

Are Latino children of Mexican origin with asthma less responsive to inhaled corticosteroids than white children?

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Clinical Implications

- Racial and ethnic differences in asthma burden are potentially explained by varying genetic composition, environmental exposures, and socioeconomic conditions. Latino children, particularly those of Mexican-origin, may experience less benefit from inhaled corticosteroid treatment than white children. Additional studies of treatment responsiveness with adequate representation of ethnic minorities are urgently needed.

TO THE EDITOR:

Inhaled corticosteroids (ICS) are recommended for the initial treatment of all children with persistent asthma.¹ However, our experience suggests that Latino children, particularly those of Mexican origin, may be less responsive to treatment than other children. To investigate this question, we used data from several Childhood Asthma Research and Education Network (CARE) clinical trials involving ICS treatment of toddlers and preschool children at risk of asthma. Importantly, 3 of the network's 6 clinical sites were located in states with a high percentage of Latino children of Mexican origin: California, Arizona, and Colorado.

Original data from 3 trials were harmonized: the Prevention of Early Asthma in Kids (PEAK) trial,² the Acute Intervention Management Strategies (AIMS) trial,³ and the Maintenance versus Intermittent Steroids in Wheezing Toddlers (MIST) trial.⁴ These trials enrolled children less than 5 years of age who were at risk of future asthma as evidenced by a positive modified Asthma Predictive Index score and/or documented health care utilization attributable to severe wheezing. Because of the children's young age, documentation of airway responsiveness was not required.

PEAK examined whether children treated with 24 months of fluticasone, 88 µg twice daily, would experience fewer asthma symptoms during a 12-month follow-up period than children treated with placebo. AIMS examined whether children treated with budesonide inhalation suspension, 1 mg twice daily for 7 days at the onset of respiratory infection, would experience fewer symptoms than children treated with placebo. MIST examined whether children treated with budesonide inhalation suspension, 0.5 mg once daily, would experience fewer symptoms than children treated with budesonide inhalation suspension, 1 mg twice daily for 7 days at the onset of respiratory infection. Because the intervention and control treatments varied, we used cumulative ICS exposure during the treatment period to define our intervention (higher exposure) and control (lower exposure) groups.

Our primary outcome was the number of asthma symptom days reported in daily diary records. A symptom day was any day with cough, wheeze, trouble breathing, activity limitation, unexpected respiratory-related health care utilization, or oral corticosteroid use. For each trial, symptom day counts were modeled using a negative binomial generalized linear model that controlled for study center, age, sex, ethnicity, environmental tobacco smoke exposure, run-in symptom days, skin test result, eczema history, serum IgE level, and serum eosinophil level. We included an ethnicity × intervention group interaction term as a marker of differential treatment responsiveness. Children missing covariate data and those reporting a race/ethnicity pairing other than white Latino or white non-Latino were excluded. Estimated effects from the individual trials were combined in a standard fixed-effects meta-analysis. Results are presented as incidence rate ratios (IRRs) with the corresponding 95% confidence intervals (95% CI). Statistical significance was determined by a *P* value <.05.

Of the 801 children enrolled in the 3 trials, 340 (42%) were excluded: 214 had an ineligible race/ethnicity pairing with 43% reporting black race, 95 were randomized to montelukast in AIMS, and 31 had incomplete covariate data. The final analytic sample included 461 children: 332 (72%) non-Latino white children and 129 (28%) Latino white children. On average, participants were 2.5 years of age and 68% were male. At baseline, Latino white children had fewer peripheral blood eosinophils than white children, 3.5% versus 4.8%, respectively (*P* < .001); otherwise, the measured baseline characteristics were comparable by ethnicity (Table 1).

With regard to intervention group assignment, 217 children were included in the higher ICS exposure group (intervention) and 244 were included in the lower exposure group (control). Children in the intervention group reported more run-in asthma symptom days than children in the control group, a mean (standard deviation [SD]) of 3.2 (SD 3.3) days versus 2.5 (SD 3.8) days, respectively (*P* < .001); otherwise, the measured baseline characteristics were comparable by intervention assignment (Table 1).

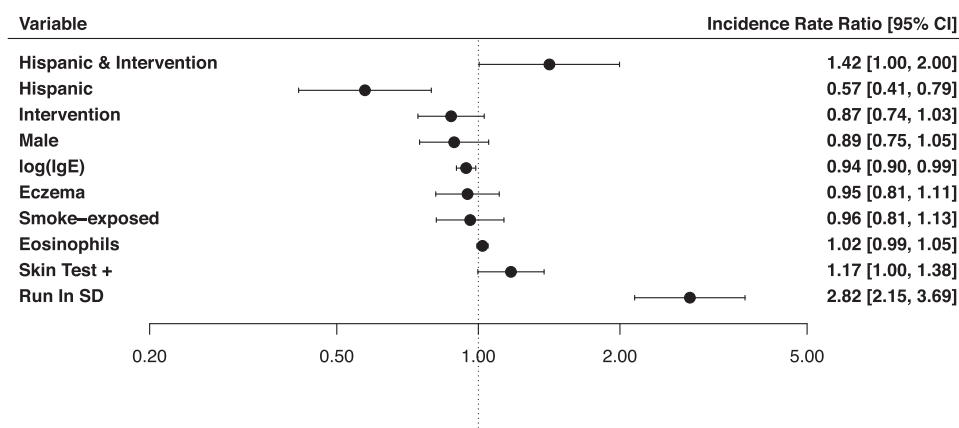
Our final adjusted model revealed 2 important findings (Figure 1). First, independent of cumulative ICS exposure, Latino white children experienced fewer symptom days than non-Latino white children, IRR 0.57 (95% CI: 0.42-0.79; *P* < .001). On average, Latino white children experienced 21 fewer symptom days a year than non-Latino white children. Second, Latino white children responded differently to ICS than non-Latino white children as evidenced by a statistically significant ethnicity × intervention group interaction term, IRR 1.42 (95% CI: 1.00-2.00; *P* = .049). On average, Latino white children experienced 6 more symptom days a year when exposed to a higher versus lower cumulative amount of ICS, 49 versus 43 symptom days, respectively. Conversely, non-Latino white children experienced 15 fewer symptom days a year when exposed to a higher versus lower cumulative amount of ICS, 60 symptom days versus 75 days, respectively.

Our data suggest that Latino white children, many of whom were of Mexican origin, may be less responsive to ICS than non-Latino white children. We previously documented a similar

TABLE I. Baseline demographic and clinical characteristics by intervention group and ethnicity

	Group		Ethnicity	
	Intervention	Control	White	Latino white
Age (y), mean (SD)	2.5 (0.85)	2.4 (0.84)	2.5 (0.82)	2.5 (0.91)
Male (%)	68	67	69	64
Ethnicity, Latino white (%)	29	27	—	—
ETS exposed (%)	32	30	29	37
Run-in symptom days, mean (SD)	3.2* (3.3)	2.5* (3.8)	2.8 (3.7)	2.7 (3.2)
Eczema (%)	51	51	54	44
Skin test positive (%)	54	57	55	56
Serum eosinophils (%)	4.6	4.3	4.8*	3.5*
Serum IgE, median (IU/dL)	46	50	47	49

ETS, Environmental tobacco smoke; SD, standard deviation.

*Significant at $P < .05$.**FIGURE 1.** Adjusted incidence rate ratios for clinical and demographic baseline predictors of asthma symptom days during the treatment period. For binary variables such as gender, the ratios reflect the difference in episode rates between the listed value and the other possible value with other covariates held at their reference level, or their mean for continuous variables. *CI*, Confidence interval; *SD*, standard deviation.

pattern of ICS responsiveness in the Treating Children to Prevent Exacerbations trial,⁵ a CARE trial of intermittent ICS treatment among school-age children.⁶ Non-Latino white children in the highest cumulative ICS exposure group experienced a delay in the time-to-first exacerbation as compared with placebo, hazard ratio 0.37 (95% CI: 0.18-0.75), whereas Latino children did not, hazard ratio 1.16 (95% CI: 0.47-2.86).⁵ This interaction was significant at $P < .01$. Similarly, a prior stratified analysis of the PEAK trial demonstrated that white children experienced fewer symptom days and less asthma-related health care utilization when treated with ICS than non-white children, many of whom were Latino.⁷

Our results must be viewed as hypothesis generating, not confirmatory. Important limitations include having a small number of Latino children despite pooling across 3 studies, enrolling toddlers and preschool children at risk of asthma rather than older children with confirmed asthma, using clinical trials that were not specifically designed to answer this question, and conducting a *post hoc* exploratory analysis that by design is vulnerable to bias and confounding.

However, a recent genome-wide association study among a unique Latino cohort identified several single nucleotide

polymorphisms that suggest a biologically plausible mechanism linking ethnicity with lung function.⁸ In addition, Latino children may experience different social conditions and environmental exposures such as poverty, urbanization, and airborne pollutions that place them at higher risk of poor asthma outcomes than non-Latino white children.⁹ Given the size and projected growth of the Latino population in the United States along with this group's historical underrepresentation in clinical trials, additional studies are urgently needed to determine optimal treatment in this population.

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