The Prediction of Major Depression in Women: Toward an Integrated Etiologic Model


Objective: The authors develop an exploratory, integrated etiologic model for the prediction of episodes of major depression in an epidemiologic sample of women. Method: Both members of 680 female-female twin pairs of known zyosity from a population-based register were assessed three times at greater than 1-year intervals. The last two assessments included a structured interview evaluation for presence of episodes of major depression, defined by DSM-III-R, in the preceding year. The final structural equation model contained nine predictor variables: genetic factors, parental warmth, childhood parental loss, lifetime traumas, neuroticism, social support, past depressive episodes, recent difficulties, and recent stressful life events. Results: The best-fitting model predicted 50.1% of the variance in the liability to major depression. The strongest predictors of this liability were, in descending order, 1) stressful life events, 2) genetic factors, 3) previous history of major depression, and 4) neuroticism. While 60% of the effect of genetic factors on the liability to major depression was direct, the remaining 40% was indirect and mediated largely by a history of prior depressive episodes, stressful life events, lifetime traumas, and neuroticism. The model suggested that at least four major and interacting risk factor domains are needed to understand the etiology of major depression: traumatic experiences, genetic factors, temperament, and interpersonal relations. Conclusions: Major depression is a multifactorial disorder, and understanding its etiology will require the rigorous integration of genetic, temperamental, and environmental risk factors.

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The probability that an individual will suffer from a major depressive episode is influenced by a number of risk factors, including gender (1, 2), premature parental loss (3), exposure to pathogenic parental rearing (4, 5), personality (6–8), a history of traumatic events (9–12), a previous history of major depression (2, 13, 14), low social support (15–18), recent stressful life events and difficulties (2, 15, 17, 19, 20), and predisposing genetic influences (21–23).

Several attempts have been made to combine these and other putative risk factors for major depression into integrated etiologic models (24–27). Furthermore, an increasing number of studies have examined the impact of several risk factors on major depression (2, 15, 28–32). However, these studies have suffered from substantial limitations, including reliance on cross-sectional assessments, neglect of important risk factor domains, and, possibly, suboptimal analytic strategies. For example, we are aware of only two studies that have
FIGURE 1. Longitudinal Structure of Data Collection for Prediction of Major Depression in Female Twins

The data were collected in three waves. The independent and intermediate dependent variables (listed in italic type) were mostly collected by mailed questionnaire at wave 1. Two predictor variables, childhood parental loss and recent difficulties, were assessed at wave 2. The ultimate dependent variable (listed in bold type), one or more episodes of major depression in the preceding 12 months, and stressful life events in the month of the episode and the prior 2 months were assessed in personal interviews at both wave 2 and wave 3.

The variables included measures of family background (30, 31) and none that have directly assessed the impact of genetic factors. Furthermore, in developing meaningful etiologic models of psychiatric disorders, a central goal should be to clarify the causal processes that interconnect risk factors (33). That is, lists of statistically significant predictor variables should be complemented by attempts to understand the pathways by which these risk factors lead to illness.

In this report we take one step in this direction by developing and testing an integrated, longitudinal model to predict 1-year prevalence of major depression in a population-based sample of female twins. These analyses are exploratory and descriptive in nature.

METHOD

Sample

This sample of Caucasian female same-sex twins was obtained from the population-based Virginia Twin Registry, formed from a systematic review of birth records in the Commonwealth of Virginia (23, 34). The twins participated in three waves of contact (figure 1), the first of which involved responses to one or both of two mailed questionnaires: 1) “Health and Life-Style Survey,” which assessed a broad array of risk factors for medical disorders and psychiatric and substance use disorders, and 2) “Health and Personality,” which focused on risk factors for depression and anxiety. The individual rate of response to these questionnaires was 64%, but the cooperation rate was higher since some nonresponding twins never received the questionnaire because of improper addresses or incorrect forwarding of mail. Of the 2,352 individuals from 1,176 twin pairs in which both members replied to one or both of these wave 1 questionnaires, we succeeded, in our second wave of assessment, in personally interviewing 2,163 (92.0%), including both members of 1,033 pairs. The interviewers were instructed to interview the twins a minimum of 12 months from the date they had completed the mailed questionnaires. Of the completed personal interviews, 89.5% were performed face-to-face and 10.7% were performed by telephone. The results were determined by using standard questions (35), photographs, and, when necessary, DNA (36).

At least 1 year after the wave 2 interview, we conducted our third wave of assessment, by personal interview; nearly all of these interviews (98.6%) were carried out by telephone. Of the original 2,163 twins who completed wave 2 interviews, 2,002 (92.6%) were interviewed in wave 3, including both members of 939 pairs. The wave 2 and 3 interviews were conducted by trained social workers blind to the status of the co-twin.

The results reported here are based on a subset of the twin pairs in which 1) both twins had completed the wave 1 “Health and Personality” questionnaire, 2) both twins were personally interviewed in both waves 2 and 3, 3) both twins had been reared together in the same household through age 16, and 4) zygosity was known. Of the 680 pairs (1,360 twins) who met these criteria, 416 were monozygotic and 264 were dizygotic. The age and years of education of this sample of 1,360 female twins at the wave 2 assessment were 30.3 years (SD = 7.8) and 13.6 years (SD = 2.0), respectively. The mean and median number of months between waves 1 and 2 and between waves 2 and 3 were 13.6 (SD = 3.1) and 12.7 and 16.8 (SD = 7.1) and 16.9, respectively (figure 1).

Diagnostic Evaluation

In both the wave 2 and wave 3 interviews all respondents were asked whether, in the last year, they had experienced any of 20 individual psychiatric symptoms, including all of the DSM-III-R criteria for major depression. The respondent answered positively regarding a symptom, follow-up questions clarified whether the symptom was “medical” (e.g., due to medication, physical illness, or pregnancy), in which case the symptom was not considered present. If two or more symptoms were endorsed, the respondent was asked which if any of the symptoms had occurred together. If symptoms had co-occurred, we then asked for the number of episodes in the past 12 months, the dates of the episodes, and the duration of the longest one. The diagnosis of major depression was made by applying, by computer algorithm, the DSM-III-R criteria for major depressive episode. An episode of major depression occurring between 1 month before and 3 months after the death of a parent, spouse, sibling, or child was assumed to be normal grief. Interrater reliability was assessed in 53 jointly conducted wave 2 interviews. The reliability for major depression during the last year was perfect (Kappa = 1.00, SD = 0.00) (37).

Predictor Variables

From the large number of variables assessed in this study, the choice of predictor variables for this analysis was guided by two conflicting principles: completeness and parsimony. We wished to choose a sufficient number of variables to cover the major risk factor domains for major depression. However, we also wanted the number of predictor variables to be small enough that the final model, if not simple, would at least be comprehensible. In addition, we sought to maximize the number of predictor variables assessed in a truly prospective fashion, which meant focusing on those assessed in our wave 1 questionnaire. The content and mode of assessment of the predictor variables in this study are outlined in table 1.

The genetic liability to major depression was assessed by a dummy variable given the value of 0 if the co-twin had no history of major depression and 1 if the co-twin had had one or more lifetime episodes. This dummy variable was multiplied by 1.0 if the twin pair was monozygotic and 0.5 if the twin pair was dizygotic. This method of modeling genetic effects in a regression analysis (80) assumes that the familial transmission of the liability to major depression is largely due to additive genetic effects (which are correlated perfectly in monozygotic twins but only 0.5 in dizygotic twins). Our analyses used lifetime (23) and 1-year (41) prevalences of major depression in this sample support this hypothesis.

Parental warmth was assessed by using an empirically derived
subscale of the Parental Bonding Instrument (4) contained in the wave 1 questionnaire and by averaging the scores given for the mother and father. To reduce the possible impact of adult psychopathology on recollections of parental behavior, we averaged the reports given by the members of each twin pair. The initial models also included parental overprotectiveness, but this variable had little predictive power and was dropped in subsequent analyses.

Childhood physical and verbal abuse, assessed at wave 2 interview, was defined as a separation from the biologic mother or father for at least a year before the age of 17 (42) that was not part of expected military duty, business travel, etc. Of the separations not due to death, over 90% were the result of divorce (42). Separations were included only if verified by both twins.

Ten major lifetime traumas were assessed at wave 1; they included sexual assault or rape, other physical assault, and life-threatening accidents or illnesses. The lifetime trauma variable was the number of items endorsed.

At wave 1 we assessed six personality constructs potentially related to risk for major depression: neuroticism and extraversion as assessed with 12 and eight items, respectively, chosen by factor analysis of the full Eysenck Personality Questionnaire (38) from a large-sample twin population (39) and subsets of the items for dispositional optimism (45), self-esteem (44), mastery (45), and interpersonal dependency (46). When multiple logistic regression was performed, in accord with the previous literature (6–8, 47–50), neuroticism was by far the strongest predictor of episodes of major depression. We examined the impact of including other personality scales in the model but found that the slight gain in explanatory power introduced thereby was more than offset by increased complexity.

The wave 1 questionnaire contained 25 items assessing seven dimensions of social support, including constructs of perceived support, objective support, and social integration (16, 18, 51): perceived relative support, perceived friend support, frequency of contact with friends, frequency of contact with relatives, frequency of religious attendance, frequency of attendance at clubs/organizations, and presence of a confidant. In a multiple logistic regression, only perceived relative support and frequency of religious attendance predicted episodes of major depression. These two variables, weighted by their regression coefficients, were combined into a single measure of social support.

Our wave 1 questionnaire contained items screening for previous episodes of major depression. We assessed the occurrence of at least three of five key depressive symptoms for at least 2 weeks, criteria that were met by 32.6% of the sample. When tested on our wave 2 data, the chance-corrected agreement between major depression defined by this algorithm and the full DSM-III-R criteria was 0.89 (37). In our wave 2 interview, we assessed lifetime history of major depression (excluding the last year) with the full DSM-III-R criteria. Although this measure of lifetime major depression is methodologically stronger, we did not use it because it was obtained at the same interview in which we examined 1-year prevalence of major depression. However, using this measure of lifetime major depression produced little overall change in the final model.

Recent difficulties, assessed at the wave 2 interview, was a sum of scores on scales reflecting interpersonal difficulties with friends and with relatives, financial difficulties, and health problems.

Recent stressful life events were assessed and dated by month at both the wave 2 and wave 3 interviews. Because of time limitations, we assessed neither the contextual features of each event nor the degree of possible independence or dependence on the subject's behavior (15). For this analysis we summed the life events occurring in the month of onset of the major depressive episode and in the prior 2 months. If the individual had no episode of major depression, life events were summed over a randomly matched 3-month epoch. Twenty-five individual events were assessed: divorce, separation, other marital problems, broken engagement, separation from close friend or loved one, severe illness or injury, robbery, assault, legal problems, loss of job, major financial problems, and death or serious illness or injury in seven classes of individuals (spouse, child, parent, twin, other sibling, other relative, and other close friend or relative). In a small number of cases (N=40), the only onset of major depression occurred in the first or second month of one of the two ascertainment periods, so that life events were not assessed for 2 months before the beginning of the episode. For subjects with an onset in the first month, we multiplied the number of life events reported in that month by 3.0. If the only onset occurred in the second month, we multiplied the number of events in that month and the preceding month by 1.5. Since in this study, as in most others, the increase in life events maximized around the time of the onset of major depression (32), this approach may overestimate the impact of life events on episode onset. To quantitate this bias, we calculated the impact of life events on major depression, assigning the median number of life events in all other onset cases to the 40 cases with onset in the first or second month. The path coefficient from life events to major depression was reduced by 13%, and no other parameters in the model changed substantially.

The ultimate dependent variable in this analysis was the presence or absence of one or more episodes of major depression experienced in the year before either the wave 2 or the wave 3 interview. Thus, we assessed 1-year prevalence of major depression twice, so that the total period of assessment for the 3,360 twins in this sample was 2 years. To be counted, an episode must have begun within one of the two 1-year epochs. If a respondent reported multiple episodes of depression, we used the first of these for dating life events. The only exception to this was that if the first episode had occurred in the first or second month of one of the two ascertainment periods, we then used the next episode.

We included in preliminary models other variables, including age, educational status, health status, and self-report symptoms of depression and anxiety measured at wave 1 (53). In each case, the additional explanatory power was too slight to justify the increased complexity.

The Model

Our final structural equation model had three independent variables that conceptually reflected the effects of congenital or childhood factors: 1) genetic risk factors, for major depression, 2) parental warmth, and 3) childhood parental loss. The model had six intermediate dependent variables, divided conceptually into three levels, the first of which consisted of three enduring personal characteristics that would be relatively stable in adult life: 1) history of lifetime traumas, 2) neuroticism (54), and 3) social support (55). The second level contained only one relatively unique variable: past history of major de-
pressure. The third level of intermediate dependent variables reflected proximal environmental experiences during the year before the two interviews: recent difficulties and recent stressful life events. The final part of the model was the ultimate dependent variable: the presence or absence of one or more episodes of major depression over the two years of assessment.

The 10 variables in this model were divided into four categories on the basis of their distributional properties: 1) quasi-continuous with approximately normal distributions (parental warmth, neuroticism, and social support), 2) quasi-continuous with very skewed distributions (lifetime traumas, last-year difficulties, and recent stressful life events), 3) polytomous (genetic risk factors—with a value of 0 if the co-twin was unaffected, 0.5 if a dizygotic co-twin was affected, and 1 if a monozygotic co-twin was affected), and 4) dichotomous (childhood parental loss, history of major depression, and major depression in last year). While variables in the first category were treated as continuous, all the other variables were analyzed by using a liability-threshold model (56, 57), which assumes that, underlying the observed di- or polytomous there is a normally distributed latent variable termed the “liability,” which is divided into one or more discrete categories by thresholds. It is this liability, rather than the observed variable itself, that we examined in this analysis.

The correlation matrix among these variables, which contained tetrachoric, polytropic, biserial, polyserial, and product moment correlations, was estimated by PRELIS I (58). The structural equation models were fitted to this correlation matrix by the method of asymptotic weighted least squares by the program Mx (59). As a tentative correction for the correlated nature of the observations in the twin pairs, we replaced the sample size provided to Mx as a function of the magnitude of shared variance in twin pairs for the ultimate dependent variable (60). We used Akaike’s information criterion (61), which reflects the goodness of fit and parsimony, to accept or reject reduced nested models.

Mx estimates the total effect of a risk factor on the ultimate dependent variable and the proportion of that total effect that is direct (i.e., a path directly from the predictor variable to the 1-year prevalence of major depression) versus indirect (i.e., mediated through other major depression variables). The proportions of effect that are indirect and direct can be meaningfully compared only for risk factors that are in similar positions in the model because, as the risk factor approaches the ultimate dependent variable, there are fewer and fewer “downstream” variables to mediate any indirect effect. From the best-fitting model we calculated the total proportion of the indirect effect of a predictor variable that occurred through its effect on other downstream predictor variables.

The model also includes correlations between the independent variables. These correlations are not estimated but are included in the final model as correlational paths (two-headed arrows). All other paths in the model are one-headed and represent standardized regression coefficients. For a general introduction to structural equation modeling, see work by Bollen (62) or Loehlin (63).

RESULTS

Test for Potential Bias

In the 2 years of follow-up covered in our wave 2 and wave 3 assessments, 222 (16.3%) of these 1,360 women reported one or more episodes of major depression meeting the DSM-III-R criteria. The rate of major depression did not differ in the 2 years of assessment ($\chi^2=0.00, df=1, n.s.$). Compared to the entire sample, the twins included in this study did not differ in their risk for major depression ($\chi^2=0.02, df=1, n.s.$). Our model assumed that a co-twin’s history of major depression is a stronger predictor of risk in monozygotic twins than in dizygotic twins. We tested this assumption by fitting the model to monozygotic and dizygotic twins separately. A co-twin’s history of major depression was a stronger predictor in monozygotic than in dizygotic twins both for past history of major depression (0.24 versus 0.11, respectively) and for prospectively assessed major depression (0.27 versus 0.09, respectively). The ratio of these coefficients did not significantly differ from the 2:1 predicted by a model of additive genetic effects. We also tested whether the 42 paths not related to a co-twin’s history of major depression were similar in magnitude in monozygotic and dizygotic twins, and we found that none differed significantly.

Best-Fitting Model

Details of model fitting and the best-fitting model (including p values for all paths) are available on request. The best-fitting model, as determined by Akaike’s information criterion, set 16 paths to zero ($\chi^2=10.57, df=16, n.s.$) and accounted for 50.1% of the variance in the ultimate dependent variable; the liability to one or more episodes of major depression over our two periods of 1-year assessment. The total effect on the liability to major depression of each of the nine risk factors, and the proportions of that effect that were direct and indirect (i.e., mediated by other variables in the model), are listed in tables 2–4.

In their total impact on the liability to major depression, the nine predictor variables divide themselves into three groups. Four had strong overall effects on the liability to major depression: recent stressful life events (total effect of 0.388), genetic risk factors (0.329), previous history of major depression (0.302), and neuroticism (0.245). Three predictor variables had intermediate effects: recent difficulties (0.207), parental warmth (0.197), and lifetime traumas (0.130). Two variables had modest effects on the liability to major depression: social support (0.082) and parental loss (0.050). The path estimates of the best-fitting model are seen in figure 2. We briefly discuss each predictor variable in turn.

Independent Variables

Genetic risk factors for major depression. Sixty percent of the impact of genetic factors on the risk for major depression was direct, and 40% was indirect (table 2). The greatest proportion of the indirect effect of genetic risk factors was through a higher risk for prior depressive episodes (43%). That is, genetic factors increased the risk for a prior depressive episode, and the presence of such an episode itself increased the risk for another episode during the period of our study. Smaller indirect effects of genetic factors on the risk for major depression operated through increased risk for recent stressful life events, higher levels of neuroticism, and greater risk for lifetime traumas. Perceived parental warmth. In marked contrast to genetic factors, parental warmth had no direct effect on the liability to future episodes of major depression (table 2).
Rather, all the effect of parental warmth on liability to major depression was indirect, mediated by other predictor variables. Nearly one-third of the indirect effect of perceived parental warmth was mediated through a lower risk of prior depressive episodes, and one-fifth each was mediated by lower levels of recent difficulties and lower levels of neuroticism. The remainder of the indirect effect of parental warmth on the liability to major depression was mediated by higher levels of social support and a lower number of lifetime traumas.

Childhood parental loss. Like parental warmth, childhood parental loss had no direct effect on the liability to major depression (table 2). Of the total indirect effect, 50% was mediated by a higher level of recent difficulties. Forty percent of the indirect effect of childhood parental loss on risk for major depression was mediated by higher levels of neuroticism, and 10% was mediated by lower levels of social support.

Intermediate Dependent Variables

Lifetime history of traumas. In the best-fitting model, lifetime history of traumas also had no direct effect on the liability to major depression (table 3). Rather, traumatic experiences affected the risk for major depression indirectly, and 50% of the risk was mediated by a higher risk for prior depressive episodes. The remaining indirect effect of lifetime traumas on liability to major depression occurred through higher numbers of recent stressful events and recent difficulties.

Neuroticism and social support. Of the substantial impact of neuroticism on the liability to major depression, slightly more than one-half (56%) was direct (table 3). Nearly all of the indirect effect (90%) occurred because neuroticism predicted prior depressive episodes. The remaining indirect effect of neuroticism was mediated by an inverse relationship between levels of neuroticism and social support. All of the modest total effect of social support on the liability to major depression was direct—high levels of social support predicted a lower risk for major depression.

Past history of major depression. Two-thirds of the large impact of a prior history of major depression on the risk for further depressive episodes was direct (table 4). The indirect effects were mediated, to approximately equal degrees, through prior depressive episodes predicting both recent difficulties (44%) and recent stressful life events (56%).

Proximal environmental factors. Most (83%) of the impact of recent difficulties on the liability to major depression was direct, although a modest proportion was indirect, as recent difficulties predicted recent stressful life events (table 4). By definition, recent stressful life events can only influence liability to major depression, and the effect was a strong one.

DISCUSSION

The goal of this study was to gain insight into the etiology of major depression by developing a preliminary integrated model for predicting 1-year prevalence of depression in a population-based sample of female twins.
In developing this model, we strove to avoid the extremes of bewildering complexity and vast oversimplification. The avoidance of great complexity involved the adoption of a number of simplifying assumptions that, while defensible, are almost certainly not entirely correct.

We organize our initial discussion around four themes in our etiologic model: genetic effects, traumatic experiences, temperament, and interpersonal relations.

**Genetic Effects**

Previous results from this sample (23), as well as from most (21, 22) but not all (64–66) previous twin and adoption studies, support the hypothesis that genetic factors play an important etiologic role in the lifetime prevalence of major depression. We have also shown in this sample that genetic factors substantially influence the risk for 1-year prevalence of major depression (41). Our present results, which use a different model with a subset of our sample and again show strong evidence for the operation of genetic factors in the etiology of major depression, are not, therefore, unexpected.

In contrast to our previous conventional twin analyses, the present study allows us to compare, for the first time to our knowledge, the importance of genetic risk factors for major depression with the importance of other specified risk factor domains. In our analysis, genetic background was the second largest risk factor for major depression, exceeded only by recent stressful life events. Consistent with our previous results (23), the present findings reconfirm that genetic factors play a "substantial but not overwhelming" role in the etiology of major depression.

Our present results also begin to clarify the pathway from genotype to phenotype for major depression. We especially wanted to know how much genetic factors act directly on the liability to major depression, as opposed to indirect effects, mediated by temperament, social support, or the predisposition to experience traumatic events. That is, do genetic factors for major depression act largely through personal characteristics that are formed by early adulthood or are they continually "on-line" throughout adulthood, actively influencing the risk for major depression?

Our results provide some support for each hypothesis. In our model, genetic factors influenced the liability to major depression by both indirect and direct paths. However, as 60% of the total effect of genes on the liability to major depression was direct, our results provide strong support for "on-line" genetic effects.
throughout adulthood. Our results suggest that a substantial proportion of the impact of genetic factors on the risk for major depression is not mediated by stable effects on temperament or by the impact of "scars" from earlier traumas or depressive episodes.

**Traumatic Experiences**

Our results provide strong evidence for the importance of traumatic experiences in the etiology of major depression. Three of our nine final predictor variables reflected either distal (childhood parental loss and lifetime traumas) or proximal (recent life events) stressful life experiences. One of these variables, recent stressful events, was the single most powerful risk factor for major depression in the model.

What is the etiology of such experiences? Consistent with previous evidence (67–71), our results suggest that, although random factors ("bad luck") are probably the most important cause of traumatic experiences, a modest proportion of the liability to such events results from stable personal characteristics. Genetic risk factors for major depression modestly predicted lifetime traumas and recent stressful life events, suggesting that to a small degree genes may influence the risk for major depression by predisposing individuals to "create" high-risk environments. We have previously termed this "genetic control of exposure to the environment" (72). The path from lifetime traumas to recent stressful life events was small and positive, suggesting that some stable personal characteristics influence the risk of traumatic events over time.

**Temperament**

Consistent with previous longitudinal research, we found that neuroticism was a robust predictor of future episodes of major depression (6–8, 50, 73). The present model provides some insights into the pathway from temperament to risk for major depression. First, consistent with most (49, 73–75) but not all (76–78) previous findings, our results suggest a modest relationship between the genetic factors that influence the risk for major depression and neuroticism. In this model, approximately 7% of the total effect of genetic factors on the liability to episodes of major depression occurred through their impact on neuroticism.

Second, a large proportion of the effect of temperament on the liability to major depression is indirect. Neuroticism both increases the risk for prior episodes of major depression and reduces levels of social support. Third, the path from neuroticism to a prior history of major depression is considerably larger than the path from neuroticism to prospectively assessed depressive episodes. By contrast, genetic factors influence both variables equally.

**Interpersonal Relations**

Our results also provide strong evidence for the importance of interpersonal relations in the etiology of major depression. This was reflected by the impact of three of our predictor variables: parental warmth, social support, and recent difficulties (which were largely, but not entirely, interpersonal difficulties). These three interpersonal predictor variables were interrelated in an understandable developmental framework. As in some previous research (79), perceived parental warmth predicted both high levels of social support and low levels of interpersonal difficulties. Individuals who saw their parents as loving may be able to form more stable and mutually supportive long-term relationships that are less prone to develop difficulties.

**Independent Variables**

Our three independent variables, which reflected congenital and childhood influences, differed markedly in the way they influenced the liability to major depression. Genetic factors had a large direct effect on the risk for major depression, while perceived parental warmth and childhood parental loss had only indirect effects (12). Genetic and early environmental influences appear to differ qualitatively in their influence on the liability to major depression in adulthood.

**CONCLUSIONS**

Consistent with findings from previous clinical and epidemiologic studies (2, 15, 28–32), our results suggest that major depression is a multifactorial disorder, the risk for which is influenced by several risk factor domains. We previously suggested (72) that the "elucidation of the etiology of psychiatric disorders will require the consideration of both genetic and environmental risk factors." We can elaborate on this by saying that, at least for major depression, several major domains of environmental risk factors must be considered. Our results provide preliminary insight into the developmental pathways through which genetic and early environmental risk factors influence temperament and more proximal environmental risk factors and how these multiple risk factor domains together regulate an individual's vulnerability to major depression.

**LIMITATIONS**

The results presented here should be interpreted in the context of six potentially important methodologic limitations. First, our approach to modeling genetic factors was crude compared to the more commonly used latent genetic and environmental factors (80). The only "genetic" variable assessed was the co-twin's history of major depression. Several other variables in our model are also influenced by familial/genetic factors, including neuroticism (35), stressful life events (70, 81), and social support (51, 82). Only in a multivariate genetic analysis incorporating causal modeling would it be possible to examine the genetic and environmental risk fac-
tors for major depression, all our predictor variables, and the interrelationship among them (80). While the development of software to permit such an analysis is underway (59), the complexity of performing and interpreting such an analysis will be daunting.

Second, the list of predictor variables included in our final model was not exhaustive. Some variables found to be important by others, e.g., age, education, depressive symptoms, coping strategies, and levels of self-esteem (2, 32, 83), were tested and excluded because they added minimal additional explanatory power. Gender, an important risk factor for major depression (1, 2), could not be studied because the sample was entirely female. Other potentially important variables, such as marital status, presence of young children in the home, and a history of nonaffective psychiatric disorders in the individual or her co-twin (15, 32), were not included to avoid excess complexity. Although preliminary analyses suggest that the overall pattern of results was robust to the addition of other variables, it is possible that the inclusion of new predictor variables might significantly alter the nature of our findings.

Third, our structural equation model assumed that variables acted on one another solely in an additive fashion. However, interactive effects, such as between social support and stressful life events, may be important in the etiology of major depression (15, 18). Given the number of potential multiplicative interactions in our model, we chose, for this initial presentation, to restrict ourselves to additive effects.

Fourth, errors of measurement were not incorporated into our model. Therefore, the parameter estimates of paths from the independent and intermediate dependent variables reflect both the predictive power of their “true score” and the reliability with which that true score is measured. Furthermore, since the reliability with which major depression is assessed in epidemiologic samples is far from perfect (84), a substantial proportion of the 49.9% of variance in liability to major depression not predicted by our model may represent error of measurement.

Fifth, we examined individuals with and without a prior history of major depression together to maximize statistical power and to examine the impact of a previous history of major depression. Because individuals with prior episodes of major depression have a higher likelihood to illness than those with no history, other risk factors correlated with that liability may have a truncated range, resulting in attenuated correlations. We tested for this effect by comparing covariance matrices of the predictor variables in subjects with and without a prior depressive episode. They did not differ significantly. Some studies have shown that risk factors for major depression are similar in subjects with and without prior episodes, while other studies have not (2, 85, 86). Further research is needed to address this important issue.

Finally, our model assumed, rather than tested, “direction of effects.” We ordered our predictor variables from our conceptual framework rather than from the data. We assumed that neuroticism and social support influence the risk for prior episodes of major depression, but the influence might, in part, be in the other direction. For neuroticism, however, we rigorously evaluated these hypotheses and found that little of the association was due to an effect of depression on neuroticism scores (73). Furthermore, in the preliminary phases of the model fitting, altering the order of our intermediate dependent variables had little overall impact on the model.

Direction of effect may be more important in interpreting the relationship between our ultimate dependent variable—1-year prevalence of major depression—and other variables in the model. For some, such as genetic predisposition or parental loss, the assumption that their association with major depression is causal is easily defended. Furthermore, as most of our variables were assessed before the ascertainment period for major depression, a direct confounding of measurement is unlikely. However, we cannot rule out that the relationship with major depression for some of our variables, such as social support, recent difficulties, or recent stressful life events, might not be entirely causal but mediated in part by other factors, such as recall bias, prodromal symptoms, or unmeasured stable personal characteristics that influence both these variables and the risk for major depression.

REFERENCES