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Effect of COVID-19 on asthma exacerbation

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Clinical Implications

- For Black/African-American and Hispanic/Latinx individuals with moderately severe asthma, there was nearly a halving of asthma exacerbations following the coronavirus disease 2019 (COVID-19) pandemic, a decrease most significant for individuals working outside of the home and in those without type 2 inflammation, suggesting environmental or common viral triggers for asthma exacerbations.

Understanding the effect of the coronavirus disease 2019 (COVID-19) pandemic, and the efforts taken to combat it, on specific diseases is difficult owing to the many ways in which COVID-19 is impacting patients and health care systems. A significant decrease in the utilization of emergency services for asthma exacerbation (AEX) has been reported.[1] However, health care system avoidance has also been reported and has resulted in delayed or decreased primary and acute care consultations, making it difficult to assess the extent to which decreased health utilization is related to patient avoidance of health services versus actual changes in asthma control.[2]

The Person Empowered Asthma Relief (PREPARE) study is a national randomized, open-label, pragmatic trial of a patient-guided, reliever-triggered inhaled corticosteroid (ICS) strategy in African American/Black (AA/B) and Hispanic/Latinx (H/L) adults (age, 18-75 years) with moderate-to-severe asthma.[3] Subject recruitment occurred at 19 clinical organizations across the United States, including 4 primary care and 6 specialty practices, and 9 combined primary and specialty care practices (Table E1; available in this article's Online Repository at www.jaci-inpractice.org). Following a single in-person appointment at enrollment, participants completed monthly questionnaires remotely either online, by phone, or by mail for 15 months. The study's primary outcome was an annualized AEX rate and exacerbations as defined by Wechsler et al,[4] self-reported via a monthly Asthma Exacerbation Questionnaire), verified and adjudicated remotely. Recruitment into the trial was initiated in November 2018 and enrollments were completed in March 2020, as COVID-19–related lockdowns were initiated. Because remote reporting of asthma control is unlikely to be affected by health care system avoidance, these data provide a unique opportunity to understand changes in asthma control during the COVID-19 pandemic.

We compared the change in annualized AEX rates between the first and the second quarters of 2019 versus the same quarters of 2020. The outcome was categorized by month and by quarter of the observation year (first quarter [Q1]: January 1 through March 31; second quarter [Q2]: April 1 through June 30). Difference-in-differences (DID) additive and multiplicative Poisson regression models with generalized estimating equations with an exchangeable correlation structure were used, with exacerbation count as a function of quarter (Q1 compared with Q2) for both 2019 and 2020, with repeated measurement on subjects across calendar quarters. The influence of relevant covariates on outcomes was assessed using multivariable regression and testing for the independent interaction between covariate and outcomes. Potential covariates were selected *a priori* on the basis of potential clinical relevance and included race, hypertension, geographic region, and place of work at enrollment (at home or working outside of the home). The effect of obesity and eosinophilic phenotypes (peripheral blood eosinophilia and fractional excretion of nitric oxide [FeNO] data, where available) were also examined. The DID effect was also examined after adjusting for the air-quality factors.

A total of 1,178 participants were included and baseline characteristics are shown in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org). There were more H/L participants and more participants from the Southwest in 2020 and no other clinically significant differences in baseline characteristics between 2019 and 2020. At entry, 55% were not working outside of the home and 72% had an AEX in the year prior to enrollment. There were a total of 682 AEX events, of which 334 (49%) occurred in the context of in-person health care contact. The AEX rates in the first and second quarters of 2019 and 2020 are shown in Figure 1. There was a significant decrease from Q1 to Q2 of 2020 compared with the same time period in 2019, with a DID of −0.47 exacerbations per year (95% confidence interval [95% CI] −0.76 to −0.19; $P = .001$) and represents a relative reduction of 41% (Table I). The AEX decreased 50% in H/L and 27% in AA/B (DID −0.64; 95% CI −1.05 to −0.24; $P = .002$ and DID−0.28; 95% CI −0.75 to 0.18; $P = .2$, respectively). Participants who worked outside of the home at study entry had a 65% decrease (DID −0.73; 95% CI −1.12 to −0.34; $P < .001$) compared with those who worked at home with a 23% decrease (DID −0.27; 95% CI −0.69 to 0.15; $P = .2$). The AEX decreases were greater for individuals without a type 2 helper T-cell phenotype. Specifically, AEX decreased by 51% (DID −0.67; 95% CI −1.13 to −0.21; $P = .004$) for individuals with blood eosinophil count below the median (192 cells/μL) and 34% above the median. For individuals with FeNO less than 50, there was an approximately 45% (DID −0.54; 95% CI −0.94 to −0.13; $P = .009$) decrease (Table I). Decreased exacerbations remained significant after controlling for changes in particulate matter 2.5 ($P = .005$), nitrogen dioxide ($P = .017$), and ozone ($P = .0028$). There were no statistically significant interactions between the AEX outcome and the prespecified covariates of by race, obesity, hypertension, geographic region, and place of work.

In this multicenter study of AA/B and H/L adults with asthma, there was a significant reduction in AEX rates with the COVID-19 pandemic. The effect was greatest in H/L individuals, those working outside the home at the time of enrollment, and those with non–type 2 inflammation (ie, low blood eosinophil count and low FeNO). Puerto Rico, the site of enrollment of most H/L subjects, showed the greatest reduction

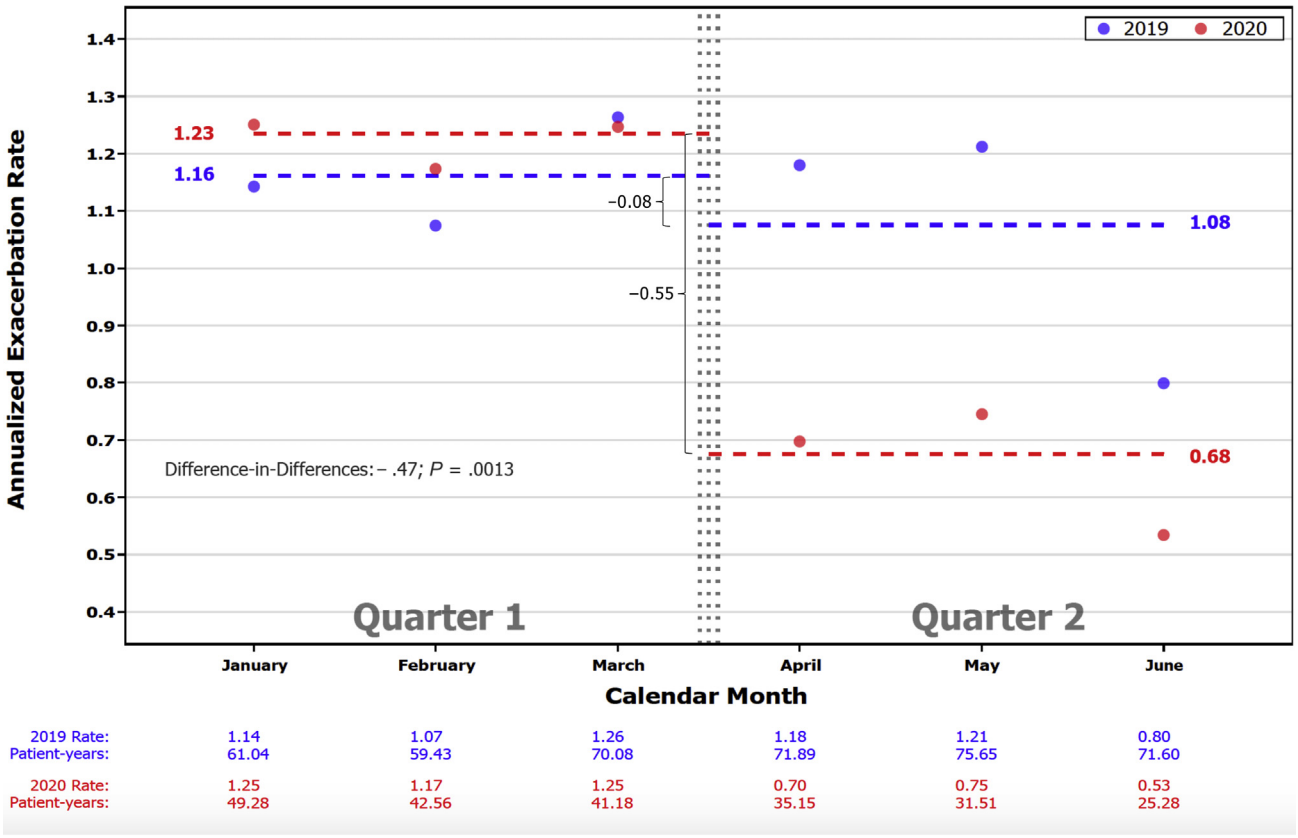

FIGURE 1. AEX rate comparing Q1 with Q2 rates for 2019 and 2020. Lines represent quarterly mean AEX; monthly AEX rates are represented by red (2020) and blue (2019) dots.

in exacerbations. Similarly, nonhypertensive patients (more likely to be H/L) also had a greater reduction.

This is the first study to assess AEX before and after the COVID-19 pandemic using data that are unlikely to be affected by health care system avoidance. Previous studies have reported reduced hospital and emergency presentations for asthma and were unable to differentiate changes in health-seeking behavior versus true reductions in in the occurrence of episodes of asthma. Thus, it is possible that the prior reports of reduced exacerbations reflect this reluctance to initiate face-to-face provider contact. Because the present data include exacerbations that did not necessarily require health care facility interaction and are entirely reported remotely, they suggest a true reduction in the totality of AEX following the pandemic. Importantly, the magnitude of this reduction is substantial, with an effect similar to that seen with biologic therapies for severe asthma.[5,6]

Potential explanations for the observed decreases in AEX may include decreased exposure to environmental and occupational factors, reduced respiratory infections, and/or changes in stress. Previous reports have highlighted that allergen exposure and viral pathogens may account for greater than half of total AEXs.[7] Consistent with this hypothesis, decreases in AEX were greatest (65%) in those who reported working outside of the home on entry to the study and may relate to reduced environmental exposures or viral exposure through person-to-person contact that may be greater in those working outside the home, which may have been reduced by subsequent relocation of the work environment. However, it is unlikely that changes in workplace location alone accounts for the dramatic reduction because occupational exposures account for between 9% and 15% of asthma cases.[8,9] The additional finding of greater reduction in individuals with low type 2 inflammation suggested that viral and/or occupational precipitants may be more important contributors to exacerbation in those individuals than in individuals with intrinsic type 2 inflammation.

Becausee we only studied AA/B and H/L patients, it is possible that our results do not generalize to the entire population. Although the magnitude of effect might be different in other racial or ethnic groups, much of the basic biology of asthma is common to all populations. Although half of our population received usual asthma care plus as-needed ICS, we do not believe that this significantly alters the impact of our findings because international guidelines recommend some form of as-needed ICS in addition to usual care for patients enrolled in our study. Workplace location details were collected at baseline, and therefore, it is possible that employment change as a result of the pandemic may have also influenced the observed decreases.

In summary, we show that total AEXs decreased by greater than 40% coincident with the onset of the COVID-19 pandemic. Reductions in exacerbation were greatest in individuals who were working outside of the home and in those without type 2 inflammation. This effect may be related to social-distancing and occupational changes and unlikely to be

TABLE I. Results of DID additive modeling including subgroup analyses

Subgroup factor	Subgroup label	AEX rate by calendar quarter				Relative change* (%)	DID (95% CI)	*P* value for DID
		Q1 2019	Q2 2019	Q1 2020	Q2 2020			
None	All patients (n = 1,178)	1.1611	1.0755	1.2349	0.6750	−41	−0.4743 (−0.7638 to −0.1847)	.0013
Race	H/L (n = 588)	1.1947	1.2306	1.2557	0.6505	−50	−0.6410 (−1.0456 to −0.2364)	.0019
	AA/B (n = 590)	1.1351	0.9600	1.2099	0.7512	−27	−0.2836 (−0.7502 to 0.1830)	.2336
Hypertension	Hypertensive (n = 481)	1.1168	1.0503	1.2506	0.7967	−32	−0.3874 (−0.8633 to 0.0886)	.1107
	Nonhypertensive (n = 685)	1.2041	1.0994	1.2389	0.5927	−48	−0.5415 (−0.9126 to −0.1704)	.0042
Employment	Works outside home (n = 529)	1.0939	1.0590	1.1551	0.3898	−65	−0.7304 (−1.1233 to −0.3375)	.0003
	Does not work outside home (n = 639)	1.2262	1.0952	1.2947	0.8940	−23	−0.2698 (−0.6859 to 0.1464)	.2039
Region	Southeast (n = 364)	0.9714	0.9242	1.4318	0.7452	−45	−0.6394 (−1.1579 to −0.1209)	.0156
	Puerto Rico (n = 101)	1.5655	1.7900	1.3458	0.2738	−82	−1.2965 (−2.3127 to −0.2803)	.0124
	Northeast (n = 473)	1.3232	1.1992	1.2943	0.9192	−22	−0.2511 (−0.7669 to 0.2647)	.3400
	Southwest (n = 70)	0.8973	0.8782	0.9751	0.4559	−52	−0.5001 (−1.6743 to 0.6740)	.4038
	Ohio Central Valley (n = 170)	0.9507	0.6358	0.8496	0.3345	−41	−0.2001 (−0.8541 to 0.4539)	.5487
Obesity	Yes: BMI ≥ 30 (n = 806)	1.1553	1.1565	1.2504	0.7884	−37	−0.4633 (−0.8069 to −0.1197)	.0082
	No: BMI < 30 (n = 371)	1.1772	0.8903	1.2038	0.3875	−57	−0.5294 (−1.0425 to −0.0164)	.0431
FeNO	FeNO low: 0-25 (n = 618)	1.1232	1.0323	1.2771	0.6481	−45	−0.5381 (−0.9433 to −0.1329)	.0092
	FeNO medium: 25-50 (n = 238)	1.1919	1.1210	1.0364	0.5048	−48	−0.4605 (−1.0717 to 0.1506)	.1397
	FeNO high: >50 (n = 131)	1.2283	0.9454	1.2220	0.9758	+4	0.0367 (−0.7530 to 0.8263)	.9275
EOS by median	Eosinophil <192 (n = 488)	0.9495	1.0271	1.2502	0.6597	−51	−0.6682 (−1.1265 to −0.2099)	.0043
	Eosinophil ≥192 (n = 505)	1.3014	1.1443	1.2166	0.7118	−34	−0.3477 (−0.7655 to 0.0700)	.1028

BMI, body mass index; *EOS,* eosinophil.
*Relative change calculated as 1 minus the calculated ratio-of-ratios.

related to reduced health care system avoidance during the COVID-19 pandemic. Given the significant morbidity associated with AEX, further investigation is required to further clarify the underlying causes of these findings.

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ONLINE REPOSITORY

TABLE E1. Study site locations

Region	Location
Northeast	New York, NY (n = 247)
	New Haven, Conn (n = 42)
	Hampden, Mass (n = 74)
Northwest	Denver, Colo (n = 58)
Southeast	Durham, NC (n = 124)
	Mecklenburg, NC (n = 18)
	Alachua, Fla (n = 74)
	Birmingham, Ala (n = 52)
	Hillsborough, Fla (n = 42)
	Orange, Fla (n = 35)
	Miami-Dade, Fla (n = 19)
Ohio Central Valley	Cuyahoga, Oh (n = 111)
	Philadelphia, Pa (n = 110)
	Cook County, Ill (n = 59)
Puerto Rico	San Juan, PR (n = 101)
Southwest	Los Angeles, Calif (n = 12)

TABLE E2. Baseline characteristics of study participants

Baseline characteristic	Patients with data in 2019 or 2020 (n = 1,178)
Age (y), mean (SD)	47.7 (13.7)
Female	987 (83.8%)
Race/ethnicity	
H/L	588 (49.9%)
AA/B	590 (50.1%)
Region of enrollment	
Southeast	364 (30.9%)
Puerto Rico	101 (8.6%)
Northeast	473 (40.2%)
Southwest	70 (5.9%)
Ohio Valley Central	170 (14.4%)
BMI, mean (SD)	35.1 (9.3)
ACT, mean (SD)	14.7 (4.4)
ASUI, mean (SD)	0.67 ± 0.21
AEX within 12 months prior to randomization	848 (72.0%)
Work outside home at baseline (n = 1,168)	
No	639 (54.7%)
Yes	529 (45.3%)
Medical history (n = 1,166)	
Heart disease	104 (8.9%)
Diabetes	293 (25.1%)
Hypertension	481 (41.3%)
Depression	423 (36.3%)
Sleep disorder	407 (34.9%)
Allergies	878 (75.3%)
COPD	33 (2.8%)
Stroke	43 (3.7%)
Chronic kidney disease	26 (2.2%)

ACT, Asthma Control Test; *ASUI,* Asthma Symptom Utility Index; *BMI,* body mass index; *COPD,* chronic obstructive pulmonary disease.