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To cite this article: Alfred Martin, Victoria Bauer, Avisek Datta, Christopher Masi, Giselle Mosnaim, Anthony Solomonides & Goutham Rao (2019): Development and validation of an asthma exacerbation prediction model using electronic health record (EHR) data, Journal of Asthma, DOI: [10.1080/02770903.2019.1648505](https://doi.org/10.1080/02770903.2019.1648505)

To link to this article: <https://doi.org/10.1080/02770903.2019.1648505>



Accepted author version posted online: 25 Jul 2019.
Published online: 08 Aug 2019.



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Development and validation of an asthma exacerbation prediction model using electronic health record (EHR) data

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ABSTRACT

Objective: Asthma exacerbations are associated with significant morbidity, mortality, and cost. Accurately identifying asthma patients at risk for exacerbation is essential. We sought to develop a risk prediction tool based on routinely collected data from electronic health records (EHRs).

Methods: From a repository of EHRs data, we extracted structured data for gender, race, ethnicity, smoking status, use of asthma medications, environmental allergy testing BMI status, and Asthma Control Test scores (ACT). A subgroup of this population of patients with asthma that had available prescription fill data was identified, which formed the primary population for analysis. Asthma exacerbation was defined as asthma-related hospitalization, urgent/emergent visit or oral steroid use over a 12-month period. Univariable and multivariable statistical analysis was completed to identify factors associated with exacerbation. We developed and tested a risk prediction model based on the multivariable analysis.

Results: We identified 37,675 patients with asthma. Of those, 1,787 patients with asthma and fill data were identified, and 979 (54.8%) of them experienced an exacerbation. In the multivariable analysis, smoking (OR = 1.69, CI: 1.08–2.64), allergy testing (OR = 2.40, CI: 1.54–3.73), obesity (OR = 1.66, CI: 1.29–2.12), and ACT score reflecting uncontrolled asthma (OR = 1.66, CI: 1.10–2.29) were associated with increased risk of exacerbation. The area-under-the-curve (AUC) of our model in a combined derivation and validation cohort was 0.67.

Conclusion: Despite use of rigorous methodology, we were unable to produce a predictive model with an acceptable degree of accuracy and AUC to be clinically useful.

Abbreviations: ACT: Asthma Control Test scores; ED: Emergency Department; EDW: Enterprise Data Warehouse; EHR: Electronic Health Record; HMO: Blue Cross Blue Shield Health Maintenance Organization of Illinois; ICC: Immediate Care Clinic; ICS: Inhaled Corticosteroids; ICS/LABA: combination ICS and Long-Acting Beta Agonists; SABA: Short-Acting Beta Agonists

ARTICLE HISTORY

Received 4 March 2019
Revised 11 July 2019
Accepted 21 July 2019

KEYWORDS

Asthma; asthma exacerbation; electronic health records; prediction models

Introduction

Asthma affects roughly 18.7 million adults and 7 million children in the United States. Total annual costs are approximately \$56 billion. Asthma accounts for 10.8 million missed school days and 14.2 million missed work days yearly and 9 deaths daily (1). Exacerbations, defined as an acute or subacute episode of progressive worsening of symptoms (2), are responsible for most of asthma's cost, morbidity, and mortality and are associated with an increase in unplanned outpatient visits, emergency department (ED) visits, and hospitalizations (3).

Preventing asthma exacerbations and the associated acute health care visits, hospitalizations, loss of productivity, and morbidity and mortality is a major public health goal. The Centers for Disease Control's (CDC) National Asthma Control Program lists the following among its Healthy People 2020 goals: Reduce the number of asthma deaths, hospitalizations, ED visits; and reduce the proportion of persons with asthma who miss school or work days (4). A rational approach to preventing exacerbations is to identify high-risk individuals and target them with interventions with proven efficacy (5). Risk factors for

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exacerbations include viral infections, smoking, and more severe baseline disease (6,7). Several asthma exacerbation prediction models have been published in recent years. Loymans et al. describe models for adult asthma exacerbation prediction in a recently published systematic review (8). Among 24 models evaluated, previous health care utilization, symptoms, and spirometric values were the most common predictors. Despite efforts to promote its use among patients with asthma (9), spirometry is underused in general, and especially in primary care (10).

Our primary purpose was to systematically characterize patients with asthma and to develop asthma exacerbation prediction models based upon electronic health records (EHRs) and related data from a large pool of patients who receive care through an integrated delivery network. Because EHRs seldom record spirometric values and symptoms or capture them in unstructured ways, we did not include these in our models. Our ultimate aim is to develop a practical, clinically useful model for predicting asthma exacerbation based on routinely collected data which EHR systems in the future can incorporate to alert clinicians of the risk of exacerbation among individuals or large groups of patients.

Methods

Data sources

Electronic data warehouse

We identified adult patients (age ≥ 18 years) through the NorthShore Enterprise Data Warehouse (EDW), a large repository of data from more than 1 million patients extracted from the Epic EHR system (Epic Systems, Verona, WI) and related billing and other databases. From structured fields (problem list, encounter diagnoses), we found all patients with at least one ICD-9 or ICD-10 diagnosis of asthma and a history of treatment for asthma between January 1, 2013 and September 30, 2016.

Data elements used

Data included gender, race, ethnicity, smoking status, use of asthma medications – inhaled corticosteroids (ICS), short-acting beta agonists (SABA), and combination ICS and long-acting beta agonists (ICS/LABA) – skin testing for aeroallergens and serum testing for aeroallergens (allergy testing), BMI status (normal, overweight, obese), Asthma Control Test scores (ACT) (11), when available, and zip code of residence. We did not have information about household

income, but used median household values by zip code as a surrogate (12). We classified income categories as low ($< \$40,000$ per year), medium ($\$40,000$ – $\$100,000$ per year), and high ($\geq \$100,000$ per year). We chose all these elements because they are generally accepted as recognized risk factors in asthma exacerbations (13–15) and they are all available in structured fields within the our EHR.

Medication usage

Prescription orders did not accurately reflect medication use by patients. Prescription fill data, by contrast, was a better proxy for adherence. Studies demonstrate that patients fill less than 50% of their prescriptions for chronic conditions (16,17). We were unable to obtain fill data for all patients with asthma with records in the EDW, but data was available for a subset of patients insured through one managed care program (Blue Cross Blue Shield Illinois). First, we classified prescriptions into four categories: systemic steroid (i.e. oral steroids), ICS, ICS/LABA, and SABA. Next, we cross-referenced these medications with Blue Cross Blue Shield Health Maintenance Organization of Illinois (HMOI) fill data. This resulted in a total of 1,787 patients for which accurate, asthma-related prescription fill data was available for our primary analysis.

Outcome measure

The primary outcome measure was asthma exacerbation, defined as the use of oral steroids for asthma, or an unplanned visit for asthma care, including care received at an immediate care clinic (ICC) or ED, or an asthma related hospitalization (18).

Statistical analysis

Among those with an asthma exacerbation, we defined the index encounter as the date of an asthma related ED visit, ICC visit, or the date on which the clinician prescribed an oral steroid. For those with no asthma exacerbation, we considered a patient's most recent asthma related office visit as their index encounter date. In both instances, we looked back to the previous 12 months for either an exacerbation or non-exacerbation.

We divided our asthma population into two groups: those carrying HMOI insurance and those carrying other insurance. We performed standard descriptive and comparative statistics between patients

Table 1. Demographic characteristics of adults with asthma based upon insurance type.

	HMOI (n = 1,787)	Non-HMOI (n = 35,888)	p-Value
Gender			.0002
Male	541 (30.3%)	12,426 (34.6%)	
Female	1,246 (69.7%)	23,461 (65.4%)	
Race/Ethnicity			<.0001
Black, non-hispanic	226 (12.6%)	2,810 (7.9%)	
Asian, non-hispanic	84 (4.7%)	1,277 (3.6%)	
Hispanic	116 (6.5%)	1,510 (4.2%)	
Other, non-hispanic	228 (12.8%)	5,478 (15.3%)	
White, non-hispanic	1,129 (63.3%)	24,734 (69.1%)	
Smoking status			.0633
Yes	101 (5.6%)	2,433 (6.8%)	
No	1,686 (94.4%)	33,455 (93.2%)	
Allergy testing			<.0001
Yes	106 (5.9%)	866 (2.4%)	
No	1,681 (94.1%)	35,022 (97.6%)	
BMI Group			.0226
Normal	500 (28.0%)	10,554 (31.2%)	
Obese	681 (38.2%)	12,294 (36.3%)	
Overweight	(32.0%)	10,557 (31.2%)	
Underweight	32 (1.8%)	464 (1.4%)	
ACT			<.0001
No ACT score	734 (41.1%)	29,771 (83.0%)	
Uncontrolled	168 (9.4%)	1,517 (4.2%)	
Controlled	884 (49.5%)	4,596 (12.8%)	
Median income			<.0001
Low	68 (3.8%)	911 (2.5%)	
Medium	1,386 (77.8%)	23,980 (67.0%)	
High	327 (18.4%)	10,912 (30.5%)	
Past visit to ED, immediate care, Hosp.			0.5984
Yes	60 (3.4%)	1,125 (3.1%)	
No	1,727 (96.6%)	34,763 (96.9%)	

with and without HMOI insurance using Chi-squared analyses (Fisher's Exact Test for cells fewer than 5) for categorical variables. *p*-Values less than .05 are considered statistically significant. Additionally, we used univariable logistic regression to identify factors significantly associated with asthma exacerbation. We incorporated multivariable logistic regression using significant predictors from univariable analyses into one final model. This model displayed odds ratios (OR) and 95% confidence intervals (CI). We then separated asthma patients into a derivation cohort (60% of HMOI patients) and validation cohort (40% of HMOI patients) for predictive modeling. We carried out multivariable logistic regression with bootstrapping of our derivation data to derive a prediction model using significant predictors from our previous model. The resulting prediction model reported parameter estimates and *p* values. We created a table to show the probability level of asthma exacerbation at the maximal specificity and sensitivity. Finally, we evaluated the performance of the model against the validation cohort and all HMOI patients with the use of Area under the curve (AUC) values.

IRB review

The Institutional Review Board informed us that this study did not meet the federal definition of human

subject research and review was not required for this work.

Results

Patient characteristics

We identified 37,675 patients with asthma. Of these 24,707 (65.6%) were female 25,863 were White, Non-Hispanic (68.6%), 2,534 (6.7%) were current smokers; 972 (2.7%) had undergone either skin or serum testing for aeroallergens; 24,103 (64.0%) were either overweight or obese; and 1,685 (4.4%) were uncontrolled (score less than 20) on the Asthma Control Test (ACT).

We compared the characteristics of the HMOI patients (*n* = 1,787) to non-HMOI patients (*n* = 35,888) (Table 1). Compared to non-HMOI, HMOI had a higher proportion of females (69.7% vs. 65.4%, *p* = .0002). Additionally, HMOI patients maintained a higher rate of African-American, Asian, and Hispanic groups and had a higher rate of allergy testing (5.9% vs. 2.4%, *p* < .0001). HMOI patients were more likely to have a completed asthma control test (ACT) in their chart (58.9% vs. 17.0%). The distribution of median household incomes differed between the HMOI and non-HMOI populations (*p* < .0001). HMOI showed larger differences than non-HMOI

patients did in low (3.8% vs. 2.5%) and medium (77.8% vs. 67.0%) income categories.

Medication use and exacerbation status

Compared to patients with no experience of exacerbation in a 12 month period, those with at least 1 exacerbation are less likely to use ICS (36.0% vs. 55.1%, $p < .0001$) and SABA (45.5% vs. 52.3%, $p < .0001$) medications (Table 2).

Univariable and multivariable analysis of predictors

We performed univariable analysis on our predictors with the outcome of asthma exacerbation to observe any significant associations. If predictor maintained significance, we would include that predictor into our

multivariable model. Of the predictors we tested, the following were considered significant: smoking status, use of ICS and SABA medications, having a skin or serum test, being obese or overweight, and having a past visit to the ED (Table 3).

In the multivariable analysis, the factors most strongly associated with increased risk of asthma exacerbation were smoking (OR = 1.69, CI: 1.08–2.64), allergy testing, both serum and skin testing (OR = 2.40, CI: 1.54–3.73), obesity (OR = 1.66, CI: 1.29–2.12), overweight (OR = 1.34, CI: 1.04–1.72), and ACT score reflecting uncontrolled asthma (OR = 1.66, CI: 1.10–2.29). The factors most strongly associated with reduced risk of asthma exacerbation were use of ICS (OR = 0.40, CI: 0.33–0.49), use of SABA (OR = 0.65, CI: 0.53–0.79). In addition, membership of the category Other, Non-Hispanic ethnicity also confers an advantage (OR = 0.59, 95% CI: 0.43–0.79) (Table 3).

We have displayed parameter estimates and 95% CI for our final prediction model (Table 4). The predictors from our multivariable regression model remained significant in our prediction model. The use of ICS and SABA meds as well as Other, Non-Hispanic ethnicity was all associated with reduced asthma exacerbation risk. In contrast, smoking, allergy testing, obesity, overweight, uncontrolled ACT score,

Table 2. Asthma medication use by exacerbation status.

Adults with asthma and HMOI insurance ($n = 1,787$)			
	Exacerbation ($n = 979$)	No exacerbation ($n = 808$)	p -Value
ICS			<.0001
Filled	352 (36.0%)	445 (55.1%)	
Not filled	627 (64.0%)	363 (44.9%)	
SABA			.0032
Filled	444 (45.5%)	423 (52.3%)	
Not filled	535 (54.5%)	385 (47.7%)	
ICS/LABA			0.7434
Filled	211 (21.5%)	169 (20.9%)	
Not filled	768 (78.5%)	639 (79.1%)	

Table 3. Univariable and multivariable logistic regression models predicting asthma exacerbation among adults with asthma and HMOI insurance ($n = 1,787$).

	Univariable analysis OR (95% CI)	Multivariable analysis OR (95% CI)
Gender (ref = Female)		
Male	0.87 (0.71, 1.06)	
Race/ethnicity (ref = Caucasian, Non-Hispanic)		
Black Non-Hispanic	1.18 (0.88, 1.58)	1.01 (0.74, 1.37)
Asian, Non-Hispanic	0.74 (0.48, 1.16)	0.78 (0.49, 1.24)
Hispanic	1.00 (0.68, 1.46)	0.87 (0.58, 1.30)
Other, Non-Hispanic	0.61 (0.46, 0.81)	0.59 (0.43, 0.79)
Smoking status (ref = No)		
Yes	1.60 (1.05, 2.43)	1.69 (1.08, 2.64)
ICS meds (ref = Not Filled)		
Filled	0.46 (0.38, 0.55)	0.40 (0.33, 0.49)
SABA meds (ref = Not Filled)		
Filled	0.76 (0.63, 0.91)	0.65 (0.53, 0.79)
ICS LABA Meds (ref = Not Filled)		
Filled	1.04 (0.83, 1.31)	
Allergy testing (ref = No)		
Yes	1.73 (1.14, 2.62)	2.40 (1.54, 3.73)
BMI group (ref = Normal)		
Obese	1.71 (1.35, 2.15)	1.66 (1.29, 2.12)
Overweight	1.34 (1.05, 1.70)	1.34 (1.04, 1.72)
Underweight	1.64 (0.79, 3.38)	1.67 (0.78, 3.59)
ACT (ref = Controlled)		
No Asthma Control Test score	0.94 (0.77, 1.14)	0.85 (0.69, 1.05)
Uncontrolled	1.50 (1.07, 2.11)	1.58 (1.10, 2.29)
Median income (ref = Medium)		
Low	0.79 (0.48, 1.28)	
High	0.81 (0.64, 1.04)	
Past visit to ED, immediate care, Hosp. (ref = No)		
Yes	3.82 (1.97, 7.39)	3.69 (1.86, 7.30)

and past visit to ED were all associated with increased risk of asthma exacerbation.

Table 5 displays the prediction model performance at various probabilities of asthma exacerbation. The model exhibited the highest sensitivity (47.8%) and specificity (79.8%) when the probability of an asthma exacerbation was 0.60. At this level, the Positive Predictive Value (PPV) of the model was 74.1% while the Negative Predictive Value (NPV) was 55.8%. This means that if the probability of a patient having an asthma exacerbation is 60%, the prediction model correctly identifies those who ultimately have an exacerbation 74.1% of the time and correctly identifies those who do not have an exacerbation 55.8% of the time. The model does not perform as well when the probability of an asthma exacerbation is less than or greater than 60% (Figure 1).

Discussion

Using data easily extracted from the EHR and EDW, as well as prescription fill data from one managed care source, we developed and evaluated an asthma clinical prediction model. Fill data, as opposed to prescription data, may give a more accurate picture with respect to actual medication use patterns (19). Previous studies have used randomized controlled

trials (20–23) or registries (24,25) while our analysis relied on extractions of structured data from the EHR. Unfortunately, in a rigorously performed study using the most sophisticated types of analysis, we were not able to demonstrate that routinely collected data from an EHR is sufficiently reliable for predicting asthma exacerbation risk.

The predictors for asthma exacerbation identified in this model, including current smoker, obesity, overweight, uncontrolled asthma defined as ACT score ≤ 19 , and visit to the ED, ICC, or hospital in the past 12 months, are consistent with prior studies (26–28). While this study demonstrated that any ICS and any SABA prescription fill was negatively associated with asthma exacerbation, prior studies have reported that filling ≥ 6 months of ICS and ≤ 2 canisters of SABA over 12 months is protective (29). The finding that SABA use was not associated with asthma exacerbation is not consistent with the literature. However, we used a dichotomous variable of SABA fill or no fill, and did not provide data on the number of canisters filled. We also did not assess how many of the ICC visits, counted as exacerbations, were due to the fact that the patient did not have a SABA inhaler at home and needed a SABA prescription. The positive association between testing for aeroallergens and asthma exacerbation may be that higher risk patients were more likely to be referred to an allergist/immunologist for subspecialty asthma care and receive additional testing. It is unclear why the asthma medication ratio, which is highly correlated with asthma exacerbations in other studies, did not show a positive relationship in the multivariable analysis in this study (30).

Low income groups have higher rates of asthma diagnosis and associated morbidity (31,32). NorthShore University HealthSystem serves a relatively affluent part of Greater Chicago. Our lowest income group may not have accurately reflected low income patients with asthma nationwide. However, the HMOI group utilized in this analysis does have a higher proportion of females, African Americans, Hispanics, and individuals of lower income (compared to the non-HMOI group) which is reflective of

Table 4. Parameter estimates for the final prediction model.

	Estimate (95% CI)
Intercept	0.614 (0.580, 0.649)
Race/Ethnicity	
Black Non-Hispanic	0.001 (−0.038, 0.041)
Asian, Non-Hispanic	0.245 (0.179, 0.310)
Hispanic	−0.095 (−0.155, −0.036)
Other, Non-Hispanic	−0.616 (−0.659, −0.573)
Smoking Status	0.658 (0.595, 0.715)
ICS Meds	−0.853 (−0.878, −0.828)
SABA Meds	−0.534 (−0.561, −0.507)
Allergy Testing (define this testing)	0.837 (0.781, 0.893)
BMI Group	
Obese	0.318 (0.289, 0.348)
Overweight	0.152 (0.121, 0.184)
Underweight	0.458 (0.363, 0.553)
ACT	
No Asthma Control Test score	−0.098 (−0.123, −0.072)
Uncontrolled	0.588 (0.534, 0.642)
Past Visit to ED, Immediate Care, Hosp.	1.342 (1.251, 1.433)

Table 5. Characteristics of final prediction model based upon probability of asthma exacerbation.

Probability of asthma exacerbation	PPV (%)	NPV (%)	Sensitivity (%)	Specificity (%)
0.20	54.8	66.7	99.8	0.4
0.30	55.2	59.4	97.8	3.9
0.40	56.9	54.8	84.8	22.3
0.50	62.2	57.0	69.8	48.6
0.60	74.1	55.8	47.8	79.8
0.70	76.3	48.3	17.6	93.4
0.80	80.4	46.4	6.3	98.1
0.90	100.0	45.4	0.5	100.0

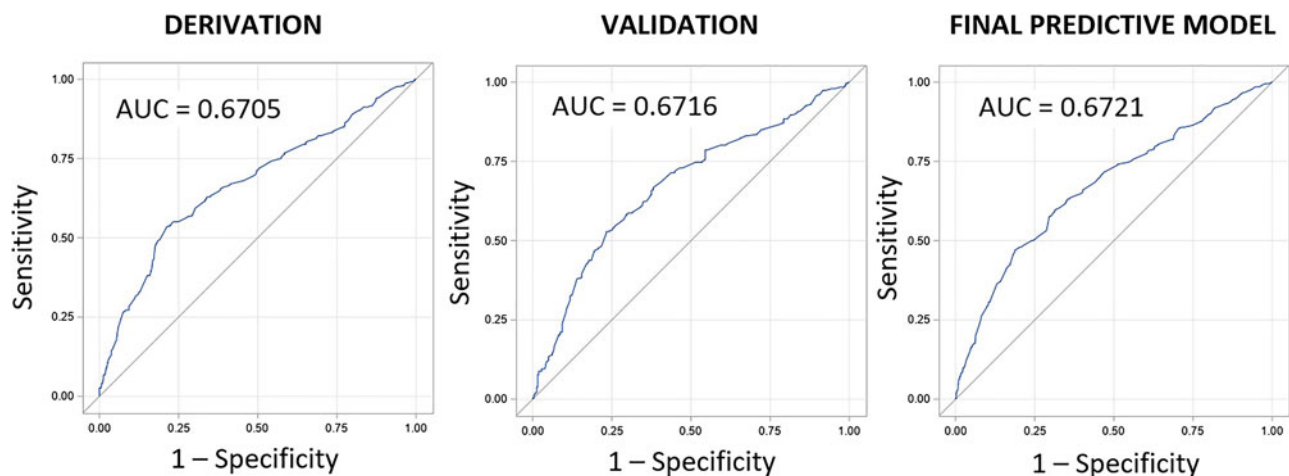


Figure 1. Demonstrates the AUC values calculated by applying the final prediction model to datasets from the derivation, validation, and combined cohorts. The AUC for the prediction model in the combined cohort is 0.67.

national data on characteristics of persons with asthma (33). This may strengthen the external validity of the results.

Limitations and future directions

This study is limited in that it only utilized patients from a single insurance plan in a single health care system using a single EHR. An important area for improvement would be the use of multicenter studies (34). The validation model and the sample, however, were racially and ethnically diverse. As such, a model of this type could be adapted to various health care systems, EHRs, and patient populations across the United States.

Several of our risk factors, while practical to collect (e.g. prior aeroallergen testing) are confounded by their inherent association with the severity of disease (i.e. patients who are more prone to exacerbations are more likely to have more intense patterns of care). In our analysis there may be room to use more predictor variables, especially more longitudinal data. Also, although our model is based on structured fields within the EHR, to obtain a more accurate representation of medication usage, we limited our modeling to patients with fill data. And while fill data is not currently typically contained within the EHR as a structured field, this fill data is becoming increasingly available (35).

Using existing, routinely collected clinical data to derive models to predict specific outcomes is becoming increasingly common. Studies based on these methods have both strengths and weaknesses. Unlike most cohort studies, this methodology can make use of the same dataset to predict a wide variety of clinical outcomes. In addition, patient populations that are

derived from the EHR may reflect more of a real-world environment than cohort studies that rely on volunteers. At the same time, issues such as missing data and the need for better evaluation should be addressed in future work of this type.

To our knowledge, this study is the first that that uses routinely collected EHR data to construct an asthma exacerbation prediction model (36). Unfortunately our analysis did not result in a clinically useful model having demonstrated a low sensitivity and AUC. However, considering the many advantages of using EHR data to construct useful predictive models it makes sense to continue to work towards creating more reliable and accurate algorithms.

Declaration of interest

Dr. Martin, Ms. Bauer, Mr. Datta, Dr. Masi, Dr. Solomonides and Dr. Rao report on conflicts of interest. Dr. Mosnaim receives research grant support from Astra Zeneca, GlaxoSmithKline and Propeller Health; owns stock in Electrocore; and serves as a consultant and/or member of a scientific advisory board for GlaxoSmithKline, Sanofi-Regeneron, Teva, Novartis, Astra Zeneca, Boehringer Ingelheim and Propeller Health. The authors alone are responsible for the content and writing of this article. This work was supported in part by the Ambulatory Primary Care Innovations Group (APCIG) of the Department of Family Medicine at NorthShore University HealthSystem and ThermoFisher Scientific. ThermoFisher Scientific did not have any role in trial design, collection, analysis, or interpretation of data, or in writing the manuscript.

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