

Positive experiences and the relationship between stress and asthma in children

S Sandberg², DC McCann², S Ahola¹, H Oja¹, JY Paton² and D McGuinness²

Department of Statistics¹, University of Jyväskylä, Jyväskylä, Finland; Departments of Child Health and Child & Adolescent Psychiatry², University of Glasgow, Glasgow, Scotland

Sandberg S, McCann DC, Ahola S, Oja H, Paton JY, McGuinness D. Positive experiences and the relationship between stress and asthma in children. *Acta Pædiatr* 2002; 91: 152–158. Stockholm. ISSN 0803-5253

Ninety children aged 6 to 13 y and suffering from chronic asthma were included in a prospective follow-up study lasting 18 mo in order to assess whether life events involving substantial positive effects on the child can protect against the increased risk associated with stressful life events. The main outcome measures included positive life events, positive long-term experiences, severely negative life events, chronic psychosocial stress and new asthma exacerbation. The results showed that, provided they occurred in close proximity to severely negative life events, positive life events, generally related to the child's own achievements, afforded protection against the increased risk of a new asthma exacerbation precipitated by severe events in children whose lives were marked by low to medium levels of chronic stress. No such effect was found in children exposed to high chronic stress nor did long-term positive experiences, such as when the child has a rewarding hobby, affect the asthma risk.

Conclusion: Life events with a definite positive effect can counteract the increased risk of an asthma exacerbation precipitated by a severely negative life event, provided the chronic stress is only of low to medium level. Because this protective influence does not apply where there is high chronic stress, reducing this condition must be seen as a priority in children suffering from asthma, as these children are also more vulnerable to negative life events precipitating asthma exacerbation.

Key words: *Asthma, children life events, psychosocial stress*

Seija Sandberg, Raphael House, Victoria Centre, Pettits Lane, Romford RM1 4HP, UK (Tel. +44 1708 796 800, +44 7711 344 717, Fax. + 44 1708 761 893, e-mail. seija.sandberg@btinternet.com)

In a great many studies, it has consistently been found that children suffering increased psychosocial stress are significantly more likely to experience illness and hospitalization as well as to use health services more frequently than other children (1–3). Stress in the form of early parenting difficulties has been shown to predict the onset of asthma by the age of 3 y in children genetically at risk (4). Apart from predisposing to asthma and precipitating its development, high levels of stress also predict higher overall asthma morbidity in children (5–6) and are correlated with their poorer quality of life (7).

Acute stressful life events, both on their own and in conjunction with high chronic stress, have been shown to increase the risk of new attacks in children who already have asthma (8). In a study of 90 paediatric asthma patients, using a within-subject, over-time analysis of continuous asthma data collected prospectively for 18 mo, severely negative life events (i.e. those that carry a long-term threat to the child's physical or psychological well-being) significantly increased the

risk of an acute exacerbation over the subsequent 3 to 6 wk. However, if, in addition, the child were living under conditions of high chronic stress, the risk would be further increased and also brought forward in time—asthma exacerbation taking place within a fortnight following a severe event.

To date, the possible ameliorating effects of positive life events and ongoing favourable situations on the impact of stressful experiences in children have attracted little attention. The lack of systematic studies in this field does, however, stand in contrast to the rather commonly accepted clinical and theoretical viewpoints about positive experiences protecting children against stress (9). Of the studies involving children that are available, three deal with positive experiences in relation to somatic manifestations (10–12), and two with psychiatric disorders (13–14).

The recent life event histories of children with alopecia areata were examined in two studies, with disparate results (10–11). In one of these studies fewer positive events were detected in the patient group (10);

in the other study no such differences were found (11). In a further study (12) positive life events were found to exert a significant beneficial effect on diastolic blood pressure in healthy adolescents. Furthermore, the two interview-based studies pursuing the possible protection offered by positive experiences, such as positive life events and recent achievements, against psychiatric morbidity yielded negative results (13–14).

The present prospective follow-up study of the impact of positive experiences in children with definitive asthma addresses many of the methodological limitations of previous research. Its strengths over previous studies include independent measurement of asthma and psychosocial experiences through continuous asthma monitoring, high-quality, standardized interview measurement of life experiences, statistical methods allowing intra-individual variations over time to be examined, and an account taken of each child's personal history in relation to past asthma exacerbation and life events. More importantly, as a prospective study, it not only allows us to time the association between life events and disease exacerbation, but also to investigate the effect of positive life events on the risk caused by negative experiences, as these occurred in a time-wise relationship to one another.

Purpose of the study

The objective of this analysis, utilizing data collected in a prospective study of children with asthma, referred to above (8), was to examine whether positive life experiences can protect against the effect of negative experiences. Two hypotheses, originally set for the study, were tested: (1) The increased risk of an acute asthma exacerbation associated with severely negative life events is reduced in the presence of positive life events; (2) Positive long-term experiences such as absorbing or rewarding hobbies also ameliorate the risk caused by negative life events and chronic stressful experiences.

Methods

Design

The study was carried out as a prospective follow-up over a period of 18 mo. Separate teams, who were unaware of the other team's results throughout the study, independently assessed the asthma and life experiences.

Subjects

Ninety children aged 6 to 13 y (mean 8.6 y) and suffering from moderate to severe asthma were included in the study. All of them regularly attended a specialist asthma clinic at the Royal Hospital for Sick Children in Glasgow, Scotland. The recruitment of the sample took

place in the asthma clinic, with the child's age being the only selection criterion. Suitable subjects were approached consecutively by the respiratory consultant (JYP) to take part in the study. As the sample accrued, it was monitored for age, sex and social class (15) to ensure that the group was representative of children attending the clinic. The gender ratio was 54% (49M) 46% (41F), and the social class distribution, based on the occupation of the main breadwinner, included Social Class I & II (professional/managerial) 37% (33); III NM (skilled non-manual) 19% (17); III M (skilled manual) 20% (18); IV & V (semiskilled/unskilled) 11% (10); and VI (unemployed) 13% (12). The results of a preceding pilot study, based on the same clinic population, were used for guidance regarding the sample size and its demographic composition. Of the 113 children approached, 94 (83%) agreed to take part in the study. The present analyses are based on 90 subjects who produced satisfactory asthma diary recordings and participated in all interviews over the duration of the study.

Severity of asthma

All the children had suffered from episodic asthma for a minimum of 3 y, and from continuing asthma diagnosed by a doctor in the year preceding the start of the study. All were taking prophylactic therapy with inhaled cortico-steroids, together with intermittently or regularly administered bronchodilators. A specialist respiratory consultant (JYP) supervised the asthma care of every child throughout the study. Prophylactic therapy was constantly reviewed to ensure that it was at the minimum level consistent with good control of asthma symptoms. The severity of the asthma, rated on a six-point scale from 1 to 5b (based on the British Thoracic Society's (BTS) management steps) (16), according to prescribed medication over the previous year, was scored as 3 (mild to moderate) in 35 cases, 4 (moderate to severe) in 29, and 5 (severe; collapsing original categories 5a and 5b because of small numbers) in 26 patients.

Measurement of life experiences

The Psychosocial Assessment of Childhood Experiences (PACE) (14, 17), a systematic interview-based instrument of proven reliability and validity, was used to assess the timing of occurrence, nature and impact of discrete life events and long-term psychosocial experiences. Best-estimated life events (combining information from each child and parent interview) that were either severely negative or markedly positive, and long-term experiences with either highly negative or highly positive impacts on the child were used. All life events and long-term experiences relating to the child's asthma were rigorously excluded in the assessment. The PACE was administered on three occasions: at baseline (covering the previous year), at 9 mo and at 18 mo

(with the preceding 9-mo period being considered on each occasion).

A severely negative life event was defined as an event that carried a high degree of long-term contextual threat, i.e. the level of threat caused or implied by the life event to an average child of the same age, sex and biographical characteristics as the child in question. Conversely, a positive life event was defined as an event scoring high on the scale of long-term contextual positive impact, meaning that it either brought with it an enhancement of self-esteem or an improvement in the child's life circumstances—again, taking the child's personal life history and situation into account. In addition, long-term psychosocial experiences, as present at the start of the study, were included if they had a high rating for a direct, negative or positive impact on the child. High chronic stress was defined as four or more (1 SD above the group mean) negative long-term experiences, while positive long-term experiences were simply termed as present or absent.

Severely negative events usually involved the loss of someone the child was close to (e.g. a parent, through separation, a grandparent, through death), or loss of one's sense of security (e.g. break-up of the home through divorce). The main sources of chronic stress included long-lasting illness (physical or mental illness, including substance misuse) of a close family member, marital or other family discord, a major shortfall in parenting, inadequate living conditions, and school-related stress, such as being bullied. The main positive events included receiving valued presents, joining clubs (offering a chance to participate in a desired activity and gaining new friends), or winning prizes, while the long-term positive experiences nearly always involved being a member of a sports team, or participating in some other absorbing hobby.

Monitoring of asthma

The children continuously monitored the course of their asthma by (often with the help of a parent) completing twice-daily peak flow recordings and weekly diaries reporting symptoms. The respiratory consultant (JYP) reviewed the diaries at scheduled visits to the clinic, which took place at least every 3 mo. During the visit, the old diary was collected and a new one issued. For each subject, the peak flow results were transcribed onto a spreadsheet and plotted electronically using cusum plots (18–19) to highlight falls in the peak flow. Acute asthma exacerbation was defined as a documented increase in symptoms combined with a fall in peak flow (the mean of the day's two readings) below 70% of the child's normal value.

Missing asthma data

Of the 90 children included in the study, 48 (53%) had complete records of peak flow data, while the remaining 42 children (47%) had some gaps in their diaries. The

total number of weeks in the returned diary booklets was 8130. Of these, 720 (8.9%) contained missing data. The total length of time with missing data per child varied from just 1 wk (one child) to 52 wk (one child), with the individual periods with no recordings varying between 1 wk and 36 wk. The periods of time with missing peak flow recordings were excluded from the data analyses.

Statistical methods

A dynamic logistic regression model was constructed in which the child's observation time was analysed in 2-wk periods by recording the values of the determinants for each period separately. The choice of a 2-wk time span was supported by the definitions of a severe and positive life event (with contextual threat and contextual positive impact judged at 10 to 14 d after the date of the event), and by the fact that the mean duration of asthma exacerbation was 9 d. Only those 2-w periods with no missing peak flow data were included in the analyses.

The logits of the 2-wk risk of exacerbation of asthma were then dynamically modelled using a linear predictor, describing the child's observed history up to the period under consideration and including main effect and relevant interaction terms for the child's determinants (20–22). The determinants were either fixed (age, gender, social class, baseline asthma severity, parental smoking, chronic stress and positive long-term experiences), or time dependent (severe and positive life events in the previous 6 wk, season and asthma history).

To detect the protective influence of previous positive life events against the risk caused by negative influence, interactions between these determinants were considered. A global test for interaction was constructed assuming that the protective influence of a positive life event is constant over the 6-wk time span. The estimated baseline odds and odds ratios (OR) with 95% confidence intervals (CI) were derived with the SAS software package (SAS Institute, Inc., Cary, North Carolina, USA). See the *Lancet* website (www.thelancet.com/Sandberg et al. 2000) for a detailed description, including a diagram clarifying the model used.

Results

New exacerbations, negative and positive life experiences and their associations

The mean length of observation time (date between the first and last recorded peak flow) was 620 d (range 314–757, SD 73.8). A total of 427 new asthma exacerbations occurred (mean number 4.7; mean duration 9 d), ranging from none (10 children) to 21 (1 child). In 80% of patients (340) the exacerbation, based on child-recorded data, was confirmed by clinical data; 11% (50) of the exacerbations resulted in the child being admitted to hospital.

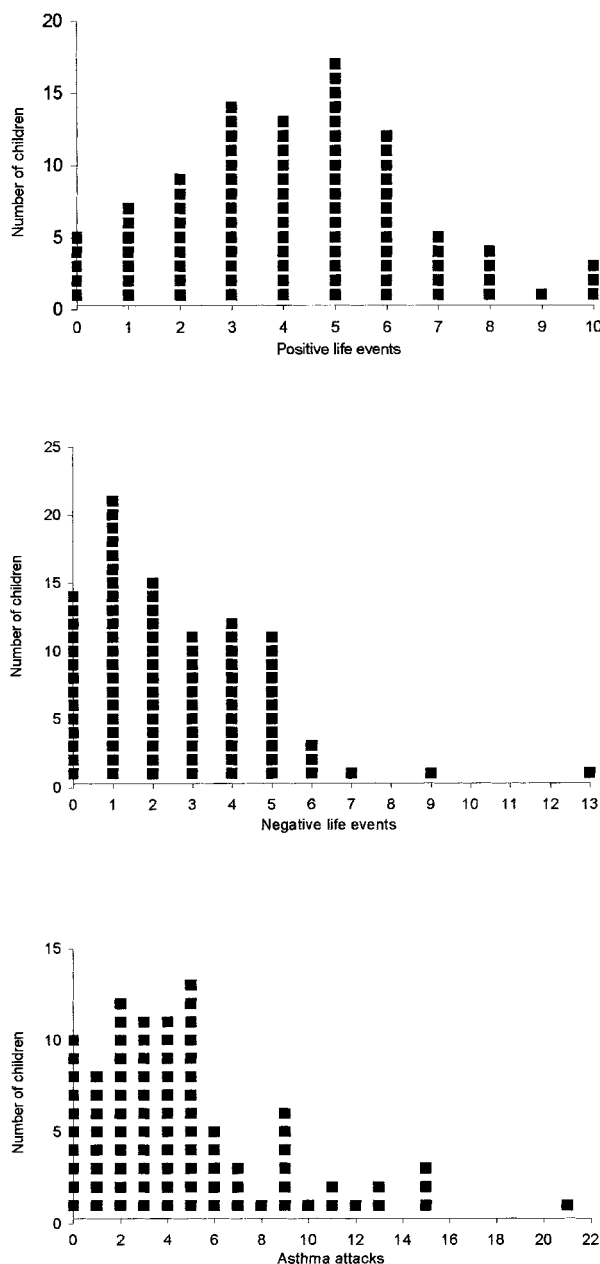


Fig. 1. Distributions of positive life events, negative life events, and asthma exacerbations according to the number of children involved in each case.

The total number of positive life events was 382 (mean 4.2), ranging from none (5 children) to 10 (3 children); of severe life events 234 (mean 2.6), ranging from none (14 children) to 13 (1 child); of positive long-term experiences 100 (mean 1.1), ranging from none to 3 (the numbers of children with 0, 1, 2 and 3 positive long-term experiences were 29, 31, 21 and 9, respectively); and of negative long-term experiences 178 (mean 2.0), ranging from none (24 children) to 8 (1

child). The distributions of asthma exacerbations and positive and severely negative life events according to the number of children affected are presented in Fig. 1.

Children with a higher number of positive life events also had more positive long-term experiences (mean number of positive events was 3.2 and 4.7 in children without and with at least one positive long-term experience, respectively), whereas there was no association between severely negative life events and chronic stress (mean number of severe events 2.7 and 2.6 in children with and without high chronic stress, respectively). Contrary to expectations, there was also an association, albeit a weak one, between severely negative life events and positive life events (50 children with fewer than the mean number (3.0) of severe events also had on average fewer (mean 3.9) positive life events, compared with 40 children with more than three severe events and an average of 4.7 positive events ($\chi^2 = 3.4$, $p = 0.07$)). The same, however, did not hold for long-term experiences. Children exposed to high chronic stress were more likely to have no positive long-term experiences compared with those experiencing low to moderate levels of chronic stress (means of positive long-term experiences .7 and 1.2 respectively; $\chi^2 = 1.9$, $p = .17$). The discrepancy was greatest in relation to more than one positive long-term experience: only 3 (15%) of the 20 children exposed to high chronic stress had two or more such positive experiences compared with 38% of the 70 children with low to medium chronic stress. The three most common types of positive life events were associated with hobbies, school, or much-desired gifts, regardless of whether the child lived in conditions of low to moderate or high chronic stress (the respective proportions of all positive events being 37%, 22% and 31%, respectively, in the former, and 20%, 10% and 30%, respectively, in the latter group).

When the 42 children with missing peak flow data were compared with the 48 without any missing values, no statistically significant differences (using the χ^2 test) were found between the two groups regarding mean number of severe events (2.7 and 2.5, respectively), positive events (4.4 and 4.0, respectively), chronic stress (means of 2.2 and 1.8, respectively), or in relation to positive long-term experiences (means of 1.1 in both instances). Nor did the two groups differ regarding the likelihood of an acute asthma exacerbation during any 2-wk period (values of .14 and .11, respectively).

Effect of positive life experiences on the risk caused by adverse experiences

The increased risk of a new asthma exacerbation following a severely negative event was in most instances affected by the presence of a positive life event in the preceding 6 wk (Table 1). Positive life events successfully cancelled the increased risk in children with low to medium chronic stress, but failed

Table 1. Odds ratio estimates for new asthma attacks associated with previous severe life events (with delays of 0–2 wk, 2–4 wk, and 4–6 wk). Odds ratio estimates were adjusted using the dynamic logistic regression model and are listed separately in four groups (high chronic stress vs low/medium chronic stress; positive life event vs no positive life events). In the low/medium chronic stress group, a positive event seems to reduce the effect of a negative event ($p = 0.01$, using a global test for interaction); this is not the case in the high chronic stress group ($p = 0.36$).

	Low/medium chronic stress				High chronic stress			
	No positive event		Positive event		No positive event		Positive event	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Severe event vs no severe event								
In previous 2 wk	0.79	0.41–1.52	0.45	0.20–1.03	3.51	1.26–9.77	2.58	0.82–8.08
2–4 wk earlier	2.21	1.30–3.76	1.09	0.54–2.24	0.90	0.24–3.41	0.68	0.15–3.18
4–6 wk earlier	2.87	1.68–4.90	1.42	0.71–2.85	0.56	0.14–2.23	0.45	0.10–1.96

to do so in the minority of children living in conditions of high chronic stress.

When there was no immediately preceding positive life event and the level of chronic stress was low to medium, severely negative events significantly increased the likelihood of an exacerbation from the 3rd to the 6th week following the events (ORs of 2.21 [95% CI 1.30–3.76], $p \leq 0.01$, and 2.87 [95% CI 1.68–4.90], $p \leq 0.01$ for the 2–4 and 4–6 wk, respectively), after which they had no effect. Positive life events occurring within the preceding 6 wk (either just before or just after the severe life event) significantly reduced the risk of a new exacerbation (Table 1). Positive events taking place at other times, however, did not affect the risk.

The risk of an acute exacerbation increased even further when severe events occurred against the backdrop of high chronic stress and were not accompanied by a positive life event. Furthermore, in this case, the rise in risk took place almost immediately, within the first 2 wk following a severe event (OR of 3.51 [95% CI 1.26–9.77], $p \leq 0.02$). However, in this context, positive life events in the preceding 6-wk period caused only a small and statistically insignificant reduction in risk (Table 1).

The possible protective role of positive long-term experiences (usually consisting of absorbing interests and rewarding hobbies) versus the detrimental effects of negative life experiences (severe events and chronic stress) was investigated by adding them to the model. Their presence or absence, however, did not affect the risk of new exacerbations once the effects of severely negative life events, chronic stress and positive events were taken into account (OR of 0.88 [95% CI 0.67–1.16], $p = 0.17$). It would, of course, have been ideal to examine the effect of severe events on risk under each of the possible eight conditions determined by presence/absence of high chronic stress, positive long-term experiences and positive life events. However, owing to the small number of children in the high chronic stress group, such a division would hardly have produced reliable results.

Discussion

We have shown (8) that severely negative life events significantly increase the likelihood of an acute asthma exacerbation in the subsequent 6 wk. By way of contrast, this study focuses specifically on the impact of positive life events and positive long-term experiences. The data presented here indicate that, allowing for the baseline asthma severity, positive life events, provided they occur in close proximity to the negative ones and there is no exposure to high chronic stress, can counteract the increased exacerbation risk associated with negative events. However, this protective effect applies only when positive events either closely precede or follow the negative ones. Neither positive events taking place at other times nor positive long-term experiences, such as having an absorbing hobby, appear similarly capable of modifying the risk stemming from negative experiences.

Role of positive life events in stress asthma relationship

The findings presented here further strengthen the likely importance of stress on the course of childhood asthma, and also indicate that positive life events can in some situations protect against the effects of stress. It is generally held that the nature of most negative life events make them difficult to predict, and therefore difficult to avoid. This was also largely the case in our study where children who were not exposed to high chronic stress were concerned. Among these children, as in previous studies, the majority of severely negative life events were unpredictable and frequently involved loss, such as in parental separation, the death of a grandparent, or when a close friend's family moved away. Similarly, the few weeks' delay between a negative life event and the increase in risk is in keeping with previous findings.

The relatively small number of children living in conditions of high chronic stress differed from the others not only in the degree, but also the types of chronic adversities experienced. On average, they had

five times the rate of poverty/poor housing, physical infirmity/psychiatric illness/alcohol dependence of a parent, family discord and school-related problems, compared with the remaining children. Their situation was further compromised by parental hostility/indifference and peer hostility/rejection, adversities that hardly ever occurred where there was no high chronic stress. Furthermore, in this group, the severely negative events immediately preceding an asthma exacerbation mostly arose directly from an existing chronic adversity that in half the cases was a family-based problem.

Possible explanations

Given the dissimilar nature and level of adversity that children with and without high chronic stress suffered, it is perhaps not unexpected that the protective effect of positive life events was also very different, with positive events ameliorating the impact of the negative ones only where there was no high chronic stress. The reasons for this may lie partly in the interconnections between chronic stress and positive life events. Unlike the negative events, positive events were usually brought about by the child's own behaviour, albeit often with parental support. Nearly half of the positive events were related to achievements in the child's pastime activities, and a quarter involved gifts (such as a bicycle or sports equipment, for instance) that enabled the child to pursue an interest, or to participate in a shared activity with his/her peers. The likely mechanism by which an event exerted its positive effect might therefore be through an enhancement of the child's self esteem, or sense of self-worth. It is also conceivable that children living under conditions of high chronic stress, some of it stemming from lack of parental guidance and support, and often associated with other forms of social disadvantage, had fewer opportunities to experience positive events in the first place. Even if they managed to achieve something through their own actions, the impact of their achievements was simply insufficient to offset the effects of high chronic stress.

Implications

How these findings might be used in the care of children suffering from chronic asthma deserves some consideration. Here, two separate issues are raised. The first relates to the rather pernicious role of multiple chronic stressors, usually stemming from the child's immediate living environment, and enhancing the risk caused by negative life events, as well as making the risk less modifiable by positive life events. The other concerns possible opportunities for children to experience positive life events, in the hope that these might help to offset the detrimental effects of the unpredictable negative events that most children are likely to experience at some point in their lives. Although this makes some sense from the viewpoint of likely mechanisms (e.g. the effects of stress on the body's immune

responses) (23), the fact that only those positive life events closely associated with negative life events had a protective role is more difficult to translate into practical advice. But, of course, it is probable that a child exposed to a range of positive experiences has more chance of experiencing positive life events at a time when they may coincide with a stressful life event.

Given that a large proportion of children's positive life events relate to their interests and hobbies, it is worth noting that positive experiences such as having an absorbing interest or a rewarding hobby do not in themselves have a protective function. For this to be so, a child engaged in such interests must also have a chance to achieve something in them. However, just encouraging children who suffer from asthma to join clubs, etc., in the hope that this will result in self-esteem-enhancing accomplishments is not necessarily the answer. Indeed, many children in our study had joined several sports clubs and other pastime activities, which they were then forced to leave with a sense of disappointment, either because the challenges were too great for their health, or because of a lack of parental support.

Finally, the results also indicate the need for heightened sensitivity to the needs of those children with asthma who also live under conditions of high chronic stress. As the child's experience of chronic stress is mostly in the home and in school, more help should be offered to these children and their families by persons they come in contact with in the educational, social and medical welfare services.

Acknowledgements.—This study was supported by the Medical Research Council, UK (grant G9102413N) and the Academy of Finland (grant 41224). We express our gratitude to both of these organizations. We are also indebted to the children and their parents for their generous cooperation in the study and thank Dr Clive R. Hillary for his valuable contribution during the data-gathering stage.

References

1. Grey M. Stressors and children's health. *J Pediatr Nurs* 1993; 8: 85–91
2. Haavet OR, Grünfeld B. Are life experiences of children significant for the development of somatic disease? A literature review. *Tidsskr Nor Lægeforen* 1997; 117: 3644–7
3. Turner Cobb JM, Steptoe A. Psychosocial influences on upper respiratory infections in children. *J Psychosom Res* 1998; 45: 319–30
4. Mrazek DA, Klinnert M, Mrazek PJ, Bower A, McCormick D, Rubin B, et al. Prediction of early-onset asthma in genetically at-risk children. *Pediatr Pulmonol* 1999; 27: 85–94
5. Randolph C, Fraser B. Stressors and concerns in teen asthma. *Curr Probl Pediatr* 1999; 29: 82–93
6. Wade S, Weil C, Holden G, Mitchell H, Evans R, III, Kruszon-Moran D, et al. Psychosocial characteristics of inner-city children with asthma: a description of the NCICAS psychosocial protocol. National Cooperative Inner-City Asthma Study. *Pediatr Pulmonol* 1997; 24: 263–76
7. Mishoe SC, Baker RR, Poole S, Harrell LM, Arant CB, Rupp NT. Development of an instrument to assess stress levels and quality of life in children with asthma. *J Asthma* 1998; 35: 553–63

8. Sandberg S, Paton JY, Ahola S, McCann DC, McGuinness D, Hillary CR, et al. The role of acute and chronic stress in asthma attacks in children. *Lancet* 2000; 356: 982–7
9. Goodyer IM. Life experiences, development and childhood psychopathology. Wiley: Chichester, 1990
10. Liakopoulou M, Alifieraki T, Katideniou A, Kakourou T, Tselalidou E, Tsiantis J, et al. Children with alopecia areata: Psychiatric symptomatology and life events. *J Am Acad Child Adolesc Psychiatry* 1997; 36: 678–84
11. Reeve EA, Savage TA, Bernstein GA. Psychiatric diagnoses in children with alopecia areata. *J Am Acad Child Adolesc Psychiatry* 1996; 35: 1518–22
12. Caputo JL, Rudolph DL, Morgan DW. Influence of positive life events on blood pressure in adolescents. *J Behav Med* 1998; 21: 115–29
13. Goodyer IM, Wright C, Altham P. Recent achievements and adversities in anxious and depressed school-age children. *J Child Psychol Psychiatry* 1990; 31: 1063–77
14. Sandberg S, Rutter M, Giles S, Owen A, Champion L, Nicholls J, et al. Assessment of psychosocial experiences in childhood: methodological issues and some illustrative findings. *J Child Psychol Psychiatry* 1993; 34: 879–97
15. Office of Population Censuses and Surveys. Classification of occupations. HMSO: London, 1980
16. British Thoracic Society. Guidelines on the management of asthma in children. *Thorax* 1993; 48S: 1–24
17. Glen S, Simpson A, McGuinness D, Drinnan D, Sandberg S. Testing the reliability of a new measure of life events and experiences in childhood: The Psychosocial Assessment of Childhood Experiences (PACE). *Eur Child Adolesc Psychiat* 1993; 2: 98–110
18. Kinsey SE, Giles FJ, Holton J. Cusum plotting of temperature charts for assessing antimicrobial treatment in neutropenic patients. *Br Med J* 1989; 299: 775–6
19. Wohl H. The cusum plot: its utility in the analysis of clinical data. *N Engl J Med* 1977; 296: 1044–5
20. Alho OP, Läärä E, Oja H. How should relative risk estimates for acute otitis media in children under 2 years be perceived? *J Clin Epidemiol* 1996; 49: 9–14
21. Bonney GE. Logistic regression for dependent binary observations. *Biometrics* 1987; 43: 951–73
22. Oja H, Alho OP, Läärä E. Model-based estimation of the excess fraction (attributable fraction): day care and middle ear infection. *Stat Med* 1996; 15: 1519–34
23. Boyce WT, Chesney M, Alkon A, Tschann JM, Adams S, Chesteman B, et al. Psychologic reactivity to stress and childhood respiratory illness: results of two prospective studies. *Psychosom Med* 1995; 57: 411–22

Received June 25, 2001; revision received Oct. 23, 2001; accepted Nov. 15, 2001