Regular Articles

Causal Relationship Between Stressful Life Events and the Onset of Major Depression

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Objective: Stressful life events are associated with the onset of episodes of major depression. However, exposure to stressful life events is influenced by genetic factors, and these factors are correlated with those that predispose to major depression. The aim of this study was to clarify the degree to which stressful life events cause major depression. **Method:** The authors assessed the occurrence of 15 classes of stressful life events and the onset of DSM-III-R major depression over a 1-year period in female twins ascertained from a population-based registry. The sample contained 24,648 person-months and 316 onsets of major depression. Stressful life events were individually rated on contextual threat and dependence (the degree to which the stressful life event could have resulted from the respondent's behavior). The nature of the relationship between stressful life events and major depression was tested by 1) discrete-time survival analysis examining the relationship between dependence and the depressogenic effect of stressful life events and 2) a co-twin control analysis. **Results:** While independent stressful life events were significantly associated with onsets of depression, when level of threat was controlled, the association was significantly stronger for dependent events. The odds ratio for onset of major depression in the month of a stressful life event was 5.64 in all subjects, 4.52 within dizygotic pairs, and 3.58 within monozygotic pairs. **Conclusions:** Stressful life events have a substantial causal relationship with the onset of episodes of major depression. However, about one-third of the association between stressful life events and onsets of depression is noncausal, since individuals predisposed to major depression select themselves into high-risk environments.

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Since first studied over 30 years ago by Holmes and Rahe (1), stressful life events have been a major focus of psychiatric epidemiology (2–6). In particular, numerous investigations have found a correlation between the occurrence of stressful life events and the

subsequent onset of an episode of major depression (e.g., references 7–11). Less certain, however, is the nature of the relationship between major depression and stressful life events. In particular, it remains unclear to what extent stressful life events cause subsequent onsets of depression and to what extent the occurrence of stressful life events and onsets of depression are correlated for other reasons.

Although concerns about a noncausal association between stressful life events and major depression have been expressed for a long time (2, 7, 12), the salience of this problem has been increased by two recent sets of findings. First, numerous studies have now shown that exposure to stressful life events is substantially influenced by genetic factors (13–17). Individuals do not experience stressful life events at random; rather, some

individuals have a stable tendency to select themselves into situations with a high probability of producing stressful life events. Second, the genetic risk factors for stressful life events are positively correlated with the genetic risk factors for major depression (18, 19). That is, a genetically influenced set of traits both increases individuals' probability of selecting themselves into high-risk environments likely to produce stressful life events and increases their vulnerability to major depression.

In this report, we explore the nature of the relationship between stressful life events and the onset of episodes of major depression in a population-based sample of female twins. First, we compare the risk of onset of an episode of major depression associated with dependent versus independent stressful life events. Ratings of event dependence reflect the plausibility that the stressful life event could have resulted from the respondent's own behavior (20, 21). Dependent stressful life events and onsets of depression might be associated because such stressful life events directly increase the risk of major depression (i.e., a causal relationship) and/or because some third set of factors such as genetic vulnerability predisposes to both stressful life events and major depression (i.e., a noncausal relationship). By contrast, the association between independent stressful life events and the onset of major depression is likely to be entirely causal, because such events are supposed to be unrelated to an individual's own behavior, resulting mostly from "bad luck."

Second, using a co-twin control design (22, 23), we examine the relationship between stressful life events and major depression in the entire sample and then within dizygotic and monozygotic twin pairs. Since monozygotic twins share both their entire genetic and familial-environmental backgrounds, the association between stressful life events and onsets of depression within monozygotic pairs provides another estimate of the degree to which these events may cause onsets of depression.

METHOD

The Caucasian, female, same-sex twins studied are part of a longitudinal study of genetic and environmental risk factors for common adult psychiatric disorders (24). The twins, ascertained from the population-based Virginia Twin Registry, were eligible to participate if both members of the pair had previously responded to a mailed questionnaire, to which the individual response rate was about 64%. The final cooperation rate was certainly higher, since a proportion of the questionnaires never reached the intended twin. In our first personal interviews, we interviewed 92% of the eligible individuals, mostly face-to-face. Written informed consent was obtained before all face-to-face interviews, and verbal assent was obtained for all phone interviews. Zygosity was determined blindly by standard questions (25), photographs, and, when necessary, DNA (26).

Since these original interviews we have completed two further waves of phone interviews with 2,002 (92.6%) and 1,898 (87.7%) of the original sample. The mean number of months between the first and third interviews was 61.3 (SD=5.1). The mean age of the participating twins at the third wave was 35.1 years (SD=7.5).

Measures

In the third wave of interviews, we assessed the occurrence over the year before interview of 14 individual symptoms that represented the disaggregated nine "A" criteria for major depression in DSM-III-R (e.g., two items for criterion A4 to assess separately insomnia and hypersomnia). For each symptom reported, interviewers probed to ensure that it was due to neither physical illness nor medication. Respondents then aggregated the symptoms reported into co-occurring syndromes. If depressive syndromes occurred, respondents were asked to date, to the nearest month, their onset and remission. The diagnosis of major depression was made by computer algorithm incorporating the DSM-III-R criteria, except criterion B2 (which excludes depressive syndromes considered to be "uncomplicated bereavement"). In 53 twins, the 1-year prevalence of major depression and the dating of the depressive episode were assessed with excellent reliability according to the kappa statistic (27) (kappa= 1.00 and kappa=0.97, respectively).

To help ensure that ratings of stressful life events were not influenced by knowledge of clinical outcomes, our interview required that information on stressful life events be collected and rated before the assessment of psychiatric symptoms experienced in the last year. We assessed the occurrence, to the nearest month, of 11 "personal" events (events that occurred primarily to the informant): assault (assault, rape, or mugging), divorce/separation (divorce, marital separation, broken engagement, or breakup of other romantic relationship), financial problems, serious housing problems, serious illness or injury, job loss (laid off from a job or fired), legal problems (trouble with police or other legal trouble), loss of a confidant (separation from other loved one or close friend), serious marital problems, having been robbed, and serious difficulties at work. We also assessed four classes of "network" events (events occurring primarily to, or in interaction with, an individual in the respondent's social network). These event classes consisted of serious trouble getting along with an individual in the network, a serious personal crisis of someone in the network, the death of an individual in the network, and serious illness of someone in the network. In these analyses, we defined the network as consisting of the respondent's spouse, child, parent, co-twin, and nontwin siblings. In a prior wave of this study, we assessed the interrater reliabilities for the occurrence and dating of our stressful life event categories for 53 jointly interviewed twins and found them to be in the good to excellent range, with kappa values equaling 0.93 and 0.82, respectively (28).

Each reported stressful life event was rated by the interviewer with respect to the level of long-term contextual threat and dependence. Following Brown (29), we trained our interviewers to rate "what most people would be expected to feel about an event in a particular set of circumstances and biography, taking no account of what the respondent says either about his or her reaction or about any psychiatric or physical symptoms that followed it" (p. 24). Following Brown (29), long-term contextual threat was rated on a 4-point scale: minor, low moderate, high moderate, and severe.

The dependence of a stressful life event, conceptualized as the probability that any aspect of the respondent's own behavior contributed to the event, was also rated on a 4-point scale: clearly independent, probably independent, probably dependent, and clearly dependent. For stressful life events involving interpersonal difficulties, interviewers were instructed to assume that the events were dependent unless convincing evidence to the contrary was presented. In these analyses, we dichotomized stressful life events into those clearly or probably independent and those clearly or probably dependent. The reliability of our ratings of long-term contextual threat and dependence was determined by both an interrater and a test-retest design. Interrater reliability was assessed by having experienced interviewers, blind to the original codings, review tape recordings of the interview sections in which 92 randomly selected individual stressful life events were evaluated. Test-retest reliability was obtained by blindly reinterviewing 191 respondents at a mean interval of 4 weeks. We obtained 173 scored life events that were reported to have occurred within 1 month of one another and that we assumed represented the same event. We assessed reliability on these 4-point scales with Spearman correlations (r_s) and weighted kappas(30). For long-term contextual threat, for test-retest reliability, r_s=0.60 and

kappa=0.41, while for interrater reliability, r_s=0.69 and kappa=0.67. For dependence, for test-retest and interrater reliabilities, r_s=0.77, kappa=0.63, and r_s=0.89, kappa=0.79, respectively.

Statistical Analysis

We conducted an event history analysis using a discrete-time approach (31, 32), examining each "person-month" of observation, which contained information about which, if any, stressful life events occurred in that month and whether an episode of major depression started in that month. Each observation record also included three covariates: age, previous history of major depression within the 1-year time frame of the study, and the hazard rate for major depression for that month (to correct for an unequal distribution of depression onsets over the study year). When a twin experienced an episode of major depression, she was censored from the sample until she was again at risk for a new onset (i.e., having recorded an end to that depressive episode). She then reentered the sample with the variable "previous history of major depression" updated. We had, in our sample, a number of women who reported chronic depressions that began before our period of ascertainment. These individuals were not considered to have an onset of major depression in the first study month and were censored from the sample for the entire period in which they reported meeting criteria for major depression. Our discrete-time survival model assumed that if the same individual experienced multiple onsets of major depression within the study period, the same underlying processes operated in all onsets.

These analyses treated each individual person-month as an independent observation. The risk of having an onset of major depression was modeled as the dependent variable in a logistic regression. Allison (31) has shown that under the assumption of independence of the individual observations, such a model produces the true maximum-likelihood estimators and artifactually inflates neither the sample size nor the test statistic. The odds ratios for major depression, given stressful life events, were calculated from the logistic regression coefficient controlling for all the covariates outlined above. In these analyses, we examined only the onset of major depression in the month of event occurrence, because most of the depressogenic impact of stressful life events in this sample occurs shortly after the event (28, 33).

In the co-twin control method, we compared the observed association between stressful life events and onsets of depression in the entire study group with that found within pairs of dizygotic and monozygotic twins. (For a detailed description of the logic of this method, see reference 23.) Briefly, if the correlation between a risk factor (here, stressful life events) and an outcome (here, episodes of major depression) is entirely causal, then the associations between risk factor and outcome should be similar in the general population and within dizygotic and monozygotic twin pairs. If the correlation is partly noncausal and mediated by familial-environmental factors that predispose to both the risk factor and the outcome, then the associations will be similar in dizygotic and monozygotic twins, and both will be lower than the association seen in the general population. If, however, the correlation is partly noncausal and mediated by genetic factors that predispose to the risk factor and to the outcome, then the magnitude of the observed associations should be as follows: entire sample > within dizygotic twins > within monozygotic twins. If the correlation between the risk factor and outcome is entirely noncausal and mediated by genetic and/or familial-environmental factors, then that correlation within monozygotic twin pairs should approach zero. Since monozygotic twins share both their genetic and familial-environmental backgrounds, the risk factor-outcome correlation within monozygotic pairs provides an estimate of the causal component of that association.

The co-twin control method can be appropriately applied only to personal stressful life events, because members of a twin pair would share many of their network events (e.g., illness of a parent). Although our hypotheses were nearly always directional (e.g., stressful life events increase the risk of major depression), two-tailed p values are reported. We do not present a formal test for the observed trends in odds ratios with this method.

TABLE 1. Odds Ratios for the Onset of DSM-III-R Major Depression in 1,898 Female Twins in the Month of, and 1–3 Months After, Stressful Life Events Rated as Probably or Definitely Independent of Respondent Behavior

Life Event	Odds Ratio for Onset of Major Depression[a]			
	In Month of Event	1 Month After Event	2 Months After Event	3 Months After Event
Personal				
Assault	25.36***	4.31	—[b]	—[b]
Divorce/separation	5.22	—[b]	—[b]	—[b]
Financial problems	5.85***	2.75	4.31**	2.36
Serious housing problems	7.24***	2.71	1.25	1.26
Serious illness or injury	3.10**	0.70	0.76	0.43
Job loss	3.95*	—[b]	—[b]	—[b]
Legal problems	3.81	—[b]	4.55	10.81**
Loss of confidant	3.17*	1.05	3.19*	1.28
Serious marital problems	8.39*	14.26***	—[b]	4.29
Being robbed	2.74	1.40	1.42	5.01**
Serious work problems	2.44	1.82	1.87	2.74
In subject's social network				
Serious trouble getting along with an individual	5.04***	2.46	1.79	2.23
Serious personal crisis	2.32***	0.65	0.78	0.74
Death	6.29***	0.81	0.86	1.00
Serious illness	2.50***	1.12	0.98	0.43

[a] Odds ratios are calculated from logistic regression of person-months (N≈24,648), and their significance is determined by Wald chi-square test (df=1).
[b] Not estimable because of small cell sizes.
* p<0.05.   **p<0.01.   ***p<0.001.

RESULTS

The sample contained 24,648 individual person-months of exposure and 316 onsets of major depression. Across all stressful life events, ratings of long-term contextual threat and dependence were positively correlated (r_s=0.23, N=2,971, p<0.0001), meaning that dependent events had higher threat ratings than independent events. Therefore, we controlled for long-term contextual threat levels in examining the relationship of event dependence and risk of major depression.

Across all categories of stressful life events, event occurrence was strongly associated with an increased risk for the onset of a depressive episode (χ^2=157.0, df=1, p<0.0001). Ratings of dependence significantly interacted with the occurrence of a stressful life event in predicting onsets of depression (χ^2=6.9, df=1, p=0.01; odds ratio=1.82), indicating that dependent stressful life events were more strongly associated with the occurrence of a depressive episode than were independent events.

Examined across all categories of stressful life events, however, definitely or probably independent events strongly predicted the occurrence of an onset of major depression (χ^2=58.1, df=1, p<0.0001; odds ratio=2.85; 95% confidence interval [CI]=2.18–3.73).

Table 1 presents the results for individual definitely or probably independent events and onset of depression. Of the 15 stressful life events, 11 were significantly associated with the onset of major depression in the month of occurrence, and two others in subsequent months. When we restricted stressful life events to those rated as definitely independent, results were similar: $\chi^2=30.1$, df=1, p<0.0001; odds ratio=2.33; 95% CI=1.72–3.15.

When we examined only personal stressful life events, the odds ratio for onset of a depressive episode in the month in which the event occurred was 5.64 in the entire sample ($\chi^2=171.2$, df=1, p<0.0001). Within pairs of dizygotic twins (who share the same family background and, on average, half their genes), a personal stressful life event was associated with an increased risk for an onset of major depression at an odds ratio of 4.52 ($\chi^2=44.9$, df=1, p<0.0001). Within monozygotic twin pairs (who share their family background and all their genes), a personal stressful life event was associated with an increased risk for an onset of major depression at an odds ratio of 3.58 ($\chi^2=39.1$, df=1, p<0.0001).

DISCUSSION

The aim of this study was to clarify the degree to which the relationship between stressful life events and major depression is due to stressful life events contributing directly to onsets of depression. We addressed this question in two ways, which reassuringly yielded similar results. Consistent with prior studies (e.g., references 8 and 9), events judged to be independent of the respondent's behavior were strongly and significantly associated with the risk of onset of depressive episodes. Within monozygotic twin pairs, matched both for genotype and family environment, stressful life events were strongly and significantly associated with subsequent episodes of major depression. These findings argue strongly that the observed association between stressful life events and major depression is, at least in part, causal.

However, when we controlled for event severity, dependent stressful life events were more strongly associated with onsets of depression than were independent events. Furthermore, the strength of the association between stressful life events and major depression was lower in matched twin pairs than in the entire sample. Consistent with our prior analysis (19) this association was lower in monozygotic twins than in dizygotic twins. This is the pattern of results expected if part of the observed association between stressful life events and onsets of depression is mediated by shared genetic risk factors. In aggregate, these findings strongly argue that the observed association between stressful life events and major depression is, at least in part, noncausal.

Our findings allow us to make a rough estimate of the proportions of the association between personal stressful life events and major depression that are causal and noncausal. We found that the probability of an onset of depression was about 80% greater for dependent than for independent stressful events. In our sample, about 55% of all personal stressful life events were rated as dependent. If the association between major depression and the 45% of all stressful life events that are independent is entirely causal, and the association between major depression and the 55% of dependent stressful life events is about 55% causal (1/1.8), then the total proportion of the association between stressful life events and major depression that is causal is approximately $0.45+0.55\times0.55\approx0.75$, or 75%. We also found that the odds ratio for stressful life events was about 58% greater in the general sample than within monozygotic twin pairs. If the odds ratio within monozygotic twin pairs accurately reflects the causal component of the association between onset of major depression and stressful life events, then the total proportion of the association between stressful life events and major depression that is causal can be estimated at 1/1.58, or about 65%. Given the different assumptions and potential biases of these two different methods, the estimates agree rather closely.

These results should be interpreted in the context of six potential methodologic limitations. First, the sample is entirely female, and the same relationship between stressful life events and major depression may or may not hold in males. Second, because the sample comes from twin pairs, nonindependence of observations from members of a pair is a possible problem. However, the correlation within twin pairs for the dependent variable in these analyses (month of occurrence of a depressive onset) was too low in these data (kappa=0.01) to be of practical concern. Third, our ratings of long-term contextual threat and dependence were made by interviewers rather than by blind "second judges." While they were carefully trained to rate only on the basis of the objective characteristics of the stressful life event, subjective biases cannot be ruled out. Fourth, both the stressful life events and the onsets of major depression were rated retrospectively for the 1-year period before the interview. Although they were assessed in separate parts of the interview, part of the observed association could be spurious and result from biased recollection. Fifth, our sample contained a mixture of first-onset and recurrent cases of major depression. We applied the co-twin control method to first-onset cases only, collapsing data on monozygotic and dizygotic twins together to achieve a stable estimate. The excess odds ratio between stressful life events and major depression in the entire sample versus within twin pairs was greater in the recurrent cases (5.46 versus 3.63, ratio of 1.50) than in the first-onset cases (6.29 versus 4.90, ratio of 1.28). These results suggest that the proportion of the relationship between stressful life events and major depression that is causal may be greater in first-onset than in recurrent episodes of major depression.

Finally, we assumed that when a stressful life event and onset of a depressive episode occurred in the same month, the stressful event came first. In a section of the interview separate from that which assessed depressive syndromes in the last year, the twins were asked, "Did something happen to make you feel that way, or did the feeling just come on you 'out of the blue'?" There were 102 twins who reported a stressful life event and onset of a depressive episode occurring in the same month and who answered this question in sufficient detail for evaluation. In 85.4% of these cases, the event reported was the same as the stressful event the respondent had previously reported as occurring in the same month. In none of the remaining cases did a review of the interview indicate that the stressful life event occurred as a result of the onset of a depressive episode.

CONCLUSIONS

Our results suggest that the experience of a stressful life event truly and substantially increases the risk of a subsequent episode of major depression. However, not all of the observed association between stressful life events and major depression is due to this causal effect. In addition, a set of genetically influenced traits, which perhaps reflect a "difficult" or "neurotic" temperament (34, 35), predispose both to exposure to stressful events and to episodes of major depression.

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