



Letters

Exposure to violence, chronic stress, asthma, and bronchodilator response in Puerto Rican children

Exposure to violence (ETV) and chronic stress may cause or worsen asthma.¹ Among Puerto Rican school-aged children, we previously reported that lifetime ETV at individual or community level is associated with increased risk of asthma.² In a separate analysis (not accounting for ETV), we showed that high levels of chronic stress are associated with reduced response to short-acting bronchodilators among Puerto Rican children with asthma.³ On the basis of these findings, we hypothesized that ETV and high chronic stress have joint detrimental effects on asthma and bronchodilator response (BDR). We tested this hypothesis in the same cohort of Puerto Rican children as in our previous studies.^{2,3}

Subject recruitment and study procedures have been previously described.⁴ In brief, 678 children (aged 6 to 14 years) with 4 Puerto Rican grandparents were recruited from randomly selected households in the metropolitan area of San Juan and Caguas (Puerto Rico) from March 2009 to June 2010, using a multistage probabilistic sampling design. Of the 678 participants, 472 were aged 9 years and older and thus eligible to complete questionnaires on ETV and chronic stress, along with spirometry. Written parental consent and assent were obtained for children who participated. The study was approved by institutional review boards of the University of Puerto Rico (San Juan, Puerto Rico), Brigham and Women's Hospital (Boston, Massachusetts), and the University of Pittsburgh (Pittsburgh, Pennsylvania).

The Checklist of Children's Distress Symptoms (CCDS),⁵ a 28-item scale, was used to assess stress symptoms in the previous 6 months, as a result of ETV. Answers for each question in the CCDS range from 1 to 5. An overall score is obtained by summing the scores for all 28 questions and then dividing by the number of questions, so the final score ranges between 1 and 5.⁵ As in previous work, high chronic stress was defined as the upper quartile (≥ 2.6 points) of the CCDS score.³ The participants also completed a modified version of the ETV scale,⁶ which measures both witnessing and direct victimization for the following 5 specific events: (1) shoving, punching, or kicking; (2) knife attacks; (3) shootings; (4) hearing gunshots; and (5) witnessing verbal abuse of the child's primary caregiver.

Disclosures: Dr Celedón has received research materials from Merck and GlaxoSmithKline (inhaled steroids) and Pharmavite (vitamin D and placebo capsules) to provide medications free of cost to participants in US National Institutes of Health (NIH)–funded studies, unrelated to the current work. The other authors have no conflicts of interest to report.

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Spirometry was conducted with an EasyOne spirometer (NDD Medical Technologies, Andover, Massachusetts), following American Thoracic Society recommendations for children.⁷ The best forced expiratory volume in 1 second (FEV₁) and forced vital capacity values were selected for data analyses. After completing spirometry, subjects were given 200 μ g of inhaled albuterol using a spacer, and spirometry was repeated after 15 minutes.

The main aim of this study was to examine whether (1) high chronic stress modifies the estimated effect of ETV on asthma (defined as physician-diagnosed asthma and ≥ 1 episode of wheeze in the previous year) and (2) ETV modifies estimated effects of high chronic stress on BDR. Our outcomes of interest were asthma (as defined previously) and BDR ($[(\text{postbronchodilator FEV}_1 - \text{prebronchodilator FEV}_1) / \text{prebronchodilator FEV}_1] \times 100$) in subjects with asthma.

Bivariate statistical analyses were conducted using Fisher exact test for categorical variables and two-tailed *t* tests for pairs of binary and continuous variables. Logistic or linear regression was used for multivariable analyses of asthma and BDR. All models included ETV scale score and/or high chronic stress and were adjusted for age, sex, and household income ($<$ vs $\geq$ \$15,000 [near median income for households in Puerto Rico in 2008–2009]).⁸ Other variables considered for inclusion in the models were body mass index z-score and current exposure to second-hand smoke (SHS); such variables remained in final models if they were associated with outcome of interest at *P* value of less than .05 or if they changed the effect estimate (odds ratio) by greater than or equal to 10%. After final models were built, we tested for interaction between ETV and chronic stress on asthma or BDR.

Compared with control subjects, subjects with asthma (cases) were younger and more likely to be boys, currently exposed to SHS, and to have higher ETV and chronic stress but lower FEV₁ and FEV₁/forced vital capacity (eTable 1). There were no significant differences in body mass index z-score, household income, or BDR between cases and controls.

Models 1 and 2 in Table 1 show results of multivariable analysis of ETV, high chronic stress, and asthma. In an analysis adjusting for age, sex, household income, and current exposure to SHS, each 1-point increment in ETV scale was significantly associated with 1.12 times increased odds of asthma (model 1). After adding high chronic stress to the model, the ETV scale remained significantly associated with asthma, but there was no significant association between high chronic stress and asthma (model 2). Moreover, there was no significant interaction between ETV and high chronic stress on asthma, either on multiplicative or additive scale (data not shown). Models 3 and 4 in Table 1 show results of multivariable analysis of high chronic stress and BDR. In this analysis, high

Table 1
Multivariable Analysis of Lifetime Exposure to Violence, Chronic Stress, and Asthma and Bronchodilator Response

Variables	Asthma				Bronchodilator response ^b			
	Model 1 ETV only		Model 2 ETV + high chronic stress		Model 3 High chronic stress only		Model 4 High chronic stress + ETV	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value	Beta (SE)	P value	Beta (SE)	P value
Each 1-point increment in ETV scale	1.12 (1.02, 1.22)	.02	1.10 (1.00, 1.22)	.04	—	—	0.46 (0.34)	.18
High chronic stress ^a	—	—	1.19 (0.73, 1.94)	.48	−4.01 (1.47)	<.01	−4.63 (1.60)	<.01
Age	0.87 (0.78, 0.96)	<.01	0.87 (0.78, 0.97)	.01	0.24 (0.35)	.49	0.12 (0.36)	.73
Male sex	1.30 (0.89, 1.91)	.18	1.31 (0.89, 1.92)	.17	1.18 (1.32)	.37	1.09 (1.35)	.42
Household income (≥\$15,000/year)	0.88 (0.58, 1.32)	.53	0.87 (0.58, 1.31)	.50	0.16 (1.41)	.91	0.22 (1.44)	.88
Current SHS exposure	1.40 (0.93, 2.11)	.10	1.41 (0.94, 2.11)	.10	1.15 (1.35)	.39	0.96 (1.39)	.49

Abbreviations: ETV, exposure to violence; SHS, second-hand smoke.

^aChecklist of Children's Distress Symptoms (CCDS) score in the upper quartile.^bIn children with asthma.

chronic stress was significantly associated with 4.0% lower BDR (model 3). In a model additionally adjusted for ETV, high chronic stress remained significantly associated with lower BDR, but there was no significant association between ETV and BDR (model 4). Moreover, we found no significant interaction between high chronic stress and ETV on BDR, either on additive or multiplicative scale (data not shown).

We recognize several limitations. First, we cannot assess temporal relationships in this cross-sectional study. Second, we only assessed the child's stress symptoms in the previous 6 months and thus cannot exclude an association between persistent pre- and/or postnatal chronic stress and asthma at school age. Third, we have limited statistical power to assess interactions with modest effects. Fourth, lifetime ETV is correlated with poverty and other risk factors for asthma. Although we accounted for household income (a measure of socioeconomic status that is highly correlated with health insurance in our cohort) and current SHS, we cannot exclude confounding by other variables, such as access to and adherence with medications. Despite these limitations, our results and previous findings suggest that one potential mechanism for the observed association between current or recent high chronic stress and reduced BDR may be persistent secretion of catecholamines leading to down-regulation of the β_2 -adrenergic receptor.³

To our knowledge, this is the first study to jointly examine ETV and chronic stress in relation to both asthma and BDR in school-aged children. We show that lifetime ETV is associated with asthma, independent of high chronic stress, in Puerto Rican children. Among Puerto Rican children with asthma, we report that high chronic stress is associated with reduced BDR, independent of ETV.

Jeremy Landeo-Gutierrez, MD*
 Anna L. Marsland, PhD[†]
 Edna Acosta-Pérez, PhD, MSc[‡]
 Glorisa Canino, PhD[‡]
 Juan C. Celedón, MD, DrPH*

*Division of Pulmonary Medicine, Department of Pediatrics
 UPMC Children's Hospital of Pittsburgh, University of Pittsburgh
 Pittsburgh, Pennsylvania

[†]Department of Psychology
 University of Pittsburgh
 Pittsburgh, Pennsylvania

[‡]Behavioral Sciences Research Institute
 University of Puerto Rico
 San Juan, PR
juan.celedon@chp.edu

Supplementary Data

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.anai.2020.03.005>.

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Appendix

eTable 1
Main Characteristics of Study Participants

Characteristic	Controls (n = 235)	Cases (n = 237)
Age (y)	11.8 (1.9)	11.5 (1.8) ^a
Male sex	109 (46.4)	134 (56.3) ^a
Body mass index z-score	0.55 (1.0)	0.73 (1.1)
Household income ≥ \$15,000/year	97 (42.5)	85 (36.3)
Current SHS exposure	78 (33.2)	101 (42.8) ^a
FEV ₁ , percent predicted	97.9 (14.6)	93.3 (13.6) ^a
FEV ₁ /FVC, percent predicted	97.4 (89.2, 100.7)	93.0 (86.6, 98.1) ^b
Bronchodilator response ^c	3.8 (6.8)	4.0 (8.5)
High chronic stress ^d	44 (18.7)	59 (25.2)
Lifetime ETV scale	3 (1, 5)	4 (2, 5) ^a

Abbreviations: ETV, exposure to violence; SHS, second-hand smoke; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity.

Values are presented as *n* (%) for binary variables, mean (SD) for normally distributed continuous variables, or median (interquartile range) for non-normally distributed continuous variables.

^a*P* < .05 for comparison between cases and controls.

^b*P* < .01 for comparison between cases and controls.

^cPercent change in FEV₁ after administration of albuterol.

^dA Checklist of Children's Distress Symptoms questionnaire score in the upper quartile.