Socioeconomic status associated with exhaled nitric oxide responses to acute stress in children with asthma

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A B S T R A C T

Although psychosocial stress has been linked to clinical asthma outcomes, controlled, laboratory paradigms that test associations between psychosocial stress and markers of airway inflammation in humans are lacking. There is also little known about how individual background characteristics may affect variability across individuals in asthma-relevant inflammatory and pulmonary responses to stress. The goals of this study were to investigate the effects of a laboratory stress paradigm on markers of airway inflammation and pulmonary function in children with asthma, and to determine why some children are more biologically responsive to stress. 38 children physician-diagnosed with asthma, and 23 healthy control children (M age = 15 years) engaged in a conflict discussion task with a parent. Pulmonary function (FEV1) was measured before and immediately after the task. Airway inflammation (indicated by exhaled nitric oxide, FeNO) was measured before and 45 min after the task (to minimize effects from spirometry). Parents were interviewed about family socioeconomic status (SES: income and occupation). In children with asthma only, there was an inverse association of SES with change in FeNO levels in response to the conflict task, meaning that as SES declined, greater increases in FeNO were observed. No changes in FEV1 were found in response to the conflict task. This study suggests that lower SES children with asthma may be more vulnerable to heightened airway inflammation in response to stress.

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1. Introduction

Stress has long been thought to contribute to a number of diseases, including asthma. Clinical evidence supports this hypothesis. For example, experiencing an acute negative life event (e.g., death of a close family member) in the context of chronic stress increased the risk of a subsequent asthma attack in children by nearly 3-fold (Sandberg et al., 2000). Parental stress also has been linked to more frequent symptoms, poorer daily functioning, and greater health care service utilization in children with asthma (Shalowitz et al., 2001; Weil et al., 1999).

Researchers have attempted to understand the biological mechanisms underlying these effects by studying real-world stress. For example, stressors such as school exams are associated with greater mobilization of eosinophils into sputum and blood following allergen challenge, greater in vitro production of the Th-2 cytokine IL-5 in patients with asthma, and a decreased Th-1/Th-2 ratio of cytokine production in atopic individuals (Hoglund et al., 2006; Kang et al., 1997; Liu et al., 2002). Children whose caregivers report high levels of stress have greater stimulated production of the pro-inflammatory cytokine TNF-α, as well as reduced production of the Th-1 cytokine IFN-γ (Wright et al., 2004). In addition, stressful experiences such as exposure to violence and parental conflict have been associated with decreased pulmonary function (Suglia et al., 2008). Furthermore, the relationship between daily stress and pulmonary function has been found to be mediated by airway inflammation (Kullowatz et al., 2008).

While these studies are clearly informative, there remain limitations to the conclusions that can be drawn. First, the naturalistic setting, while closer to the real-world, can make alternative confounding explanations difficult to rule out. Second, variability in stress responsiveness across individuals with asthma remains less well-understood. For example, we know that social group characteristics, such as low socioeconomic status (SES), are associated with increased inflammatory signaling, as marked by higher levels of C reactive protein and IL-6, and greater stimulated production of Th-2 cytokines (Chen et al., 2003, 2006; Hemingway et al., 2003; Panagiotakos et al., 2005). SES refers to an individual's position within a social hierarchy, and can be defined both in terms of the social prestige ascribed to an individual, as well as in terms of the material resources an individual possesses, with both having been associated with health outcomes (Adler et al., 1993; Krieger...
et al., 1997). Hence social group characteristics such as SES may also determine variability in inflammatory responses in the context of asthma.

In asthma, the fractional concentration of exhaled nitric oxide (FeNO) is a non-invasive marker related to airway inflammation. FeNO is elevated in children with asthma (Kovesi and Dales, 2008; Pijnenburg and de, 2008; Strunk et al., 2003). FeNO levels are related to asthmatic airway inflammation indicated by bronchial wall inflammation (Payne et al., 2001), sputum eosinophilia (Jatakanon et al., 1998), and airway hyper-responsiveness (Strunk et al., 2003). FeNO levels increase as asthma control deteriorates (Jones et al., 2001), and decrease when treatment reduces airway inflammation (Beck-Ripp et al., 2002; Bratton et al., 1999; Kharitonov et al., 2002; Montuschi et al., 2007; Sorkness et al., 2007; Straub et al., 2005a,b).

The present study had two goals: (1) to document the effects of a standardized stressor on markers of airway inflammation (as reflected by FeNO) and pulmonary function in children with asthma vs. healthy children; and (2) to understand which background characteristics may account for variability in FeNO or pulmonary function changes in response to stress. Based on previous research reviewed above, we hypothesized that SES would be associated with changes in pulmonary function and FeNO following an acute laboratory stressor, such that as SES declined, pulmonary function would be reduced and FeNO would increase in children with asthma.

2. Method

2.1. Participants

Thirty-eight children physician-diagnosed with asthma and 23 healthy control children were recruited from Vancouver, BC. Children ranged in age from 10–20 years, were fluent in English, free of acute respiratory illness, had not received prednisone for at least 2 weeks, and had no other chronic illnesses (other than asthma). Asthma severity was determined from the NAEPP/EPR2 Guidelines based on symptoms and medication use, paralleling the approach of previous researchers (Bacharier et al., 2004). Atopic status was determined by the presence of both positive parental report of child allergic status and positive screening of serum IgE antibodies to common allergens (ImmunoCAP Phadiatop, Uppsala, Sweden). Details regarding sample characteristics are presented in Table 1. The protocol was approved by the UBC Research Ethics Board. Written consent was obtained from parents, and assent from children.

2.2. Procedures

All visits occurred in the afternoon. Baseline FeNO and then spirometry measures were first taken on children. Children and parents were then brought together and participated in a family conflict task. Immediately after the task, spirometry was re-assessed in children. Forty-five minutes later, post-task exhaled nitric oxide was assessed in children. This timing of post-task measures was meant to capture changes in spirometry, which occur rapidly following an acute stimulus, while at the same time minimizing the ability of spirometry to reduce FeNO readings (Kissoon et al., 2002; Silkoff et al., 1999; Terada et al., 2001). To achieve both of these goals, we opted to assess spirometry immediately after the stressor task, and then collect FeNO measures 45 min later. The FeNO protocol is also consistent with the time frame of other studies in healthy populations of acute stressors and inflammation (Miller et al., 1999; Schedlowski et al., 1993).

2.3. Measures and task

2.3.1. Acute stressor task

Families participated in a standardized laboratory family conflict task. First, parents and children independently completed the Potential Parent Child Conflict scale (Donenberg and Weisz, 1997), a questionnaire that asks respondents to rate the amount of disagreement they have with their parent/child in a number of domains (e.g., household chores, friendships, etc.). A research assistant selected the topic that on average, parents and children disagreed the most about. Families were then asked to spend 8 min discussing their disagreements related to this topic and trying to reach a resolution. Conflict discussions between parents and children have been shown to be an ecologically valid yet controlled stressor that alters physiological parameters (Granger et al., 1994, 1996; Klimes-Dougan et al., 2001). To test effects on physiology in the present study paradigm, we assessed blood pressure (BPM-100, VSM MedTech, Coquitlam, BC) in children during a 10 min rest (three readings spaced 1 min at the end of rest) and as well during the conflict discussion (five readings spaced 1 min apart at the beginning of conflict); Blood pressure increases in response to conflict discussions between family members have been established in previous research (Ewart et al., 1991).

2.3.2. Pulmonary function

Pulmonary function was assessed via spirometry (Vmax/Spectra, SensorMedics, Yorba Linda, California), according to American Thoracic Society guidelines (American Thoracic Society, 1995). Measures were taken at least 4 h after the last use of a short-acting beta agonist and at least 24 h after the last use of a long-acting beta agonist. Measurement included forced expiratory volume in the first second (FEV1) percent predicted.

### Table 1
Descriptive information about sample.

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th></th>
<th>Healthy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (range 10–20 years)a</strong></td>
<td>15.0</td>
<td>2.8</td>
<td>15.9</td>
<td>2.0</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>68</td>
<td>57</td>
<td>65</td>
<td>57</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>58</td>
<td>74</td>
<td>60</td>
<td>72</td>
</tr>
<tr>
<td>Asian</td>
<td>26</td>
<td>17</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Other</td>
<td>16</td>
<td>9</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild intermittent</td>
<td>13</td>
<td>12</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Mild persistent</td>
<td>45</td>
<td>44</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>Moderate persistent</td>
<td>29</td>
<td>28</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>Severe</td>
<td>13</td>
<td>12</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Atopic</td>
<td>55</td>
<td>13</td>
<td>52</td>
<td>13</td>
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<tr>
<td>FEV1/FVC</td>
<td>0.76</td>
<td>0.12</td>
<td>0.84</td>
<td>0.08</td>
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<tr>
<td>ICSa</td>
<td>6.0</td>
<td>6.3</td>
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<td>0</td>
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<tr>
<td>ICS dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>73</td>
<td>27</td>
<td>73</td>
<td>27</td>
</tr>
<tr>
<td>Medium</td>
<td>27</td>
<td>0</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Beta agonistsb</td>
<td>5.1</td>
<td>6.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Baseline FEV1%</td>
<td>99.6</td>
<td>16.6</td>
<td>99.0</td>
<td>8.4</td>
</tr>
<tr>
<td>Post-task FEV1%</td>
<td>90.0</td>
<td>14.1</td>
<td>97.0</td>
<td>7.0</td>
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<tr>
<td>Baseline FeNO (ppb)</td>
<td>58.5</td>
<td>57.5</td>
<td>22.8</td>
<td>24.4</td>
</tr>
<tr>
<td>Post-task FeNO (ppb)</td>
<td>53.5</td>
<td>51.5</td>
<td>21.4</td>
<td>23.5</td>
</tr>
</tbody>
</table>

ICS = inhaled corticosteroids. FEV1 = forced expiratory volume in 1 s percent predicted. FeNO = fractional concentration of exhaled nitric oxide in parts per billion. FEV1/FVC = ratio of FEV1 to forced vital capacity.

a Age range for asthma group: 10–20 years; age range for healthy group: 11–18 years.

b Number of days taken in previous 2 weeks, range for both medications in the asthma group was from 0 to 14 days.
2.3.3. Airway inflammation

As a marker of airway inflammation, exhaled nitric oxide was measured via a chemiluminescence analyzer (Aerocrine AB, Stockholm, Sweden), according to American Thoracic Society guidelines (American Thoracic Society/European Respiratory Society, 2005). The NIOX system was used (Aerocrine AB, Stockholm, Sweden), which uses a resistive device that provides a constant low expiratory flow rate and vellum closure. Participants were seated, exhaled to residual volume, inserted a mouthpiece, inhaled to total lung capacity, and then exhaled for 10 s at a constant flow rate of 0.05 L/s + 10%. Visual cues on the computer provided guidance about maintaining constant flow rate. The measurement ended when a plateau of 4 s was observed (variance criterion of 10% or 5 ppb). Repeated exhalations were conducted until three values were obtained that varied by less than 10%. No caffeine, food, or exercise was allowed for one hour prior to the start of testing. The measure reported is the average of three acceptable readings, expressed as fraction of exhaled nitric oxide (FeNO).

2.3.4. Family socioeconomic status (SES)

SES has been conceptualized both in terms of the material resources an individual possesses, as well as the social prestige that an individual has within a particular social context (Krieger et al., 1997). To capture each of these aspects currently, two measures of SES were used: annual family income, and parent occupational status. As an indicator of material resources, parents reported on the family's total gross income for the past 12 months before taxes. As an indicator of social prestige, parent report of occupations were coded according to the Socioeconomic Index for US Census occupations, a validated index that assigns scores to each Census occupation, with a range from 7 to 80 (Hauser and Warren, 1997). In two-parent families, the higher occupational status of the two-parents was used. These types of measures are recommended by the MacArthur Foundation Research Network on Socioeconomic Status and Health (http://www.macses.ucsf.edu).

2.3.5. Covariates

Covariates included demographic characteristics (child age, gender, ethnicity), asthma severity, atopic status, the number of days the child used inhaled corticosteroids in the past 14 days, and the number of days the child used a beta agonist over the past 14 days.

2.4. Data analyses

Multiple linear regression analyses using SPSS 15.0 were conducted to test study hypotheses. Change scores for FEV1 and FeNO (post minus pre-stressor task) were calculated as dependent variables. Our primary hypothesis was that change in FEV1 and FeNO would vary by SES in children with asthma. Because change scores may vary as a function of baseline levels, we first regressed each dependent variable change score onto the baseline levels of FEV1 or FeNO. Next each dependent variable was regressed onto (1) group status (asthma vs. healthy); (2) SES (either family income or parent occupation); and (3) the interaction between group and SES. This allowed us to test the hypothesis that SES would be associated with change in FEV1/FeNO among children with asthma, but not healthy children. Significant interactions were plotted and interpreted following the recommendations of Aiken and West (Aiken and West, 1991).

In subsequent analyses, we addressed the possibility that any relationships of group status or SES with FEV1/FeNO were due to other confounding variables. Demographic (age, gender, ethnicity) and biomedical variables (atopic status, asthma severity, days of inhaled corticosteroid use, and days of beta agonist use) were thus entered alongside SES in the above regression analyses. This allowed us to test whether effects of group status, SES, or their interaction on FEV1/FeNO change remained significant above and beyond the influence of these factors.

3. Results

3.1. Participant characteristics

Children with asthma and healthy children did not differ in terms of age, sex, or ethnicity (all ps > 0.15). Children with asthma had a range of severity (13% mild intermittent, 45% mild persistent, 29% moderate, 13% severe), and 71% were currently being prescribed inhaled corticosteroid medication. Further details on the characteristics of this sample can be found in Table 1.

There was a main effect of group on FEV1%, such that children with asthma had lower FEV1 % predicted both at baseline and post-task compared to healthy children (t = 2.26, p < 0.05, and t = 2.11, p < 0.05, respectively). There was also a main effect of group on FeNO. As expected, children with asthma had higher FeNO levels, both at baseline and post-task compared to healthy children (t = 4.02, p < 0.001, and t = 4.12, p < 0.001, respectively). There was no main effect of time, meaning that on average across the sample, there was no significant change in FEV1 or FeNO from pre-task to post-task (ps > 0.25). See Table 2.

3.2. Family conflict as a stressor

To test whether the family conflict task was experienced as stressful, we examined differences in blood pressure and heart rate from baseline to task. Across all children, all physiological measures showed significant increases from baseline to task (SBP: t = 2.09, p < 0.05, DBP: t = 3.78, p < 0.001, HR: t = 3.41, p < 0.01), indicating that the task was stressful for children.

3.3. Effect of psychosocial stress on exhaled nitric oxide

There were significant interactions of family SES with group status in predicting FeNO responses to the psychosocial stressor, both for family income (b = −2.74, SE = 1.36, p = 0.05) and parent occupation (b = −3.93, SE = 1.46, p = 0.01). Fig. 1 presents a graphical illustration of these interaction effects, in which the linear association between SES and FeNO change is graphed separately for children with asthma and healthy children. Among children with asthma, there was an inverse association such that the lower the family SES, the greater children's increase in FeNO from pre-stressor to post-stressor, or conversely, the higher the family SES, the greater the decrease in FeNO from pre- to post-stressor (b = −2.07, SE = 1.01, p = 0.05). Among healthy children, there was no significant relationship between SES and FeNO change (see Fig. 1).

Table 2

<table>
<thead>
<tr>
<th></th>
<th>Asthma</th>
<th>Healthy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Mean 58.48</td>
<td>22.78</td>
</tr>
<tr>
<td>SD</td>
<td>57.51</td>
<td>24.45</td>
</tr>
<tr>
<td>Median</td>
<td>34.80</td>
<td>14.45</td>
</tr>
<tr>
<td>25th</td>
<td>23.50</td>
<td>10.20</td>
</tr>
<tr>
<td>75th</td>
<td>74.85</td>
<td>24.68</td>
</tr>
<tr>
<td>Post-task</td>
<td>Mean 53.51</td>
<td>21.35</td>
</tr>
<tr>
<td>SD</td>
<td>51.54</td>
<td>23.51</td>
</tr>
<tr>
<td>Median</td>
<td>34.15</td>
<td>13.30</td>
</tr>
<tr>
<td>25th</td>
<td>20.68</td>
<td>8.70</td>
</tr>
<tr>
<td>75th</td>
<td>71.75</td>
<td>19.30</td>
</tr>
</tbody>
</table>
We next tested whether demographic or biomedical confounding variables might explain these associations of SES with FeNO change in children with asthma. After controlling for baseline FeNO values, atopic status, asthma severity, inhaled corticosteroid use, beta agonist use, age, sex, and ethnicity, the interaction between group status and SES predicting FeNO change in response to the psychosocial stressor (not due to baseline FeNO levels. Associations between FeNO and family income are significant in children with asthma (b = –2.97, SE = 1.07, p = 0.01), but not among healthy children (b = 0.51, SE = 0.61, p = 0.42).

### 3.4. Effect of psychosocial stress on pulmonary function

There was no interaction of either family income or parent occupation with group status in predicting change in FEV1% after the psychosocial stressor (b = 0.46, SE = 1.44, p = 0.75, and b = –1.41, SE = 1.53, p = 0.36, respectively).

### 4. Discussion

This is the first study that we are aware of to use a laboratory stress paradigm to investigate changes in a marker of airway inflammation (FeNO) in children with asthma. It is also the first to document inverse associations of SES with FeNO change in children with asthma, such that lower SES children showed greater increases in FeNO, whereas higher SES children showed greater decreases in FeNO, after a conflict task with their parents. In contrast, healthy children did not show these patterns. The fact that these associations persisted in children with asthma after controlling for atopic status, asthma severity, medication-taking behaviors, and demographic factors such as age, suggests that the FeNO effects cannot be attributed to these alternative explanations. Moreover, SES accounted for 6.6–8.8% of the variance in FeNO change, and represented a medium-size effect, according to the effect size conventions (Cohen, 1988).

Previous research has documented that naturally occurring stressors (such as exam stress) are associated with greater airway inflammation in induced sputum samples, as well as greater production of Th-2 cytokines and a decreased Th-1/Th-2 ratio.
Previous animal studies have demonstrated that experimental manipulations of stress alter airway inflammation in mice (Forsythe et al., 2004; Joachim et al., 2003). Our study extends this work to humans, and as well, highlights the importance of understanding social group differences in humans, given that inflammatory responses to an acute stressor were greater as SES declined. This finding suggests that in order to anticipate the magnitude of an individual’s biological response to stress, it is useful to understand broader social context variables (Chen and Miller, 2007). For example, the socioeconomic background a child comes from may shape perceptions of stress and coping responses in ways that affect biological responses to stress (Chen et al., 2004, 2006).

Our study findings are also consistent with human work that has documented physiological effects of acute psychological stressors on airway resistance, pulmonary function, cholinergic pathways, and leukocyte counts in patients with asthma (Kang and Fox, 2000; Miller and Wood, 1994, 1997; Rietveld et al., 2000; Ritz et al., 2001; Ritz, 2004). Our study provides another plausible biological pathway through which stress may impact asthma outcomes, in drawing links to markers of airway inflammation. In addition, the present study is consistent with previous research that has shown that acute stress can influence immune markers, although this research tends to be conducted in healthy adults without disease-specific measures (Segerstrom and Miller, 2004). We note that our study did not find effects of acute stress on pulmonary function. However, it has become increasingly clear that there is poor correlation between different measures of asthma activity and severity (e.g., spirometry and FeNO levels (Strunk et al., 2003)), thus allowing for a disconnect between FEV1 and FeNO changes in response to stress. Other potential explanations for these findings may be limitations in the timing of collection of these measures, or in the type of measure collected (forced exhalation spirometry, rather than respiratory resistance or airway responsiveness measures).

How would an acute stressor come to affect FeNO in children with asthma? One speculative pathway involves the induction of nitric oxide (NO) production by the hormonal endproducts of the autonomic nervous system, epinephrine and norepinephrine. These hormones can be released within minutes into circulation during acute psychological stressors like the one used here (Malkus et al., 1994), and they can induce NO production in macrophages stimulated with lipopolysaccharide (Chi et al., 2003; Lin et al., 2005). This process is partially dependent on catecholamine-mediated upregulation of inducible nitric oxide synthase (iNOS) (Chi et al., 2003), a gene whose promoter bears a cyclic AMP binding protein response element that can transduce adrenergic signals in leukocytes (Kohm and Sanders, 2000). In the present study, the increases in blood pressure and heart rate seen during the task are consistent with the notion that the stressor may have increased epinephrine and norepinephrine, but it remains unclear whether such effects were of sufficient magnitude or duration to affect iNOS expression.

Limitations of this study include the preliminary nature of the protocol time frame. Because this is the first study that we are aware of to investigate the effects of a standardized, laboratory psychosocial stressor on FeNO, guidelines have not been established regarding optimal time frames for assessing FeNO post-stressor. In order to both capture acute effects of the stressor on lung function and to minimize effects of spirometry on FeNO, we collected spirometry measures immediately post-task, and FeNO readings 45 min later. We were unable to do repeated assessments given the established effects of spirometry on FeNO (Kissoon et al., 2002; Silkoff et al., 1999). The present study provides some preliminary suggestion of SES differences in acute stress effects on FeNO; however, future studies would need to replicate this findings focusing on repeated FeNO measures (without spirometry) over a longer period of time in order to establish the optimal time frame for detecting effects on FeNO. A second limitation is the lack of psychological measures collected regarding the stressor task. Other limitations include the infeasibility of manipulating socioeconomic status for causal conclusions, and the relatively small sample size and wide age range. Age during childhood may have significant effects on immune and pulmonary measures, although in this study, age was controlled in all analyses to account for these potential effects as much as possible. We also note that this sample consisted of a high percentage of minorities, primarily Asian. Finally, although FeNO is becoming increasingly accepted as a marker of airway inflammation, there is debate about whether it plays a causal role in disease pathogenesis (Sanders, 1999).

The strengths of this study include the acute, laboratory stress paradigm combined with the collection of a marker of airway inflammation in both children with asthma and healthy children. While the design of our study involved an acute laboratory stressor, the findings suggest the possibility that interventions to reduce real-life stress may protect against the relatively greater increases in airway inflammation among lower SES children with asthma. Previous research has found that an intervention involving written disclosure and processing of stressful life experiences improved pulmonary function in a sample of patients with asthma (Smyth et al., 1999); this or other stress-management interventions could have similar benefits for airway inflammation. Overall, the present study indicates that SES is negatively associated with FeNO response to an acute stressor in children with asthma. Given that lower SES individuals are more likely to experience stressors (Brady and Matthews, 2002), this suggests that they may also be more vulnerable biologically to the effects of stress relative to their higher SES counterparts. Hence we need to better understand the stressors and the responses that they evoke in order to begin to address the greater asthma morbidity that many low SES children experience in our society (Miller, 2000; Simon et al., 2003).

Conflict of interest

All authors declare that there are no conflicts of interest.

Acknowledgment

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