Association of Small Life Events With Self Reports of Tic Severity in Pediatric and Adult Tic Disorder Patients: A Prospective Longitudinal Study

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Background: Clinical experience suggests an association between stressful life events and fluctuations in symptom severity of tic disorder patients. The aim of the present study was to examine this possible relationship in a prospective longitudinal design.

Method: Two groups of patients with tic disorder according to the research criteria of the Tourette Syndrome Classification Study Group were included in this study (Sept. 2001 through March 2002): a pediatric group aged from 7 through 16 years (N = 25) and an adult group aged 18 years and older (N = 32). During a 12-week period, participants were asked weekly to fill out questionnaires regarding the occurrence of small life events and self ratings of tic severity.

Results: Twenty-four of 25 patients in the pediatric group completed the study, and 28 of 32 patients in the adult group completed the study and reported at least 1 life event. In the adult group as a whole, we found a weak but statistically significant correlation between negative small life events and tic severity during the same week ($r = 0.268$, $p < .001$). However, only a minority of individual pediatric (21%) and adult (18%) patients demonstrated significant relationships between the frequency of small life events and tic severity in the same week or 1 week later ($p \leq .05$), with undesirable small life events positively associated with tic severity in some patients and negatively associated with tic severity in other patients.

Conclusion: Contrary to traditional views, in general, life events do not account for changes in tic severity. Only in a minority of tic disorder patients do fluctuations in symptom severity appear to be associated with possibly stressful small life events.

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Symptoms of tic disorders typically show a pattern of waxing and waning severity over the course of time.[1] Clinical experience suggests that this fluctuation in symptom severity may be related to stressful life events, such as interpersonal conflicts, financial problems, and problems associated with work. There is a surprising lack of research on the role of stress in tic disorders. One study involving children and adolescents with Tourette's disorder identified events causing anxiety, emotional trauma, and social gatherings as associated with an increase in tics.[2] That study was based on the subjective experience of patients reported in a cross-sectional retrospective questionnaire. Previously, in a similar approach involving a larger series of patients, Shapiro and coworkers[3] had identified that, according to the patients' own impression, tics tend to increase with certain environmental factors, such as anxiety and agitation, and tend to decrease with other factors, most notably nonanxious absorption in a task and the presence of strangers. In addition, a recent study investigated the role of psychosocial stress at 2 timepoints separated by 4 months in a cohort of children and adolescents with Tourette's disorder and/or obsessive-compulsive disorder.[4] It demonstrated that patients with Tourette's disorder and/or obsessive-compulsive disorder experienced significantly more psychosocial stress than did age-matched healthy controls. Moreover, that study found that symptom severity correlated with severity of experienced daily life stressors but not with indices of major life events. No other prospective, longitudinal data are available with regard to a possible association of stressful life events and tic symptom fluctuations.

Evidence for links between psychosocial stress and symptom fluctuations has repeatedly been found for a broad range of disorders, particularly infectious[5,6] and autoimmune conditions.[7] The best predictors of changes in symptom severity have consistently been relatively frequent small irritants of daily life, generally referred to as daily hassles.[8] Examples include arguments with friends, being criticized or having problems with (school)work, or being confronted with unexpected financial burdens.

The Inventory of Small Life Events (ISLE) is one well-known and well-validated diary-type scale in which the occurrence of such concrete small life events

can be scored.[9] It covers events in major areas of life, that is, family, work, leisure, household, financial state, health/illness, nonfamily relations, crime/criminal activity, education, religion, and transportation. A children's version, the Small Events Inventory-Child Reports, is also available.[10]

We used these scales in a pediatric and an adult cohort of tic disorder patients to investigate the possible relationship between weekly reports of small life events and self-ratings of tic severity in a prospective longitudinal design over a period of 12 weeks. Our hypothesis was that there would be a correlation between small stressful life events and changes in tic severity over time.

METHOD

Subjects

Two groups of tic disorder patients were included in this study—that is, a pediatric group of patients aged from 7 through 16 years and an adult group aged 18 years and older.

All patients with a tic disorder could enter the study only if they fulfilled the research criteria for a definite tic disorder according to the Tourette Syndrome Classification Study Group.[11] These criteria require observable tics to be present during the clinical interview to allow for study entry, ensuring the inclusion of patients objectively demonstrating tics. Excluded from the study were subjects with a known IQ below 70. None of the subjects who were willing to participate in the study fulfilled this exclusion criterion. Presence of comorbid diagnoses, which we did not record systematically, was not a criterion for exclusion.

The tic disorder patients were recruited from the outpatient clinic of the Child and Adolescent Psychiatry Center, Groningen, the Netherlands, or from the Dutch Tourette Syndrome patient's association. Subjects were initially recruited by letters sent to a number of patients at our center with a known clinical diagnosis of a tic disorder and to members of the patient's association. From our child and adolescent psychiatry center, 35% of approached patients were initially interested to participate. The aim and procedure of the study were fully explained to the subjects before written consent was requested. If the subjects were under the age of 18 years, the parents were informed as well, and the written informed consent of the parents and the subject's assent were obtained. Patients were informed that we intended to study the relationship between small life events and changes in tic severity over time. However, we did not explicitly reveal the specific study hypothesis. The study was approved by the Dutch central medical-ethical committee. To assess tic severity at study entry, we used the motor and vocal scores of the Yale Global Tic Severity Scale (YGTSS), which records tic severity over the past week.[12] The sum of both scores was used as a measure of total tic severity. We decided not to use the impairment rating of the YGTSS in order to minimize possible confounding with stress ratings, since the impairment ratings may partially reflect perceived psychosocial stress. Diagnostic assessment and rating of tic severity were performed by 1 of 2 authors (either P.J.H. or M.P.S.) experienced in the diagnosis of tic disorders.

Twenty-five tic disorder patients entered the pediatric study group: 17 from the patient's association and 8 from our outpatient center. All patients from the patient's association had in the past been referred to a mental health service. The adult group of tic disorder patients consisted of 32 patients: 24 from the patient's association and 8 from our outpatient center. Again, all patients from the patient's association had in the past been referred to a mental health service. Table 1 shows demographic data, tic severity, and medication status at study entry of both patient groups.

Table 1. Characteristics of Pediatric and Adult Patients With Tic Disorder at Study Entry

Characteristic	Pediatric Group (N = 25)	Adult Group (N = 32)
Age, mean (SD), y	13.0 (2.7)	36.1 (14.6)
Range	7–16	18–64
Gender, N (%)		
Male	19 (76.0)	20 (62.5)
Female	6 (24.0)	12 (37.5)
Medication status, N (%)		
None	11 (44.0)	18 (56.3)
Clonidine	3 (12.0)	0
Clonidine + neuroleptic	2 (8.0)	0
Neuroleptic	9 (36.0)	11 (34.4)
Antidepressant	0	3 (9.4)
Symptom severity[a]		
Motor tics score		
Mean (SD)	12.6 (5.7)	14.4 (3.8)
Range	4–25	9–25
Vocal tics score		
Mean (SD)	5.6 (5.8)	9.0 (6.4)
Range	0–25	0–25
Total score		
Mean (SD)	18.2 (9.1)	23.4 (8.4)
Range	8–50	10–50

[a]According to the Yale Global Tic Severity Scale.

Procedure

During 12 consecutive weeks, on a chosen fixed day of each week, participants were asked to fill out a questionnaire created for this study. On this questionnaire, both pediatric and adult participants were asked to rate the weekly severity of their tics on a 10-point scale in which 0 represents no tics, 1 represents minimal tics, and 10 represents the worst tics ever. When participants were children, parents were allowed to assist the children in filling out the questionnaire. However, parents and children were instructed that the child's judgment should form the basis of the scores.

In addition, for pediatric patients, the questionnaire contained a Dutch translation of the Small Events

Inventory-Child Reports.[10] This scale contains 41 different everyday events that are meaningful indicators of the level of stress in the child's life as well as indicators of positive transactions between the child and the social world. There are 29 desirable items on the scale, whereas the remaining 12 items are undesirable events. Respondents were asked to indicate whether each event happened once, twice, 3 times, more than 3 times, or not at all during the preceding week.

The weekly questionnaire for the adult participants contained a Dutch translation of the undesirable items of the ISLE,[9] a total of 46 possible undesirable events covering all major domains of everyday life. We did not include desirable events in the adult ISLE because we wanted to keep the list short to increase response rates and reliability since the adult ISLE contains far more items than the pediatric version. Like the pediatric patients, adult respondents were asked to indicate whether each event happened once, twice, 3 times, more than 3 times, or not at all during the preceding week.

Finally, both pediatric and adult patients were asked to record any change in psychotropic medication regimen. We did not ask the reasons for change in medication. All questionnaires were to be mailed to us in stamped envelopes on a weekly basis.

Statistical Analysis

For the pediatric group, weekly scores of desirable events and undesirable events, respectively, were computed by adding up all reported frequencies, with a response of "more than 3 times" counted as 4 times. The same was done with regard to weekly scores of undesirable small life events for the adult patients. For each participant, Pearson correlation coefficients were computed between weekly scores of events and weekly ratings of tic severity. In addition, we computed Pearson correlation coefficients between weekly scores of events and weekly ratings of tic severity for the pediatric group and adult group as a whole. For the latter analyses, we used z scores of tic severity and small life events scores. These z scores were based on each individual's ratings across the 12-week study period. Also, we performed the same correlation analyses between tic severity and life events score of the preceding week. To investigate whether there is an association between the initial level of tic severity, as rated by the clinician, and frequency of small life events, we computed Pearson correlation coefficients between YGTSS measures and first-week small life events scores, in both the pediatric and the adult group. Also, in both study groups, we looked for an overall relationship between the patients' average number of undesirable and, in the case of the pediatric patients, desirable life events and the average subjective tic severity over the study period, again using Pearson correlation coefficients. In addition, Pearson correlation coefficients were computed for both patient groups between the total YGTSS baseline scores and the subjective tic severity ratings from the same week to get preliminary data on the validity of the subjective ratings. Finally, to rule out medication effects, in both the pediatric and adult patient groups, we used the paired-sample t test to test for possible differences in subjective tic severity in the week in which the medication was changed and subjective tic severity 1, 2, 3, and 4 weeks later. Patients were part of the analyses only when they participated for more than 2 weeks and reported at least 1 small life event during the study period. Two-tailed p values less than .05 were considered significant.

RESULTS

Response Rate

The pediatric group returned a total of 241 questionnaires for a response rate of 80.3%. One pediatric patient decided to withdraw from the study after 1 week. Without this patient, the response rate was 83.3%. The adult patient group returned a total of 317 questionnaires for an overall response rate of 82.6%. One adult patient decided to withdraw after 1 study week, and another adult patient withdrew after 2 weeks. Without these patients, the response rate of the adult patient group was 87.2%. Finally, the response rate of the 28 adult patients (290 questionnaires returned) who were part of the statistical analyses was 86.3% (2 adult patients reported no undesirable life events over the entire study period and were removed from the analyses).

Subjective Tic Severity Ratings

The mean subjective tic severity for the pediatric group was 5.1 (SD = 2.4; range, 1–10). For the pediatric group, the mean difference between the highest and lowest subjective tic severity rating for each individual over the 12-week period was 4.0 (SD = 1.4; range, 1–8). The mean subjective tic severity for the adult group was 6.0 (SD = 1.9; range, 1–10). For the adult group, the mean difference between the highest and lowest subjective tic severity rating for each individual over the 12-week period was 3.5 (SD = 1.6; range, 0–7). Finally, we identified significant correlations between the total YGTSS baseline scores and the subjective tic severity ratings from the same week in both the pediatric ($r = 0.599$, $p = .002$) and the adult patient groups ($r = 0.503$, $p = .006$).

Small Life Events Scores

The mean weekly rating of desirable small life events in the pediatric group was 32.2 (SD = 18.2; range, 0–81), whereas the mean weekly rating of undesirable small life events in the pediatric group was 2.9 (SD = 3.9; range, 0–20). In the pediatric group, the mean difference between the highest and lowest weekly desirable small life events frequency rating for each individual over the

12-week period was 31.3 (SD = 16.1; range, 5–70) versus a mean difference between the highest and lowest weekly undesirable small life events frequency of 7.3 (SD = 4.5; range, 2–20). The first week's desirable life events score demonstrated a significant inverse correlation with the baseline vocal (r = –0.437, p = .029) and total (r = –0.447, p = .025) tic scores but not with motor tic scores (r = –0.342, p = .095). No such significant or nearly significant correlations were found between the first week's undesirable life events scores and baseline indices of tic severity.

In the adult group, the mean weekly rating of undesirable small life events was 6.6 (SD = 7.8; range, 0–78). Two adult patients reported no undesirable small life events over the entire study period, and 2 other subjects participated for no more than 2 weeks. One of the 2 latter subjects reported a high number of undesirable life events regarding the only week of participation. Without these 4 subjects, the mean weekly rating of undesirable small life events in the adult group was 6.9 (SD = 6.7; range, 0–35). For the adult group without the aforementioned 4 subjects, the mean difference between the highest and lowest weekly undesirable small life events frequency rating for each individual over the 12-week period was 11.9 (SD = 7.8; range, 2–35). In the adult group, no significant or nearly significant correlations were found between first-week undesirable life events scores and baseline indices of tic severity.

Changes in Medication

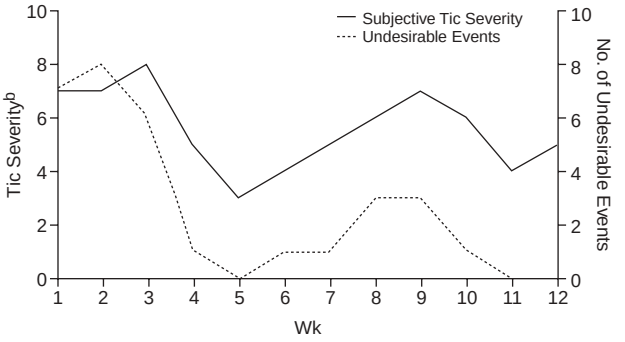
In the pediatric group, participants reported 19 changes in their use of psychotropic medication, or in 8.1% of all weekly ratings. In the adult group, a change was reported 38 times, or in 12.6% of all weekly ratings. In both the pediatric and the adult patient groups, no statistically significant relationship was found between subjective tic severity during the week in which the medication was changed and subjective tic severity 1, 2, 3, and 4 weeks later (paired sample t tests).

Association Between Subjective Tic Severity and Small Life Events

Of 24 pediatric patients who returned more than 2 questionnaires, 19 (79%) showed no statistically significant correlation between weekly ratings of tic severity and weekly frequencies of desirable small life events or weekly ratings of undesirable life events during the same week or 1 week earlier. Of the remaining 5 pediatric patients (21% of the total group), 2 showed a significant relationship between tic severity and desirable events during the same week, albeit in opposite directions (r = –0.723, p = .008 and r = 0.781, p = .022), 1 patient showed a negative relationship between 1-week–lagged desirable events and tic severity (r = –0.535, p = .022), and another patient showed a significant positive relationship between 1-week–lagged undesirable events and tic severity (r = 0.607, p = .048). Finally, 1 pediatric patient showed a positive correlation between desirable life events and tic severity during the same week (r = 0.720, p = .044) as well as a negative correlation between tic severity and 1-week–lagged undesirable life events (r = –0.811, p = .027). In the pediatric group as a whole, no statistically significant correlation was found between weekly ratings of tic severity and weekly frequencies of desirable small life events or weekly ratings of undesirable life events. Also, no statistically significant correlation was found between weekly ratings of tic severity and weekly frequencies of desirable small life events or weekly ratings of undesirable life events 1 week earlier. Finally, no overall relationship was identified between the pediatric patients' average subjective tic severity over the study period and their average number of encountered undesirable (r = 0.229, p = .282) and desirable small life events (r = 0.099, p = .645).

Of the 28 adult patients who participated in the study for longer than 2 weeks and who reported at least 1 undesirable life event over the 12-week study period, 23 (82%) did not show any statistically significant correlation between weekly ratings of tic severity and weekly frequencies of undesirable small life events during the same week or 1 week earlier. Of the remaining 5 adult patients (18% of the total group), only 1 subject showed a significant relationship between tic severity and undesirable life events during the same week (r = 0.818, p = .001). This same patient also showed a significant positive correlation between tic severity and 1-week–lagged undesirable life events (r = 0.781, p = .005). Figure 1 shows the course of tic severity and number of undesirable small life events of this particular patient. The 4 remaining patients all showed a significant correlation between tic severity

Figure 1. Course of Tic Severity and Number of Experienced Undesirable Small Life Events in an Individual Adult Patient[a]



[a]Patient showed a significant relationship between tic severity and undesirable life events during the same week (r = 0.818, p = .001) and between tic severity and 1-week–lagged undesirable life events (r = 0.781, p = .005).
[b]10-point scale in which 0 = no tics, 1 = minimal tics, and 10 = the worst tics ever.

Table 2. Summary of Study Findings for Subjects With Tic Disorder Who Participated for More Than 2 Weeks and Reported at Least 1 Life Event During the Study Period

Variable	Pediatric Group N = 24	Adult Group N = 28
Questionnaires returned, N (%)	240 (83.3)	290 (86.3)
Subjective tic severity		
Mean (SD)	5.1 (2.4)	6.0 (1.9)*
Range	1–10	1–10
Weekly no. desirable events		
Mean (SD)	32.2 (18.2)	NA
Range	0–81	NA
Weekly no. undesirable events		
Mean (SD)	2.9 (3.9)	6.9 (6.7)*
Range	0–20	0–35
No relationship with small life events, N (%)	19 (79.2)	23 (82.1)
Relationship with undesirable events, N (%)	1 (4.2)	5 (17.9)
Relationship with desirable events, N (%)	3 (12.5)	NA
Relationship with both undesirable and desirable events, N (%)	1 (4.2)	NA

*$r = 0.268$, $p < .001$ for association between tic severity and number of undesirable small life events within the same week.
Abbreviation: NA = not available.

and 1-week–lagged undesirable small life events, with 2 patients demonstrating a negative correlation ($r = –.796$, $p = .006$ and $r = –0.843$, $p = .002$) and 2 patients showing a positive correlation ($r = 0.964$, $p = .036$ and $r = 0.605$, $p = .049$). In the adult group as a whole, we found a small but statistically significant correlation between undesirable small life events and tic severity during the same week ($r = 0.268$, $p < .001$). In the adult group as a whole, no statistically significant correlation was found between weekly ratings of tic severity and weekly frequencies of undesirable life events 1 week earlier. Finally, no overall relationship was identified between the adult patients' average subjective tic severity over the study period and their average number of encountered undesirable small life events ($r = –0.284$, $p = .143$). Table 2 gives a summary of the main study findings.

DISCUSSION

Tics have traditionally been considered stress-sensitive phenomena.[13] Indeed, in the adult group but not in the pediatric study group, we found a weak but statistically significant correlation between undesirable small life events and changes in tic severity. The results of correlation analyses within individuals, however, indicate that only in a small minority of around 20% of cases may fluctuations in tic severity be related to stressful small life events. Moreover, in those individuals whose tics appear to be associated with the frequency of reported small life events, the direction of the association may well occasionally be counterintuitive: we identified individual patients whose tics deteriorated in association with desirable life events, and other patients in whom undesirable small life events were associated with decrease in tic severity. We also, however, identified individual associations the other way around. Thus, there does not appear to be a general pattern of how stressful life events may be associated with fluctuations in tic severity. This is in accordance with the reports of Silva et al.,[2] who also found that tics could decrease in response to a particular environmental factor in some individual patients and could lead to an increase in tics in other patients. Examples of these ambiguous environmental factors included social gatherings, a doctor's office visit, and reading for pleasure. However, it should be stressed that only in the pediatric group did we investigate the role of desirable events.

In the present study, we focused on weekly changes in tic severity versus changes in the weekly frequencies of small life events. Indeed, the patients in this study showed rather large weekly fluctuations in self-reported tic severity. Still, in general, the frequency of reported life events, which showed similarly large weekly fluctuations, does not appear to account for the reported changes in tic severity. Despite the apparently limited role of small life events with regard to weekly fluctuations in tic severity, certain psychologically relevant environmental factors, especially anxiety-producing events, may still be associated with short-term increases in tic severity, which may only last minutes to hours and may not influence tic severity across the better part of a week. Future studies should specifically address this issue using prospective designs.

Other environmental factors may play a more profound role, as presumably do common infections.[14] It would be of interest to determine whether individual patients can be identified according to a unique responsiveness to environmental factors, such as life events or streptococcal infections.[15] Also, it would be of interest to study biological substrates of stress influences, including cortisol and the role of the hypothalamic-pituitary-adrenal axis.[16]

In future designs, frequency of small life events may be measured simultaneously with perceived stress,[17] since individuals may differ with respect to the impact of small life events. The recent study by the Yale group[4] demonstrated that patients with Tourette's disorder, compared with unaffected controls, greatly differed with regard to reported cross-sectional levels of perceived stress, including perceived severity of stress associated with everyday problems. Patients were not found to differ significantly from controls, however, with regard to the number of experienced life events, as long as discrete events were concerned. While we did not obtain weekly small life events scores from healthy controls, we did not generally encounter significant correlations between the frequency of small life events and baseline tic severity as rated by the clinician.

Taken together, the findings of Findley et al.[4] and the present study suggest that tic disorder patients may not

differ from unaffected controls with regard to the probability of having encountered life events but, rather, with regard to the levels of experienced stress associated with them. Findley et al.[4] found a significant longitudinal relationship between experienced severity of stress associated with daily life hassles and symptom severity. According to the present study, life events, per se, are generally not associated with changes in tic severity. However, it may well be that tic disorder patients are more sensitive to stress associated with daily hassles and that the findings of the study of Findley et al.[4] may in fact reflect this as a consequence rather than as a cause of changes in tic severity over time.

We intended to study the impact of daily life events on tic severity while trying to rule out the confounding influence of heightened sensitivity to life events and, thus, only assessed the frequency of concrete events, which were all, in principle, observable. Unfortunately, direct comparisons of reported small life events scores of the present study, as yielded by the ISLE, with previously reported frequencies in other patient groups[18] are hampered by differences in selection of ISLE items and ways of obtaining scores (telephone ratings versus use of self-administered questionnaires). Thus, future studies should use well-matched control subjects to investigate the issue of frequency of encountered life events and levels of perceived stress associated with them.

The relationship between psychosocial stress and tic severity is an important issue that few studies have addressed so far. It should be stressed that the present study served primarily exploratory purposes and that it has several limitations, which should be considered in future studies. First, we obtained only a single mean score for baseline tic severity at enrollment. Future studies may consider using a washout period during which a few weeks of tic fluctuations could be recorded. This might better ground a subsequent response to life events in terms of magnitude. In addition, we failed to investigate the role of major life events,[19] such as the breaking up of intimate relationships or death of beloved ones. However, the results of the study by Findley et al.[4] seem to indicate a more significant role for psychosocial stress associated with small events than with less frequent major events. Furthermore, in this study, we exclusively relied on subjective self-administered questionnaires. These correlated modestly with YGTSS scores, which should be viewed, however, against the background that participants subjectively rated their tics according to their individually experienced range of tic severity rather than according to the overall range of tic severity of tic disorder patients in general. Future studies, though, should try to objectively determine fluctuations in tic severity using established rating instruments. However, the excellent response rates in our study over a period of 12 weeks surely are an indicator of the high motivation of participants and thus of the reliability of the present data.

In conclusion, this study regarding the association between small life events and fluctuations in tic severity confirms the clinical impression that stressful life events may lead to changes in tic severity in individual patients. However, a more important conclusion is that for the majority of patients, this does not appear to be the case. Thus, clinicians should be cautious with simple psychological explanations for exacerbations in symptom severity of tic disorder patients.

Drug name: clonidine (Catapres, Duraclon, and others)

REFERENCES

1. Coffey BJ, Biederman J, Geller DA, et al. The course of Tourette's disorder: a literature review. Harv Rev Psychiatry 2000;8:192–198
2. Silva RR, Munoz DM, Barickman JF, et al. Environmental factors and related fluctuation of symptoms in children and adolescents with Tourette's disorder. J Child Psychol Psychiatry 1995;36: 305–312
3. Shapiro AK, Shapiro ES, Youg GJ, et al. Stimuli-induced changes in severity of symptoms. In: Shapiro AK, Shapiro ES, Youg GJ, et al., eds. Gilles de la Tourette Syndrome. 2nd ed. New York, NY: Raven Press; 1988:179–187.
4. Findley DB, Leckman JF, Katsovich L, et al. Development of the Yale Children's Global Stress Index (YGCSI) and its application in children and adolescents with Tourette's syndrome and obsessive-compulsive disorder. J Am Acad Child Adolesc Psychiatry 2003;42:450–457
5. Leserman J, Petitto JM, Golden RN, et al. Impact of stressful life events, depression, social support, coping, and cortisol on progression to AIDS. Am J Psychiatry 2000;157:1221–1228
6. Turner Cobb JM, Steptoe A. Psychosocial influences on upper respiratory infectious illness in children. J Psychosom Res 1998;45: 319–330
7. Zautra AJ, Hamilton NA, Potter P, et al. Field research on the relationship between stress and disease activity in rheumatoid arthritis. Ann N Y Acad Sci 1999;876:397–412
8. Twisk JW, Snel J, Kemper HC, et al. Changes in daily hassles and life events and the relationship with coronary heart disease risk factors: a 2-year longitudinal study in 27–29-year-old males and females. J Psychosom Res 1999;46:229–240
9. Zautra AJ, Guarnaccia CA, Dohrenwend BP. Measuring small life events. Am J Community Psychol 1986;14:629–655
10. Kanner AD, Feldman SS, Weinberger DA, et al. Uplifts, hassles, and adaptational outcomes in early adolescents. J Early Adolesc 1987;7: 371–394
11. The Tourette Syndrome Classification Study Group. Definitions and classification of tic disorders. Arch Neurol 1993;50:1013–1016
12. Leckman JF, Riddle MA, Hardin MT, et al. The Yale Global Tic Severity Scale: initial testing of a clinician-rated scale of tic severity. J Am Acad Child Adolesc Psychiatry 1989;28:566–573
13. Leckman JF. Tourette's syndrome. Lancet 2002;360:1577–1586
14. Hoekstra PJ, Kallenberg CG, Korf J, et al. Is Tourette's syndrome an autoimmune disease? Mol Psychiatry 2002;7:437–445
15. Garvey MA, Giedd J, Swedo SE. PANDAS: the search for environmental triggers of pediatric neuropsychiatric disorders. Lessons from rheumatic fever. J Child Neurol 1998;13:413–423
16. Chappell P, Riddle M, Anderson G, et al. Enhanced stress responsivity of Tourette syndrome patients undergoing lumbar puncture. Biol Psychiatry 1994;36:35–43
17. Cobb JM, Steptoe A. Psychosocial stress and susceptibility to upper respiratory tract illness in an adult population sample. Psychosom Med 1996;58:404–412
18. Zautra AJ, Hoffman J, Potter P, et al. Examination of changes in interpersonal stress as a factor in disease exacerbations among women with rheumatoid arthritis. Ann Behav Med 1997;19:279–286
19. Fernandez E, Sheffield J. Relative contributions of life events versus daily hassles to the frequency and intensity of headaches. Headache 1996;36:595–602