with a range of asthma control, and data collected according to a uniform protocol. In addition, because data from this registry relied on self-report, we had notable rates of missing data, which may inherently introduce bias. Nonetheless, we found statistically significant differences across smoking-based subgroups, further reinforcing distinct features belonging to patients with asthma who smoke.

In summary, smokers with asthma are overrepresented by males and blacks, and have worse control of asthma, yet lower

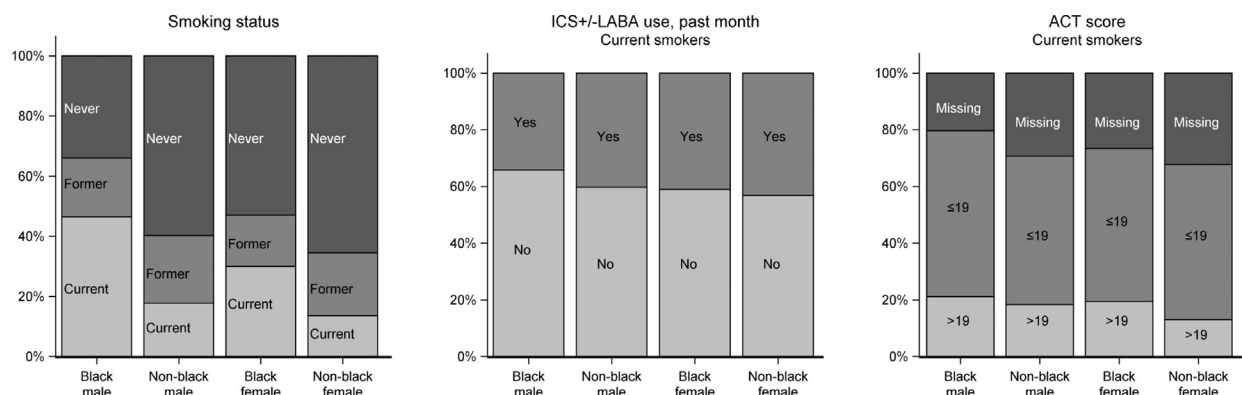


FIGURE 1. Proportions of smoking status and, among current smokers, ICS use in the past month and ACT score by race-sex subgroups. Data were derived from all 2285 adults with asthma in the registry. Black males had higher rates of current smoking, but were less likely to be taking ICSs containing medication despite a majority having low ACT scores. *LABA*, Long-acting β -agonist.

rates of ICS use, compared with former and never-smoking patients with asthma. There is compelling need to develop improved treatments aimed at smoking cessation and asthma control for this important demographic.

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