

# Depressed children with asthma evidence increased airway resistance: "Vagal bias" as a mechanism?

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**Background:** Depression is prevalent in pediatric asthma, and implicated in asthma morbidity and mortality. Pathways linking stress, depression, and asthma are unknown.

**Objectives:** To examine, under controlled laboratory conditions, pathways by which depressive states affect airway function via autonomic dysregulation.

**Methods:** Participants were 171 children with asthma, age 7 to 17 years, presenting to an emergency department for asthma exacerbation. Forty-five children with asthma and high depressive symptoms (D) were contrasted with 45 with low/no depressive symptoms (ND). Depressive symptoms, asthma disease severity, vagal and sympathetic reactivity to film stressors, airflow (FEV<sub>1</sub>), and airway resistance were compared between the groups. A subgroup with greater airway reactivity (nonmedicated FEV<sub>1</sub> < 80% predicted) was also studied.

**Correlations among variables were examined for the entire sample.**

**Results:** Groups did not differ in demographics, disease severity, medications, or adherence. The D group with FEV<sub>1</sub> < 80% predicted showed greater airway resistance throughout all conditions ( $P = .03$ ), and vagal bias in the film stressors. The D group's vagal response was significant for the sad stimuli: family distress/loss ( $P = .03$ ), dying ( $P = .003$ ), and death ( $P = .03$ ). The ND group showed sympathetic activation to sad stimuli: loneliness ( $P = .04$ ) and dying ( $P = .04$ ). Depressive symptoms were correlated with respiratory resistance ( $r = .43$ ;  $P = .001$ ) and vagal bias in scene 3 ( $r = .24$ ;  $P = .03$ ), and vagal bias (scene 3) was correlated with postmovie airway resistance ( $r = 0.39$ ;  $P = .004$ ).

**Conclusions:** Children with asthma and depressive symptoms manifest vagal bias when emotionally stressed. Those with depressive symptoms and FEV<sub>1</sub> < 80% manifest greater airway resistance. Depression, vagal bias, and airway resistance were intercorrelated for the full sample. (J Allergy Clin Immunol 2009;123:1000-1008.)

**Key words:** Asthma, depression, children, vagal, pulmonary function, airway resistance, autonomic nervous system, dysregulation

Asthma is a clinical syndrome characterized by variable airflow obstruction, airway hyperresponsiveness, and cellular inflammation.<sup>1</sup> Prevalence of childhood asthma ranges from 5% to 15%, depending on country,<sup>2</sup> and asthma prevalence in children is increasing.<sup>3</sup> Triggers include allergens, infections, exercise, cold air, and emotions. Mechanisms of airway constriction include immune/inflammatory and cholinergic/vagal pathways, which are complexly interrelated.<sup>4,5</sup> Compromised adherence is well established as a pathway by which stress and depression contribute to pediatric asthma morbidity.<sup>6</sup> Clinical and empirical findings also point to stress and emotions as direct psychobiologic influences in asthma morbidity<sup>7-12</sup> and mortality.<sup>13-15</sup> Mechanisms of airway constriction (immune/inflammatory and cholinergic/vagal) point to 2 possible psychobiologic pathways: (1) psychoneuroimmunologic, and (2) psychophysiologic (autonomic nervous system; ANS). There is robust support implicating immune/inflammatory processes as psychobiologic pathways.<sup>12</sup> However, the ANS plays a crucial role in stress response, and the cholinergic/vagal mechanism of airway constriction makes the ANS plausible as an additional psychobiologic pathway. Studies, including our own, support ANS involvement as a mechanism in the impact of stress and depression on asthma.<sup>16-19</sup>

## Depression and ANS pathways in asthma

Depression, as well as asthma, is considered by the World Health Organization to be a global health problem, and individuals with medical illnesses are particularly prone to depression.<sup>20</sup> A recent controlled study showed that 16.3% of youth with asthma had major depressive disorder compared with 8.6% of youth without asthma,<sup>21</sup> and a meta-analysis reports elevated levels of depressive symptoms in children with asthma.<sup>22</sup> Depression has been implicated in disease activity<sup>23</sup> and mortality,<sup>13,24</sup> and antidepressant medications have been demonstrated to have positive effects on asthma.<sup>25-27</sup> Miller and Strunk<sup>13</sup> showed that asthma death in children was associated with previous hopelessness and despair, family stress, and separation or loss. On the basis of these findings and animal research associating maternal loss with depressive states, and ANS shifts from sympathetic to vagal

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**Abbreviations used**

ANS: Autonomic nervous system  
 CDI: Children's Depression Inventory  
 D: Group with high depressive symptoms  
 ED: Emergency department  
 ND: Group with very low or no depressive symptoms  
 PEP: Pre-ejection period  
 R<sub>int</sub>: Respiratory resistance interrupter technique  
 RR: Respiratory rate  
 RSA: Respiratory sinus arrhythmia

activation,<sup>28</sup> specifically as related to medical illness in human beings,<sup>29</sup> Miller developed the Autonomic (ANS) Dysregulation Model of the effect of depressed emotional states on asthma (see this article's Fig E1 in Online Repository at [www.jacionline.org](http://www.jacionline.org)). This model proposes that hopelessness/depression/de-spair are accompanied by a pattern of ANS dysregulation (specifically cholinergic/vagal bias), which potentiates airway instability and airway compromise in asthma.<sup>30,31</sup> "Vagal bias" is defined herein as a preponderance of vagal over sympathetic reactivity.

The ANS model does not address etiology or cause of depression or asthma, but rather provides hypotheses regarding impact of depressive emotional states on airway function and asthma disease activity. The reasoning behind the ANS model parallels that of a current stress-immune model proposing that stress affects asthma by altering (via stress-immune pathways) the magnitude of airway inflammatory response to irritants, allergens, and infections.<sup>12</sup> The ANS model hypothesizes that depressive states affect asthma by altering (via ANS pathways) the magnitude of vagal/cholinergically mediated airway response to asthma triggers. The purpose of the current study was to examine the ANS Dysregulation Model's hypothesized links among depressive states, ANS dysregulation, and airway function in children with asthma.

**METHODS****Design**

Children with asthma and high versus low depressive symptom scores were compared with respect to their vagal and sympathetic reactivity, vagal bias, and airway function at baseline and in response to emotionally evocative film stressors. In addition, the associations among these variables were examined by correlational analyses.

**Subjects**

Subjects were 171 children with asthma, age 7 to 17 years, recruited from an emergency department (ED) after treatment for asthma exacerbation. Exclusion criteria were (1) comorbid chronic medical conditions other than asthma or atopy, (2) psychosis, and (3) pharmacotherapy treatment for depression. The study had Human Subjects Institutional Review Board approval, and informed consents/assents were obtained (see Recruitment and Informed Consent and Table E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

**Procedure**

Children were contacted by our recruiter from the ED after their treatment for an asthma exacerbation. Patients and caregivers were invited to participate in a study of how stress may affect asthma. Eighty-six percent of those

contacted met inclusion criteria, 66% of those eligible agreed to participate in the study, and 81.5% completed the study. There were 3 consecutive weekly (8 AM) visits to the study center, with visit 1 occurring 2 to 6 weeks after the child's initial presentation to the ED. The variable time interval for visit 1 allowed for stabilization of the asthma exacerbation and resolution of the effects of oral steroid bursts, when prescribed. All asthma-relevant medications were withheld for 12 hours before each study visit (with proper safety precautions) and resumed after visit completion. At visit 1, to establish diagnosis, a clinical asthma evaluation and pulmonary function tests, including nonmedicated baseline and postbronchodilator assessments, were performed at the Asthma Clinic. At visit 2, identical evaluation of pulmonary function took place during a second visit to establish a reliable index of baseline pulmonary function and airway reactivity. At visit 3, nonmedicated baseline pulmonary function tests and ANS measures were obtained. Child depressive symptoms were assessed. Subjects viewed in entirety an emotionally evocative, and at times distressing, movie, during which continuous ANS respiration and targeted pulmonary function measures were obtained.

**Movie protocol.** Electrodes were placed on the child to collect continuous electrocardiographic and cardio-impedance data, from which indices of vagal and sympathetic activation and respiration rate were derived. The movie *E.T.: The Extra-Terrestrial* was used to present a variety of stressful emotional provocations. Baseline and eleven 1-minute scenes (3 scary, 6 sad, 2 happy) were preselected for analysis. The emotion type and intensity of the scenes were validated by child report after the movie. Airway function was assessed premovie, after the death scene, and after the movie (see this article's Table E1 in the Online Repository at [www.jacionline.org](http://www.jacionline.org) for scene content).

**Measures**

**Demographics.** Information was obtained by telephone during enrollment. Race/ethnicity was self-identified using USA National Institutes of Health categories. Parents' highest level of education was a proxy for socioeconomic status (see Table E2 in the Online Repository for details).

**Children's Depression Inventory.**<sup>32</sup> The Children's Depression Inventory (CDI) is a 27-item self-report. The maximum score is 54, with scores 12 and above suggestive of clinical depression. The CDI has high internal consistency and extensive validation.<sup>33</sup> Previous studies in our laboratory have established the reliability, validity, and predictive value of the CDI as an index of depressive symptoms in pediatric asthma.<sup>23,34,35</sup>

**Asthma disease severity.** National Heart, Lung, and Blood Institute Criteria (Expert Panel Report, Updated 2002)<sup>36</sup> were used to establish disease severity. The rating is based on objective measures of pulmonary function (FEV<sub>1</sub>) and frequency of daytime and nighttime symptoms.

**Medication adherence.** Medication adherence was assessed with an evidence-based telephone interview procedure adapted for asthma<sup>37</sup> with high reliability and validity,<sup>38</sup> and a robust association with asthma inhaler adherence as assessed by electronic monitoring and canister weights.<sup>39,40</sup>

**Physiologic measures.** Vagal activation was indexed by respiratory sinus arrhythmia (RSA), derived from the high-frequency (ie, respiratory) band of power spectral analysis (fast Fourier transform) of the frequency distribution of cardiac interbeat intervals taken from electrocardiographic recordings.<sup>41</sup> Sympathetic activation was indexed by pre-ejection period (PEP), measured by using both electro and impedance cardiography. PEP corresponds to the time interval in milliseconds from the electrocardiographic Q-point (onset of ventricular depolarization) to the B-point of the dZ/dt impedance waveform (onset of left ventricular ejection). PEP is the most widely accepted, reliable, and valid noninvasive measure of pure sympathetic activation.<sup>42,43</sup> Respiration rate was derived from the Z0 wave of the impedance cardiogram.

**Pulmonary function measures.** Airflow (FEV<sub>1</sub>) was measured by spirometry according to American Thoracic Society criteria. Airway resistance was assessed by using the respiratory resistance interrupter technique (R<sub>int</sub>). The interrupter technique measures resistance by having the subject breathe normally into a tube.<sup>44</sup> Although FEV<sub>1</sub> is the clinical gold standard, it is effort-dependent and relatively insensitive, whereas R<sub>int</sub> measures are not effort dependent and are highly sensitive, with reported clinical utility.<sup>45</sup>

We used both methods to capitalize on the strengths of each and to provide convergent validation. FEV<sub>1</sub> and R<sub>int</sub> were measured 5 times (3 baseline and 2 emotional stimulus conditions) to obtain a highly reliable characterization of airway function for each child.

### Data reduction and processing

From the entire sample ( $n = 171$ ), 90 subjects were selected to establish 2 contrast groups. We identified as depressed (D) those subjects scoring above the depression screen clinical cutoff (CDI score  $>11$ ;  $n = 45$ ). Subjects with the lowest scores (CDI score  $<4$ ;  $n = 45$ ) were designated as a nondepressed (ND) comparison group. Because of technical difficulties with the apparatus, we have R<sub>int</sub> data for 130 (76%) subjects in the entire sample ( $n = 171$ ), and for 60 (67%) of the 90 subjects in the contrast groups ( $n = 32$  for D and  $n = 28$  for ND).

To examine the effects on patients whose airways were more reactive, we constituted a subsample of subjects based on degree of bronchodilator response<sup>45,46</sup> and level of FEV<sub>1</sub>. We determined that FEV<sub>1</sub> prebronchodilator to postbronchodilator difference scores were highly correlated with their baseline nonmedicated scores ( $r = -.42$ ;  $P = .000$ ). We selected nonmedicated baseline FEV<sub>1</sub>  $<80\%$  predicted as a cutoff score, and tested it by comparing bronchodilator response for subjects with FEV<sub>1</sub>  $>80\%$  versus those with FEV<sub>1</sub>  $<80\%$ . FEV<sub>1</sub> difference scores were significantly greater for the subjects with nonmedicated FEV<sub>1</sub>  $<80\%$  predicted, thus validating this as a cutoff for more versus less airway reactivity ( $P = .000$ ). For the full sample of 171 subjects, 62 (36%) had FEV<sub>1</sub>  $<80\%$  predicted. For the contrast groups, 32 (36%) had FEV<sub>1</sub>  $<80\%$  predicted. Analyses were performed for subjects with the full range of FEV<sub>1</sub> scores as well as for this subsample of subjects whose airways were deemed more reactive.

### Data analysis

The statistical analyses were designed to test whether children with asthma with high depressive symptoms were more likely to show vagal bias and decrements in airway function than those with low/no depressive symptoms when viewing the emotionally distressing movie scenes. First we examined each subject's vagal response and sympathetic response to the scenes separately. Next, to index vagal bias (ie, preponderance of vagal over sympathetic reactivity), we subtracted degree of sympathetic response from vagal response for each subject for each scene. Finally we compared the D subjects' averaged vagal bias scores, and the ND subjects' averaged vagal bias scores, for each scene to see whether depressive symptoms were associated with vagal bias. FEV<sub>1</sub> and R<sub>int</sub> scores for the D and ND groups were compared under 3 baseline and 2 emotional stimulus conditions.

To measure associations between depressive symptoms and airway function, and vagal bias and airway function, correlational analyses were used. To obtain the most accurate assessment of association we used the larger (nonstratified for D and ND) recruitment sample ( $n = 171$ ) for the correlational analyses. We concentrated on vagal bias in S3 (family distress/loss), S8 (E.T. dying), and S9 (E.T. death) because, based on previous research, these scenes were expected to have the greatest impact.

Distributions were examined for outliers (none were found), and means and SDs were calculated for all study variables. Vagal and sympathetic reactivity scores were computed by calculating within-subject change scores (for RSA and PEP separately) from the premovie baseline to each movie scene. To assess vagal bias, we converted within-subject vagal and sympathetic reactivity scores to  $z$  scores to make the units compatible. Vagal bias was then computed for each subject by calculating the difference between the  $Z_{\text{vagal reactivity}}$  and  $Z_{\text{sympathetic reactivity}}$  (see the Online Repository for explication). This approach has subsequently been tested and validated.<sup>47</sup> Vagal bias scores were averaged for each scene for the D and ND groups separately. Independent  $t$  tests were used to test differences between the D and ND groups. Pearson correlation was used to assess associations.

## RESULTS

There were no significant differences in age, sex, race, or parental education between the D and ND groups. There also were no significant differences in controller medications (including

inhaled steroids), although slightly more D children were prescribed these medications. There likewise were no significant differences in rescue or allergy medications prescribed, nor in medication adherence (see this article's Tables E2-E5 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)). Except for the selection variable, child depression score, there were no significant group differences in the baseline index variables (see this article's Table E6 in the Online Repository at [www.jacionline.org](http://www.jacionline.org)).

### RSA and respiration rate

Respiratory sinus arrhythmia is influenced by breathing parameters, and ignoring respiration may introduce measurement error and confounds.<sup>48</sup> We measured respiration rate (RR) continuously throughout the laboratory protocol. There were no group differences in RR at baseline or during any scenes, nor was RR related to the baseline to stimulus change scores. We therefore infer that RSA was not confounded by RR in the comparisons made in our sample.

### ANS reactivity in D versus ND groups

There were no group differences in vagal and sympathetic activation at baseline. The D group showed a consistent pattern of greater vagal reactivity and sympathetic withdrawal in response to the emotional provocations, whereas the ND group showed consistent sympathetic activation. The D group showed significantly greater vagal activation in response to 3 sad scenes compared with the ND group: S3, the family distress/loss scene ( $P = .03$ ); S8, the E.T. dying scene ( $P = .003$ ); and S9, the E.T. death scene ( $P = .03$ ; Fig 1, A). The D group showed sympathetic withdrawal, whereas the ND group showed sympathetic activation, in response to 2 sad scenes: S5, the E.T. lonely scene ( $P = .04$ ) and S8, the E.T. dying scene ( $P = .04$ ; Fig 1, B). Furthermore, the D group showed consistently greater vagal bias compared with the ND group throughout the emotional provocations. These differences achieved significance during sad scenes: S3, family distress/loss ( $P = .02$ ), S5, E.T. lonely ( $P = .04$ ), S8, E.T. dying ( $P = .001$ ), and S9, E.T. death ( $P = .01$ ; Fig 1, C; see this article's Table E7 in the Online Repository at [www.jacionline.org](http://www.jacionline.org) for mean RSA and PEP scores).

### Pulmonary function in D versus ND groups

Average FEV<sub>1</sub> and R<sub>int</sub> scores at baseline (nonmedicated) were reliably, inversely correlated ( $r = -.41$ ;  $P = .000$ ), indicating convergent validity of the measures. There were no significant differences for FEV<sub>1</sub> under any conditions; therefore, FEV<sub>1</sub> data are not reported further. There were no significant differences in R<sub>int</sub> between the D and ND contrast groups. In the subsample of subjects with baseline FEV<sub>1</sub>  $<80\%$  predicted (D,  $n = 12$ ; ND,  $n = 12$ ), the D showed robustly and significantly higher airway resistance (R<sub>int</sub>) for each of the baseline and emotion conditions compared with the ND group (Fig 2). There were no significant differences in pulmonary change scores before to after scenes, or before to after the movie for any group.

### Associations among depressive symptoms, vagal bias, and airway resistance

To assess degree of association among the variables posited as links in pathways affecting asthma, we examined correlations

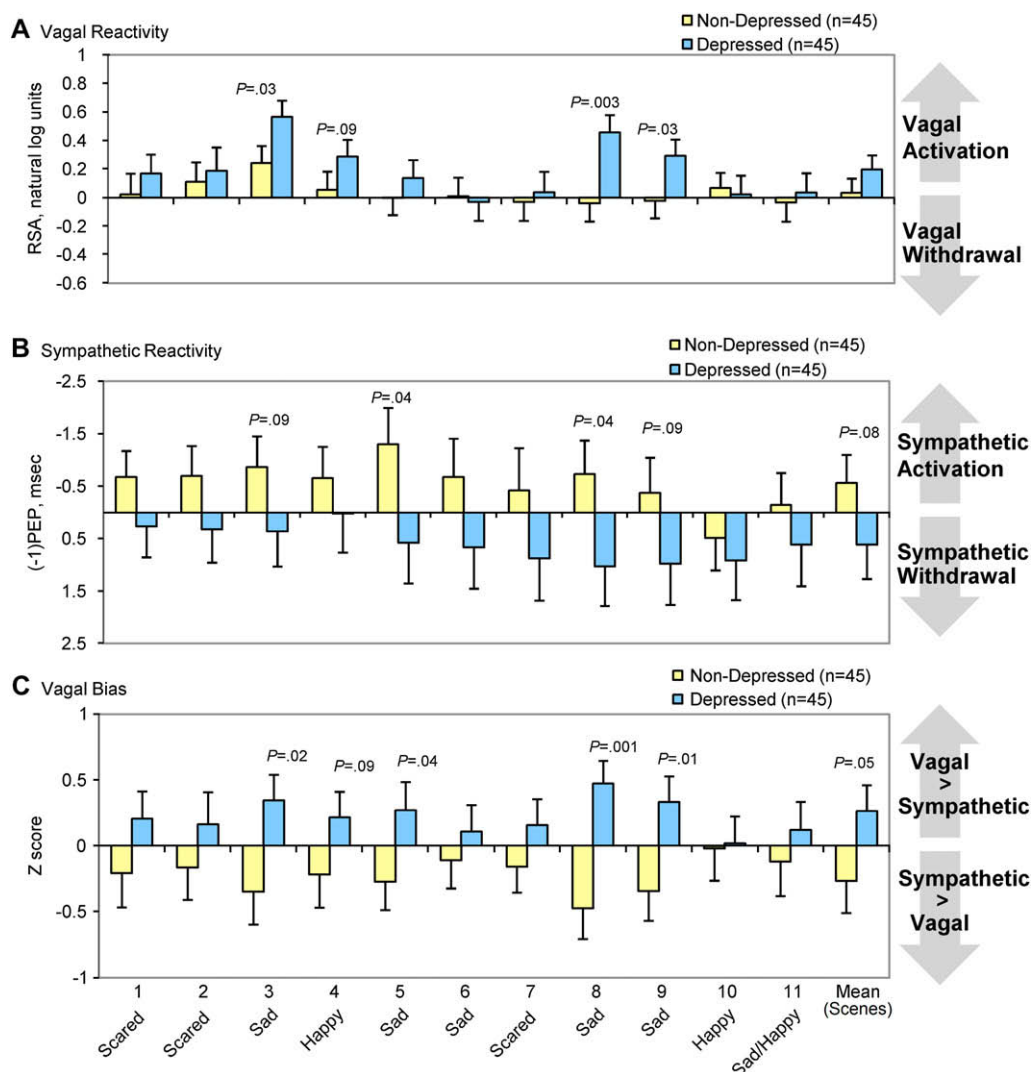


**FIG 1.** Vagal reactivity, sympathetic reactivity, and vagal bias in response to emotional scenes. Vagal (RSA) reactivity (**A**), sympathetic (PEP) reactivity (**B**), and shows vagal bias ( $Z_{\text{vagal reactivity}} - Z_{\text{sympathetic reactivity}}$ ) (**C**) of the ND ( $n = 45$ ) and D ( $n = 45$ ) groups to the 11 preselected emotional scenes of the movie. Data are mean values; error bars indicate SE. RSA values are directly related to level of vagal activation, whereas PEP values are inversely related to sympathetic activation. Therefore, for ease of interpretation, all PEP change scores were inversed (ie, multiplied by  $-1$ ) so that graphic representations of vagal and sympathetic reactivity (ie, activation and withdrawal) would be in the same direction.

among CDI, vagal bias, and  $R_{\text{int}}$ . To obtain the most accurate assessments, we examined associations for the entire sample for which we had  $R_{\text{int}}$  data ( $n = 130$ ) and then examined the associations for the subsample of children with  $\text{FEV}_1 < 80\%$  predicted, nonmedicated ( $n = 62$ ).

For the full sample, there were no significant correlations between CDI and  $R_{\text{int}}$ , nor between vagal bias and  $R_{\text{int}}$ . However, CDI was correlated, as predicted, with vagal bias in S3 (the family distress/loss scene), S8 (E.T. dying scene), and S9 (E.T. death scene;  $r = .15$ ,  $P = .03$ ;  $r = .24$ ,  $P = .001$ ; and  $r = .20$ ,  $P = .005$ , respectively).

For the children with more reactive airways (nonmedicated  $\text{FEV}_1 < 80\%$  predicted), CDI was correlated with  $R_{\text{int}}$  in all conditions, and with the overall mean  $R_{\text{int}}$  ( $r = .43$ ;  $P = .001$ ). In addition, CDI was correlated with vagal bias in S3, the family distress/

loss scene ( $r = .24$ ;  $P = .03$ ), and vagal bias during S3 was correlated with postmovie  $R_{\text{int}}$  ( $r = .39$ ;  $P = .004$ ; Fig 3, A-C). Scenes 8 and 9 (E.T. death and dying) showed similar patterns of association but did not achieve significance. Exploratory analyses of the other scenes showed no consistent patterns of associations.

## DISCUSSION

To our knowledge, this is the first published study to examine psychophysiological pathways linking emotional stress, depressive symptoms, ANS dysregulation, and pulmonary function in asthma. Children with asthma and high depression scores showed preponderance of vagal over sympathetic reactivity—that is, vagal bias—in their responses to

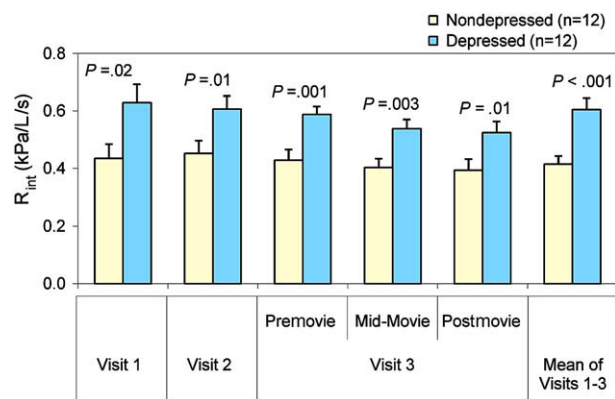


**FIG 2.** Differences in respiratory resistance between the D and ND groups. Respiratory resistance ( $R_{int}$ ) for the subset of subjects (ND,  $n = 12$ ; D,  $n = 12$ ) whose airways are more reactive (nonmedicated  $FEV_1 < 80\%$  predicted).  $P$  values are for the differences in respiratory resistance between the D and ND group. Data are mean values; error bars indicate SE.

laboratory-induced emotional stress, a pattern that could negatively affect airway function. In contrast, children with asthma without depressive symptoms showed greater preponderance of sympathetic (over vagal) reactivity, a pattern that would be considered typical and adaptive in response to emotional stress, and one that would not likely affect airway function negatively. Vagal reactivity and vagal bias were most pronounced during scenes which portrayed family distress/loss, death, and dying. Furthermore, degree of depressive symptoms was associated with degree of vagal bias during the family distress/loss scene, and respiratory resistance postmovie was associated with degree of vagal bias during the family distress/loss scene. In the subgroup of children with more reactive airways selected for high and low depression, the depressed children showed significantly higher airway resistance than those with low/no depressive symptoms, throughout all conditions of the study. Furthermore, the level of depressive symptoms measured using the entire unselected sample of children with more reactive airways was robustly correlated with  $R_{int}$  for every baseline and stress condition. This relationship did not hold for the children with less reactive airways ( $FEV_1 > 80\%$ ). To our knowledge, this is the first report in the literature demonstrating an association between depressive symptoms and increased airway resistance. These findings are consistent with Miller's ANS Dysregulation Model and thus provide evidence for an understudied, but potentially clinically relevant, psychobiologic pathway (ie, autonomic) by which stress and depressive states may influence asthma disease activity. Specifically, we propose that ANS dysregulation (ie, vagal bias) may be one mechanism by which depression and stress influence airway function in asthma.

Subjects in this study did not show a decrease in  $FEV_1$  or increase in airway resistance in response to the emotional stimulation of the movie. Other laboratories have found a direct effect. Aboussafy et al<sup>49</sup> demonstrated, using a math and cold-pressor stress paradigm, an association between vagal activation and decrease in airflow in adults with asthma. Ritz et al<sup>19</sup> found an association between vagal activation and respiratory resistance during slides representing depressive emotions. It is possible that the emotional challenge of the movie paradigm used in our study may not have elicited

sufficiently intense emotional distress, thus limiting the ability to effect pulmonary changes. It is also possible that acute depressive emotions and stress do not directly trigger airway resistance. An alternative explanation is that depressive distress does not affect airway function directly, but rather amplifies the cholinergic response of the airways to other triggers. This possibility, as yet untested, is consistent with the ANS model, which proposes that chronic stress or depression accompanied by vagal bias potentiates the effects of asthma triggers, environmental as well as emotional.<sup>31</sup> This interpretation is analogous to the proposition by Chen and Miller<sup>12</sup> that stress does not directly affect airway function, but rather potentiates inflammatory responses to allergic and environmental triggers. Their research, and that of others, shows that children with asthma subjected to chronic plus acute stress exhibited down-regulation of the  $B_2$ -adrenergic receptor<sup>50</sup> and lower salivary  $\alpha$ -amylase output, indicating lower sympathetic activity.<sup>51</sup> Although these studies did not report pulmonary effects, the findings do point to neurophysiologic mechanisms that may importantly interrelate, or be parallel pathways, with vagal bias in affecting airway function.

Other studies lend support to a direct psychobiologic effect of stress and distress on asthma. Sandberg et al,<sup>52,53</sup> in a study of children with moderate to severe asthma, found that negative life stressors were associated with increased risk of subsequent asthma exacerbations, especially against a backdrop of high chronic stress. The findings reported herein, for the scenes portraying family distress/loss, death, and dying, connect with the literature demonstrating family distress and interpersonal loss as emotional conditions highly linked to asthma morbidity<sup>54,55</sup> and mortality.<sup>13</sup> Furthermore, it was the family distress/loss scene that showed consistent associations among depressive symptoms, vagal bias, and postmovie airway resistance. These findings reinforce previous results from our laboratory associating family relational stress with child depression and increased asthma disease activity.<sup>56</sup> These results also converge with others' findings regarding the effects of stressful home life on glucocorticoid and  $B_2$ -adrenergic mechanisms affecting asthma,<sup>50,51</sup> and with the case-controlled child asthma death study by Miller and Strunk<sup>13</sup> in which family disturbance, separation and loss, and hopelessness/despair were predictors of death consequent to a life-threatening asthma attack. The current study suggests that an ANS dysregulation mechanism (vagal bias) may account for some of the effect of these family stress and depression factors as they relate to asthma morbidity and mortality in children.

The increase in vagal reactivity observed in the loss, death, and dying scenes is 2 to 5 times greater in depressed versus nondepressed children, and may represent a vagal surge. Neural (ie, vagal) influences on the airway are virtually instantaneous, whereas an inflammatory response is delayed. In a study of children who died of asthma, Reid<sup>57</sup> reported that some children examined postmortem had patent airways, with no signs of cellular inflammation or mucus plugging. This observation is consistent with an explanation that the acute lethal effect in these cases may have been mediated vagally, because vagal stimulation causes airway constriction via smooth muscle contraction, which could obliterate the lumen of small bronchi and bronchioles.<sup>58</sup> Such neural effects would be relaxed after death. It is widely observed that that high vagal tone is physiologically protective for many medical conditions. However, our findings

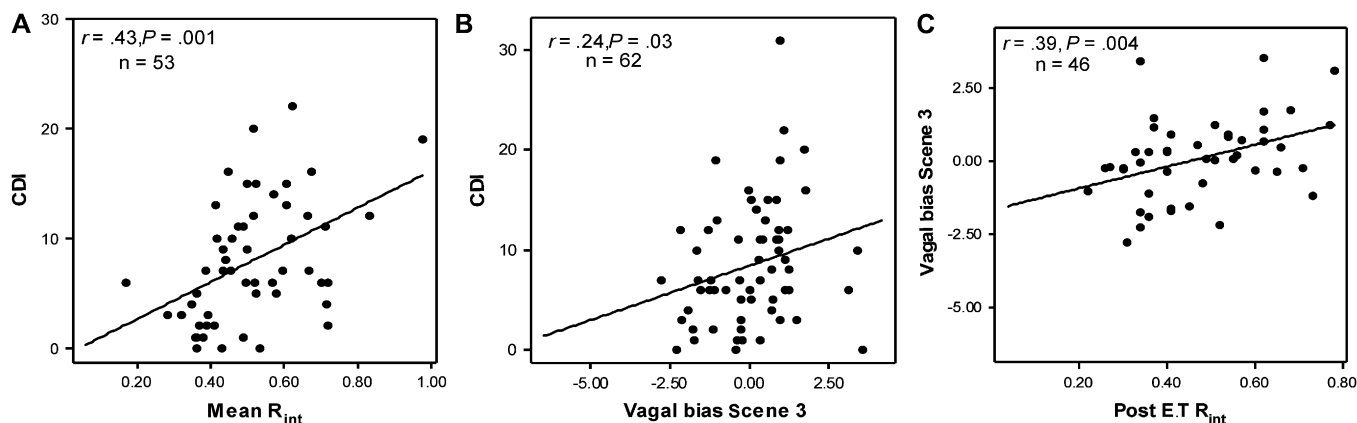


**FIG 3.** Associations among depressive symptoms, vagal bias, and respiratory resistance. Scatter plots showing the correlations (for all subjects with nonmedicated  $FEV_1 < 80\%$  predicted) between depressive symptoms (CDI) and respiratory resistance ( $R_{int}$ ) (A), between CDI and vagal bias B at scene 3 (family distress/loss) (B), and between vagal bias at scene 3 and postmovie  $R_{int}$  (C).

indicate that depressive states are accompanied by a type of ANS dysregulation (vagal bias) that results in greater vagal reactivity and acute vagal surges under conditions of emotional stress, which could be problematic for asthma. Reports, including a meta-analysis, indicate improvement in airflow for some patients when ipratropium (an anticholinergic, parasympatholytic agent) was used adjunctive to  $\beta_2$ -agonists for the treatment of acute asthma exacerbations.<sup>59</sup> One might speculate that those patients who responded to this treatment may have had depressive states with accompanying vagal bias. These medical findings, taken together, further implicate vagal bias, including greater vagal reactivity and surge, as potential contributors to asthma disease activity.

### Limitations and future directions

The research reported herein examines a pathway model. However, the design of the current study cannot prove causal direction of the pathways proposed. Significant findings in support of the model under investigation will not rule out alternative or coactive pathways of influence (eg, genetic, environmental, allergic, or immune pathways). Indeed, the depression-ANS pathways observed in this study, stress-immune pathways observed in other studies, and stress-non-adherence pathways are not mutually exclusive, but rather are likely part of a complex interrelated system of pathways and mechanisms by which stress and depression influence asthma.<sup>12,31</sup>

Because the sample size of depressed children with asthma and  $FEV_1 < 80\%$  was relatively small in our study, the results need to be replicated with a larger sample. Furthermore, studies are needed to examine whether degree of airway reactivity moderates the effect of depressive states and stress on asthma. In addition, it would be important to examine whether children with asthma may move in and out of vulnerability to depressive effects on airway function as their airways are rendered more and less reactive by other factors, such as nonadherence, colds, infections, and seasonal allergic responses.

The current study hypothesized that acute emotional stress accompanied by vagal bias would increase airway resistance,

which the findings did not support. A related hypothesis, which warrants testing, is that depressed children with asthma mount vagally potentiated airway constriction in response to nonemotional triggers, such as allergens, infections, or exercise. Psychoneurobiological connections between ANS, neuroendocrine, and immune regulation and dysregulation also need to be investigated, along with genetic polymorphisms that may moderate the effect of stress on physiological systems related to depression and asthma.<sup>60</sup>

It is well documented that medication treatment and adherence are factors in disease activity in asthma.<sup>61,62</sup> In our study, there were no differences between groups in medication prescribed or medication adherence, thus strengthening the interpretation of a direct psychobiological pathway such as that proposed in the ANS dysregulation model. However, depression likely does affect adherence, which in turn affects disease activity. Thus, longitudinal studies are needed to examine systematically the distinct and overlapping aspects of psychobiologic and adherence pathways together in the same investigation.

Depression and asthma are significant public health problems. To date, study designs investigating depression, stress, and asthma are at some distance from clinical intervention. We are aware of only 1 randomized clinical trial indicating that pharmacologic treatment for depression improved asthma, along with depression, in depressed adults with asthma.<sup>63</sup> Antidepressant medication may improve asthma in depressed children with asthma as well, but this remains to be tested. Findings herein also point to the importance of assessing emotional condition, including family distress, separation, and interpersonal loss (which may cause depressive states), as factors that could respond to intervention. Furthermore, the findings reported herein point to the importance of testing empirically the positive effect of treating depression for decreasing vagal bias and improving pulmonary function in asthma.

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**Clinical implications: Screening for depressive symptoms may be helpful in asthma management. Psychosocial intervention and targeted use of antidepressants and/or anticholinergic asthma medications may prove beneficial adjuncts in the treatment of depressed patients with asthma.**

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## SITE, RECRUITMENT, AND INFORMED CONSENT

The emergency department (ED) at Women and Children's Hospital of Buffalo is the sole pediatric ED in Buffalo, yielding a sample from a wide range of asthma severity, socioeconomic status, and race, in a manner minimally subject to selection bias by service delivery. Attempts were made to contact all age-appropriate admissions to the ED for asthma symptoms from October 2003 through June 2005. Contact was established with 53.7% of the available subject pool. Some potential subjects were not contacted because the study schedule was filled, subjects had previously participated, or they could not be reached. Eighty-eight percent of contacted families were eligible. Sixty-one percent of those eligible enrolled. Retention rate from visit 1 to visit 3 was 81.5%. The study was approved by the Institutional Review Board of Women and Children's Hospital of Buffalo. Consent and assent (children) were obtained.

## NATIONAL HEART, LUNG, AND BLOOD INSTITUTE CRITERIA FOR ASTHMA DISEASE SEVERITY

National Heart, Lung, and Blood Institute Criteria for Asthma Disease Severity<sup>E1</sup> were used to establish diagnosis and characterize level of disease. The disease severity rating is based on configuration of objective measures of pulmonary function (FEV<sub>1</sub>; average of 3 measures, approximately 1 week apart, with medication withheld) along with frequency of daytime and nighttime symptoms. Disease severity was determined by the research nurse and asthma specialist with independent rating (blind) by a master's-level health clinician (81% perfect agreement; 91% agreement within 1 step). All discrepancies were reconciled by reviewing chart data, and consensus scores were used in analyses.

## AUTONOMIC MEASURES

Data acquisition took place in a room with minimal electrical interference. Four measures were derived during the reactivity protocol: interbeat interval of the heart period, RSA, PEP, and RR.

We recorded electrocardiogram to derive interbeat interval of the heart period and compute RSA, and impedance cardiograms to derive PEP and RR. Data were acquired using a H1C-2000 Bio-Electric Impedance Cardiograph<sup>E1,E2</sup> (Bio-Impedance Technology, Inc, Chapel Hill, NC) and cardiac signals were monitored by and interfaced to a PC-based computer using the software Mindware HRV2.1 (Mindware Technologies Ltd). Disposable spot electrodes were placed in the tetrapolar configuration on the neck and chest. The 2 outer (current) electrodes were placed on the back over the fourth cervical vertebra and the ninth thoracic vertebra, and the 2 inner (recording) electrodes were placed on the ventral thorax at the suprasternal notch and xiphoid process. A 4-mA AC current at 100 kHz was passed through the 2 current electrodes, and Z<sub>0</sub> and dZ/dt signals were acquired from the 2 recording electrodes. Although band electrodes provide more accurate volumetric impedance measures (such as cardiac output), time intervals (eg, PEP) are equally accurate using spot electrodes, which are more comfortable for young children.<sup>E4</sup> Electrocardiogram was derived from thoracic electrodes. Electrocardiogram and the impedance waveforms were inspected for artifact, edited, and processed by using Mindware HRV 2.1 and visual inspection. Interrater

reliability was established ( $r = 0.90$ ) for research staff scoring data.

## SYMPATHETIC ACTIVATION

Sympathetic activation was indexed by PEP, which is defined as the time interval in milliseconds from the electrocardiogram Q-point (corresponding to the onset of ventricular depolarization) to the B-point of the dZ/dt waveform (corresponding to the onset of left ventricular ejection). PEP is inversely related to sympathetic activation. Electrocardiogram, basal thoracic impedance (Z<sub>0</sub>), and the first derivative of the impedance signal (dZ/dt) were collected continuously throughout the protocol and used to compute PEP. The impedance data (Z<sub>0</sub>, dZ/dt) were ensemble averaged within 1-minute epochs, verified, and quantified by Mindware IMP 2.1 (Mindware Technologies Ltd, Gahanna, Ohio).

## VAGAL ACTIVATION

Vagal activation was indexed by the high frequency (ie, respiratory) band of power spectral analysis (fast Fourier transform) of the frequency distribution of the interbeat interval (high-frequency heart rate variability) taken from the continuous recording of the electrocardiogram.<sup>E5</sup>

RSA scores were then derived. The magnitude of RSA in 1-minute intervals was estimated as the natural logarithm of the high frequency of heart period power spectrum within the frequency bandpass associated with respiration (0.15-0.45 Hz). The computational approach from which high-frequency heart rate variability was derived in this study is a standard one considered to be appropriate by an international review committee of the Society for Psychophysiological Research.<sup>E6</sup> The RSA scores were derived and computed by Mindware IMP 2.1.

## PULMONARY MEASURES, INSTRUMENTATION, AND METHODS

Airflow was indexed by FEV<sub>1</sub>, corrected for race and sex, using a portable spirometer (Renaissance # 200, Nellcor Puritan Bennett LLC, Boulder, Colo) according to American Thoracic Society Criteria.<sup>E7</sup> Respiratory resistance was assessed using Rint, with an instrument called MicroRint developed by Micro Direct, Inc (Lewiston, Maine). This instrument is a compact and fully portable computerized data recording meter measuring airways resistance. The instrument uses the interrupter technique to measure airway resistance with a method that requires the subject only to breathe normally into a tube. During transient interruption of airflow (100ms), produced by a shutter in a breathing device, alveolar pressure equilibrates rapidly with pressure at the mouth. By measuring the flow immediately before the occlusion, the ratio of flow to pressure indexes airway resistance. Occlusion occurs 10 times during a test (about 2 minutes), and median values of Rint are calculated, which have demonstrated reliability and validity in children.<sup>E8-E12</sup> FEV<sub>1</sub> is the clinical gold standard, but forced expiratory volume measures are effort-dependent and relatively insensitive to minor changes in airway resistance. R<sub>int</sub> measures are taken during normal breathing activity, and thus are not effort-dependent.

R<sub>int</sub> is a highly sensitive, but therefore less stable, measure, and less well established clinically. We used both methods to capitalize on the strengths of each and to provide for convergent validation, with R<sub>int</sub> always preceding FEV<sub>1</sub> measures to prevent the

effect of the forced maneuver of FEV<sub>1</sub> from affecting the measure of airway resistance by R<sub>int</sub>.

### CALCULATION OF VAGAL BIAS

The purpose of calculating vagal bias was to construct a measure that would reflect autonomic regulation/dysregulation, which requires that both measures of vagal and sympathetic activation be incorporated into the same score. This is based on the assumption that a true characterization of autonomic regulation requires simultaneous consideration of both branches of the autonomic nervous system, because it is the net effect of the 2 branches that has the ultimate effect on the end organ, in this case the airways.<sup>E13,E14</sup>

To assess vagal bias (ie, the preponderance of vagal over sympathetic activation), the following procedures were used:

1. Within-subject RSA scores from baseline to each scene were computed for all subjects (n = 90).
2. Within-subject PEP change scores from baseline to each scene were computed for all subjects (n = 90).
3. RSA change scores for each scene were transformed to Zrsa change scores across the (n = 90) sample.
4. PEP difference scores for each scene were transformed to Zpep change scores across the (n = 90) sample.
5. Within-subject vagal bias scores for each scene were computed by the formula [Zrsa change + Zpep change]. PEP is inversely related to sympathetic activation; therefore, this equation is equivalent to subtracting sympathetic change from vagal activation change.
6. Mean (SD) vagal bias scores were computed for the D and ND groups, separately.

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**TABLE E1.** Description of movie scenes

| Scene | Description                                                                                                                                                                                                                                                                                              | Emotion          |
|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| 1     | Trucks come screeching to a halt in a dark forest. A man gets out and surveys the area with a flash light. E.T. is hiding in the forest, whimpering.                                                                                                                                                     | Scared           |
| 2     | Elliot is tracking foot prints and discovers E.T. in the bushes. They both are startled and scream, and E.T. runs away, overturning trash cans.                                                                                                                                                          | Scared           |
| 3     | Elliot's mother and siblings are sitting at dinner. The family becomes distressed as the topic of the estranged husband/father is brought up. Mother withdraws and cries. The children become upset.                                                                                                     | Sad (separation) |
| 4     | E.T. is at home rummaging through the fridge. He opens a can of beer, drinks it and becomes drunk. Meanwhile, Elliot, in a class at school, lets out a loud burp because of the connection he has with E.T.                                                                                              | Happy            |
| 5     | E.T. and Elliot are in the forest. E.T. is lonely thinking of his parents and wants to go home. Elliot, afraid of losing E.T., tries to persuade E.T. to stay, saying that they can grow up together. E.T. says no, both are sad.                                                                        | Sad (separation) |
| 6     | Elliot's mom finds E.T. lying on the floor and looking really ill, surrounded by the children. Elliot says that E.T. and he are dying. Mom panics, forces the children to go downstairs, and leaves E.T. lying there alone. E.T. cries out in despair and reaches for Elliot as Mom carries Elliot away. | Sad (separation) |
| 7     | Government agents invade Elliot's house. The children and their mom are surrounded and can't escape. The agents close in on E.T.                                                                                                                                                                         | Scared           |
| 8     | E.T. and Elliot are lying next to each other in a hospital and appear to be dying. Doctors work to save them. Elliot talks to E.T., trying to get him to stay alive. E.T. appears to be giving up.                                                                                                       | Sad (separation) |
| 9     | E.T. appears to be dead. Elliot stands alone and talks to E.T., who is lying motionless in a casketlike container. Elliot says that he will never leave E.T. and that he loves him. Elliot then closes the lid on E.T.                                                                                   | Sad (separation) |
| 10    | E.T. revives and Elliot screams in joy. E.T.'s people are returning to get him and he is so happy that he is chanting "E.T. phone home." Elliot tries to quiet E.T. so that the grown-ups around them won't notice.                                                                                      | Happy            |
| 11    | E.T., Elliot, and Elliot's family and friends are in the forest to say goodbye as E.T. returns home on his spaceship. E.T. asks Elliot to leave with him, and Elliot asks E.T. to stay. Both decline, and express sadness. They hug and say goodbye, crying.                                             | Sad/happy        |

**TABLE E2.** Demographic characteristics of the sample

| Characteristics                       | Total sample<br>(n = 171) | Subsample<br>(n = 90) | Subsample by group |               | $\chi^2$ or <i>t</i> value | <i>P</i> value |
|---------------------------------------|---------------------------|-----------------------|--------------------|---------------|----------------------------|----------------|
|                                       |                           |                       | ND<br>(n = 45)     | D<br>(n = 45) |                            |                |
| Age (y), mean (SD)                    | 11.4 (2.7)                | 11.8 (2.7)            | 11.6 (2.5)         | 12.0 (3.0)    | −0.81                      | .42            |
| Male, no. (%)                         | 93 (54.4)                 | 48 (53.3)             | 27 (60.0)          | 21 (46.7)     | 1.70                       | .43            |
| Race, no. (%)*                        |                           |                       |                    |               | 4.85                       | .18            |
| African American                      | 117 (68.4)                | 64 (71.1)             | 34 (75.6)          | 30 (66.7)     |                            |                |
| Caucasian                             | 26 (15.2)                 | 12 (13.3)             | 6 (13.3)           | 6 (13.3)      |                            |                |
| Hispanic                              | 20 (11.8)                 | 10 (11.1)             | 2 (4.4)            | 8 (17.8)      |                            |                |
| Biracial                              | 7 (4.1)                   | 4 (4.4)               | 3 (6.7)            | 1 (2.2)       |                            |                |
| Highest education of Parents, no. (%) |                           |                       |                    |               | 2.91                       | .41            |
| Less than high school                 | 33 (19.3)                 | 16 (17.8)             | 5 (11.1)           | 11 (24.4)     |                            |                |
| High school graduate                  | 66 (38.6)                 | 32 (35.6)             | 17 (37.8)          | 15 (33.3)     |                            |                |
| Some college                          | 52 (30.4)                 | 30 (33.3)             | 17 (37.8)          | 13 (28.9)     |                            |                |
| College graduate and above            | 20 (11.7)                 | 12 (13.3)             | 6 (13.3)           | 6 (13.3)      |                            |                |

The demographic characteristics of the D and ND subjects were highly similar, and there were no differences for any measure.

\*Race was self-reported. There was 1 missing case in the total sample.

**TABLE E3.** Medications prescribed for patients

| Medication                                                             | ND (n = 45)<br>n (%) | D (n = 45)<br>n (%) |
|------------------------------------------------------------------------|----------------------|---------------------|
| Controller                                                             |                      |                     |
| Inhaled corticosteroid                                                 | 7 (15.6)             | 9 (20.0)            |
| Leukotriene                                                            | 3 (6.7)              | 4 (8.9)             |
| Inhaled, long-term combination                                         | 2 (4.4)              | 5 (11.1)            |
| Inhaled corticosteroid and leukotriene                                 | 1 (2.2)              | 4 (8.9)             |
| Leukotriene and inhaled, long-term combination                         | 3 (6.7)              | 2 (4.4)             |
| Inhaled corticosteroid, leukotriene, and inhaled long-term combination | 1 (2.2)              | 1 (2.2)             |
| Rescue                                                                 |                      |                     |
| $\beta$ -Agonist                                                       | 39 (86.7)            | 42 (93.3)           |
| Anticholinergic and $\beta$ -agonist                                   | 0                    | 0                   |
| Burst                                                                  |                      |                     |
| Oral steroids                                                          | 3 (6.7)              | 1 (2.2)             |
| Allergy                                                                |                      |                     |
| Nasal                                                                  | 4 (8.9)              | 4 (8.9)             |
| Oral                                                                   | 3 (6.7)              | 3 (6.7)             |
| Nasal and oral                                                         | 4 (8.9)              | 3 (6.7)             |
| Psychoactives                                                          |                      |                     |
| Antidepressant                                                         | 0                    | 1 (2.2)             |
| Attention Deficit Hyperactivity Disorder                               | 1 (2.2)              | 0                   |
| Other medication                                                       |                      |                     |
| Antibiotics                                                            | 1 (2.2)              | 0                   |
| Others (analgesics, non-steroidals, antacids, multivitamins)           | 2 (4.4)              | 3 (6.7)             |

**TABLE E4.** Medications prescribed for ND versus D participants at time of entry into study

| Medication  | ND<br>(n = 45) | D<br>(n = 45) | <i>P</i> value |
|-------------|----------------|---------------|----------------|
| Controller* | 17 (37.8)      | 25 (55.6)     | NS             |
| Rescue†     | 39 (86.7)      | 42 (93.3)     | NS             |
| Burst‡      | 3 (6.7)        | 1 (2.2)       | NS             |
| Allergy§    | 11 (24.4)      | 10 (22.2)     | NS             |

\*Controller medications include Flovent, Azmacort, Pulmicort, Singulair, and Advair.

†Rescue medications include albuterol, Proventil, Xopenex, Maxair, and Atrovent.

‡Burst medications include prednisone, Prelone, and Orapred.

§Allergy medications include Nasocort, Beconase, Flonase, Nasonex, Rhinocort, Zyrtec, Allegra, Benadryl, Claritin, loratadine, Semprex, Sudafed, and pseudoephedrine.

**TABLE E5.** Patient adherence and physician compliance throughout the study

| <b>Adherence and Compliance</b>                                                                                     | <b>ND<br/>(n = 45)</b> | <b>D<br/>(n = 45)</b> | <b>P value</b> |
|---------------------------------------------------------------------------------------------------------------------|------------------------|-----------------------|----------------|
| Patient adherence based on patient/parent report, no. (%)                                                           |                        |                       | NS             |
| Very poor                                                                                                           | 13 (28.9)              | 8 (17.8)              |                |
| Fair                                                                                                                | 4 (8.9)                | 9 (20.0)              |                |
| Good                                                                                                                | 4 (8.9)                | 8 (17.8)              |                |
| Very good                                                                                                           | 20 (44.4)              | 18 (40.0)             |                |
| No information                                                                                                      | 4 (8.9)                | 2 (4.4)               |                |
| Physician compliance (prescription in accord with National Heart, Lung,<br>and Blood Institute guidelines), no. (%) |                        |                       | NS             |
| Below recommended regimen                                                                                           | 26 (57.8)              | 25 (55.6)             |                |
| At recommended regimen                                                                                              | 10 (22.2)              | 15 (33.3)             |                |
| Taking more than recommended regimen                                                                                | 6 (13.3)               | 3 (6.7)               |                |
| No information                                                                                                      | 3 (6.7)                | 2 (4.4)               |                |

**TABLE E6.** Mean scores and group comparisons for index variables\*

| Index variable                                           | Total sample<br>(n = 171) | D<br>(n = 45) | ND<br>(n = 45) | t Value | P value |
|----------------------------------------------------------|---------------------------|---------------|----------------|---------|---------|
| CDI                                                      | 8.33 (6.41)               | 16.96 (5.17)  | 1.80 (1.04)    | −19.27  | <.001   |
| Premovie baseline RSA (ln)                               | 7.12 (1.31)               | 7.02 (1.36)   | 7.09 (1.40)    | 0.22    | NS      |
| Premovie baseline PEP (ms)                               | 81.41 (9.88)              | 82.44 (10.85) | 83.69 (9.76)   | 0.57    | NS      |
| V1 prebronchodilator baseline FEV <sub>1</sub> %         | 88.11 (18.23)             | 85.60 (19.05) | 89.64 (17.15)  | 1.04    | NS      |
| V1 postbronchodilator FEV <sub>1</sub> %                 | 95.38 (15.42)             | 93.18 (12.26) | 98.44 (17.32)  | 1.6     | NS      |
| V2 prebronchodilator baseline FEV <sub>1</sub> %         | 83.93 (18.47)             | 82.71 (17.77) | 84.94 (19.02)  | 0.56    | NS      |
| V2 postbronchodilator FEV <sub>1</sub> %                 | 94.45 (15.30)             | 92.61 (14.81) | 95.47 (16.05)  | 0.85    | NS      |
| V1 prebronchodilator baseline R <sub>int</sub> (kPa/L/s) | 0.45 (0.18)               | 0.46 (0.21)   | 0.40 (0.14)    | −1.18   | NS      |
| V1 postbronchodilator R <sub>int</sub> (kPa/L/s)         | 0.34 (0.14)               | 0.33 (0.14)   | 0.30 (0.17)    | −0.85   | NS      |
| V2 prebronchodilator baseline R <sub>int</sub> (kPa/L/s) | 0.43 (0.17)               | 0.45 (0.20)   | 0.40 (0.13)    | −1.18   | NS      |
| V2 postbronchodilator R <sub>int</sub> (kPa/L/s)         | 0.33 (0.13)               | 0.32 (0.14)   | 0.28 (0.08)    | −1.44   | NS      |

ln, Natural log units; V1, visit 1; V2, visit 2.

\*Values are mean (SD). P values are for comparisons between the D and ND groups.

**TABLE E7.** RSA and PEP mean scores for movie baseline and scenes\*

| Scenes               | RSA (ln)       |               | PEP (ms)       |               |
|----------------------|----------------|---------------|----------------|---------------|
|                      | ND<br>(n = 45) | D<br>(n = 45) | ND<br>(n = 45) | D<br>(n = 45) |
| <i>E.T.</i> baseline | 7.09 (1.40)    | 7.02 (1.36)   | 83.69 (9.76)   | 82.44 (10.85) |
| S1 scared            | 7.11 (1.45)    | 7.19 (1.37)   | 83.02 (10.82)  | 82.71 (10.12) |
| S2 scared            | 7.20 (1.42)    | 7.21 (1.36)   | 82.99 (10.73)  | 82.76 (11.09) |
| S3 sad               | 7.33 (1.39)    | 7.59 (1.13)   | 82.83 (10.46)  | 82.81 (10.50) |
| S4 happy             | 7.14 (1.44)    | 7.31 (1.28)   | 83.04 (10.38)  | 82.46 (10.57) |
| S5 sad               | 7.08 (1.37)    | 7.16 (1.37)   | 82.40 (10.06)  | 83.02 (10.04) |
| S6 sad               | 7.09 (1.31)    | 6.99 (1.29)   | 83.02 (10.28)  | 83.11 (10.86) |
| S7 scared            | 7.05 (1.39)    | 7.06 (1.26)   | 83.27 (10.31)  | 83.32 (10.86) |
| S8 sad               | 7.05 (1.46)    | 7.48 (1.25)   | 82.96 (10.31)  | 83.47 (10.46) |
| S9 sad               | 7.09 (1.39)    | 7.31 (1.30)   | 83.63 (10.12)  | 83.42 (10.68) |
| S10 happy            | 7.15 (1.47)    | 7.04 (1.34)   | 84.18 (10.83)  | 83.36 (9.94)  |
| S11 sad              | 7.05 (1.48)    | 7.04 (1.55)   | 83.55 (10.71)  | 83.17 (9.66)  |
| Mean of 11 scenes    | 7.12 (1.31)    | 7.22 (1.20)   | 83.13 (10.24)  | 83.06 (10.15) |

\*Values are mean (SD).

# **AUTONOMIC (ANS) DYSREGULATION MODEL OF EMOTIONAL INFLUENCE ON ASTHMA**

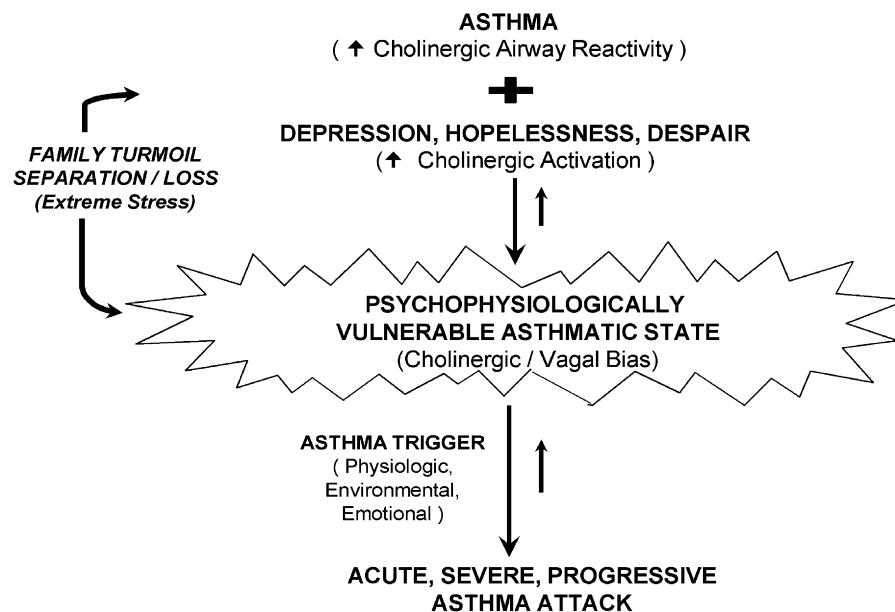


**FIG E1.** Autonomic (ANS) dysregulation model of emotional influence on asthma.