Major Depression and Generalized Anxiety Disorder

Same Genes, (Partly) Different Environments?

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• Bivariate twin analysis can determine the extent to which two disorders share common genetic, familial environmental, or individual-specific environmental risk factors. We applied this method to lifetime diagnoses of major depression and generalized anxiety disorder as assessed at personal interview in a population-based sample of 1033 pairs of female same-sex twins. Three definitions of generalized anxiety disorder were used that varied in minimum duration (1 vs 6 months) and in the presence or absence of a diagnostic hierarchy. For all definitions of generalized anxiety disorder, the best-fitting twin model was the same. Familial environment played no role in the etiology of either condition. Genetic factors were important for both major depression and generalized anxiety disorder and were completely shared between the two disorders. A modest proportion of the nonfamilial environmental risk factors were shared between major depression and generalized anxiety disorder. Within the limits of our statistical power, our findings suggest that in women, the liability to major depression and generalized anxiety disorder is influenced by the same genetic factors, so that whether a vulnerable woman develops major depression or generalized anxiety disorder is a result of her environmental experiences.

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In both clinical and epidemiologic samples, major depression (MD) and anxiety disorders, including generalized anxiety disorder (GAD), co-occur in persons at higher rates than would be expected by chance.[1,2] For disorders such as MD[3,4] and GAD,[5,6] whose etiology is probably influenced by familial factors, genetic epidemiologic approaches can test critical hypotheses about the causes of comorbidity that cannot be addressed in standard epidemiologic samples. In particular, three potential causes of comorbidity can be evaluated. First, MD and GAD may co-occur because some of the genes that influence vulnerability to depression also influence vulnerability to GAD. The degree to which the same genes influence both disorders is termed their *genetic correlation.* A genetic correlation of unity, for example, would mean that all the genes that influence the vulnerability to MD also influence the vulnerability to GAD, and vice versa.

Second, two disorders may co-occur because familial-environmental factors may predispose to both disorders. For example, certain parental rearing patterns that have impact on all children in the household may increase the risk for the development of both depression and anxiety disorders.[7,8] Third, two disorders may co-occur because nonfamilial environmental factors may increase the risk for both disorders. For example, stressful life events, to which only one member in a family is exposed, might predispose to both MD and GAD.[9,10]

The resolution of these three causes of comorbidity requires the collection of data from genetically informative samples. Family studies can distinguish the third from the first two hypothesized causes of comorbidity but cannot discriminate between genetic and familial-environmental sources of comorbidity. By contrast, twins studies can potentially resolve all three sources of comorbidity.

PREVIOUS FAMILY AND TWIN STUDIES OF DEPRESSION AND GAD

Three family studies and one twin study have, to our knowledge, addressed the question of the relationship between clinically defined MD and a GAD-like syndrome. Noyes et al[5] found similar rates for affective disorder in the relatives of probands with GAD and controls, suggesting independent transmission of the liability to GAD and MD within families. The other studies have, by contrast, suggested that the familial predisposition to GAD and MD are, to some extent, shared. Weissman et al[11] found rates for GAD to be twice as high in relatives of probands with MD vs controls. Angst et al,[2] in the only study to utilize an epidemiologic proband sample, found, using the family history method, increased rates of anxiety and depression in the parents of subjects who had anxiety only, depression only, or anxiety and depression. Finally, Torgersen,[12] in a clinical sample of Norwegian twins, found little evidence for the specificity of transmission of depression or mixed-

anxiety depression but found possible specificity for anxiety neurosis alone. Unfortunately, the sample size of his study was too small to allow rigorous statistical evaluation of competing models of transmission.

OUR PREVIOUS TWIN STUDY OF SELF-REPORT SYMPTOMS OF ANXIETY AND DEPRESSION

In 1987, we published an article in this journal that examined the relationship between self-report symptoms of anxiety and depression in a large Australian twin sample.[13] We concluded that

No evidence could be found for genes that specifically affect symptoms of depression without also strongly influencing symptoms of anxiety. By contrast, the environment seems to have specific effects, i.e. certain features of the environment strongly influence symptoms of anxiety while having little impact on symptoms of depression ... suggest[ing] that the separable anxiety and depression symptom clusters in the general population are largely the result of environmental factors.[13]

A major limitation of this report was its reliance on responses to a short symptom checklist in a mailed questionnaire. The relevance of these conclusions for clinically defined depression and anxiety was uncertain. We report herein our effort to replicate our previous finding in a more clinically meaningful context by examining the causes of comorbidity in clinically defined MD and GAD in a large population-based sample of female twins.

SUBJECTS AND METHODS

As outlined in detail previously in this journal,[4] as part of a longitudinal study of the genetic and environmental risk factors for common psychiatric disorders in women, we personally interviewed 2163 female twins from the population-based Virginia Twin Register with a mean ($\pm$SD) age of 30.1 ± 7.6 years, including both members of 1033 pairs and 97 individual twins. No male twins were studied. The refusal rate during the personal interviews phase of this project (conducted by interviewers with masters degrees in social work or at least 2 years of clinical experience) was 8%. All subjects were interviewed by someone "blind" to the psychopathologic status of their cotwin. Zygosity was determined by an algorithm based on questionnaire responses, photographs, and, where these sources were ambiguous, DNA polymorphisms[14] and yielded 590 monozygotic (MZ) pairs, 440 dizygotic (DZ) pairs, and three pairs of unknown zygosity.

Diagnoses, using *DSM-III-R* criteria,[15] were made by one of us (K.S.K.) on blind review of the interview protocols, which included adapted sections of the Structured Clinical Interview for *DSM-III-R*[16] for MD and GAD. It was also coded whether the twin met criteria for GAD only during times when she also met criteria for MD. Interrater reliabilities for the diagnosis of MD and GAD (with a minimum 1- and 6-month duration) were assessed in 53 jointly conducted interviews, with the following κ values[17]: $+.96\pm.04$, $+.77\pm.10$, and $+.73\pm.19$. The version of the Structured Clinical Interview for *DSM-III-R* from which we worked did not contain, in the GAD section, questions addressing whether the anxiety or worry affected two or more life circumstances. Thus, we considered twins to meet *DSM-III-R* criterion A for GAD if they responded positively to having a time when they were "anxious, nervous or worried more days than not."

For MD, all analyses conducted used the *DSM-III-R* criteria. For GAD, we used three definitions of illness, all modifications of the *DSM-III-R* criteria, in which subjects had to meet at least six of the 18 individual symptoms listed in criterion D. The first definition reduced the required minimum duration of illness from 6 months to 1 month and eliminated criterion C ("The disturbance does not occur only during the course of a mood disorder or a psychotic disorder"). This will be called "1-month GAD without hierarchy." The second definition, called "1-month GAD with hierarchy,"
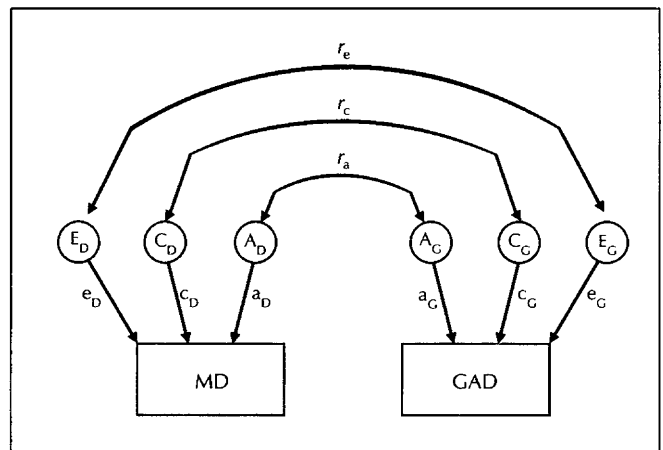

Fig 1.—A full bivariate twin model for major depression (MD) and generalized anxiety disorder (GAD). The variance in liability to each disorder is divided into that due to additive genetic effects (AD and AG), common or familial environment (CD and CG), and individual-specific environment (ED and EG). Paths, which equal standardized regression coefficients, the values of which must be squared to equal the proportion of variance accounted for, are represented by lowercase letters (a, c, and e). The phenotypic correlation between MD and GAD is, in this model, decomposed into that due to the correlation of additive genes (r_a), the correlation of common environmental risk factors (r_c), and the correlation of individual-specific environmental risk factors (r_e).

differed from the first definition only in the application of criterion C. That is, if a twin met criteria for GAD only during times when criteria were also met for MD, that twin would receive the diagnosis of GAD by the first, but not by the second, set of criteria. The third set of criteria adopted the *DSM-III-R* 6-month minimum duration of illness without a diagnostic hierarchy and is termed "6-month GAD." The full *DSM-III-R* criteria for GAD were not used because they produced low prevalences in our sample, with resulting low statistical power. In addition, multiple threshold analyses suggested that 1- and 6-month GAD could be conceptualized as disorders on a single continuum of liability.[6] Furthermore, the change from a 1-month minimum duration of illness in *DSM-III*[18] to 6 months in *DSM-III-R*[15] was made without strong empirical support, and one previous study[19] suggests that this change may have confounded rather than improved the category's validity.

STATISTICAL ANALYSIS

In standard univariate twin analysis, the goal is to decompose the variance in liability to a given disorder into genetic and environmental components. In bivariate analysis, the goal is to decompose the covariance between two disorders, such as MD and GAD, into that due to genes, common environment (those environmental experiences shared by members of a twin pair that therefore tend to make twins similar), and individual-specific environment (those environmental experiences not shared by members of a twin pair that therefore tend to make them dissimilar). The full model is illustrated in Fig 1. Basically, bivariate analysis subdivides a phenotypic liability correlation between two disorders into three parts: (1) that due to the same additive genes predisposing to both disorders (the additive genetic correlation, or r_a), (2) that due to the same common or familial environmental factors predisposing to both disorders (the common environmental correlation, or r_c), and (3) that due to the same individual-specific environmental risk factors predisposing to both disorders (the individual-specific environmental correlation, or r_e).

While univariate genetic analysis is conducted using MZ and DZ twin correlations for a single variable, bivariate analysis examines three kinds of correlations: within-variable cross-twin, within-twin cross-variable, and cross-twin cross-variable. The main logic of bivariate twin analysis is illustrated for MD and GAD in Table 1, which depicts the expected pattern of correlations

Table 1.—Logic of Bivariate Twin Analysis of Major Depression (MD) and Generalized Anxiety Disorder (GAD)

Individual-specific environment	Significant within-twin MD-GAD correlation; no cross-twin MD-GAD correlation
Common or familial environment	Significant within-twin MD-GAD correlation; significant cross-twin MD-GAD correlations equal in monozygotic and dizygotic twins
Additive genes	Significant within-twin MD-GAD correlation; significant cross-twin MD-GAD correlations twice as great in monozygotic as in dizygotic twins

Table 2.—Correlation Matrix for 1-Month GAD and MD*

| | Twin 1 | | Twin 2 | |
	MD	GAD	MD	GAD
Twin 1				
MD	...	.64±.05	.44±.06	.34±.07
GAD	.63±.06	...	.40±.07	.35±.07
Twin 2				
MD	.19±.08	.10±.08	...	.75±.04
GAD	.16±.08	.12±.08	.68±.05	...

*GAD indicates generalized anxiety disorder; MD, major depression. Correlations for monozygotic twins are above diagonal; for dizygotic twins, below.

in the comorbidity between MD and GAD as being due solely to individual-specific environment, common or familial environment, or additive genes. These examples are, however, not mutually exclusive, as it is perfectly possible for comorbidity to be due, for example, to both subject-specific environment and additive genes.

Correlations are estimated by the β-test version of the computer program PRELIS-II,[20] assuming a liability threshold model. Such a model postulates that (1) liability to illness is due to at least several genetic and environmental risk factors of small to moderate effect size so that the distribution of liability approximates normality,[21] and (2) subjects with liability above a given threshold manifest the illness. Model fitting to these correlations of liability was performed by the computer program LISREL using asymptotic weighted least squares.[22,23] The best-fitting model was chosen using Akaike's[24] information criterion (AIC), which equals χ^2 minus twice the df. The model with the most negative value of the AIC has the optimal balance of goodness of fit and parsimony, meaning that it explains most of the observed relationships between the variables with the fewest possible variables. Neither dominance genetic variance nor age effects were included in our analyses because our previous univariate analyses of MD[4] and GAD[6] failed to demonstrate consistently their importance for either disorder.

RESULTS
Prevalences

In the entire sample of 2163 personally interviewed twins, the lifetime prevalences of MD, 1-month GAD without and with hierarchy, and 6-month GAD were, respectively, 31.3%, 23.5%, 16.7%, and 5.9%. The proportion of the sample who had both lifetime MD and 1-month GAD with and without hierarchy and 6-month GAD were, respectively, 16.2%, 9.3%, and 4.6%.

The Association Between GAD and MD

The magnitude of the association between MD and GAD was assessed in two ways: tetrachoric correlation (±SE) and odds ratio (OR) (±SE). For lifetime MD and 1-month GAD without hierarchy, the association was quite strong, as indicated either by the OR (8.93±1.02) or tetrachoric correlation (.68±.02). The association was slightly weaker between MD and 6-month GAD (OR=8.50±1.85; tetrachoric correlation, +.56±.04) and considerably less robust, although still substantial, between MD and 1-month GAD with hierarchy (OR=3.91±0.05; tetrachoric correlation, +.45±.04). The magnitude of the association between the two disorders did not differ as a function of zygosity.

The Correlation Matrix

Table 2 depicts the correlation matrix between MD and 1-month GAD without hierarchy with SEs. Matrices using the

other definitions of GAD are available on request. Three results are of interest. First, the within-twin MD-GAD correlations (eg, MD in twin 1 with GAD in twin 1) are substantially higher than any of the cross-twin cross-disorder correlations (eg, MD in twin 1 with GAD in twin 2). This suggests that subject-specific experiences are contributing to the correlation between GAD and MD. Second, in both MZ and DZ twins, the cross-twin MD-GAD correlations are only slightly lower than the cross-twin within-disorder correlations (eg, MD in twin 1 with MD in twin 2). This means that if you wanted to predict twin 2's risk for GAD, you would do just about as well knowing twin 1's history of MD as you would knowing twin 1's history of GAD. Third, the cross-twin MD-GAD correlations are more than twice as great in MZ (mean, +.37) than in DZ twin pairs (mean, +.13), suggesting that genetic factors contribute to the correlation between MD and GAD.

Model Fitting: One-Month GAD Without Hierarchy

The full model (model 1, Table 3) fits well (χ^2=6.00, df=5, not significant); the parameter estimates are seen in Fig 2, top. The additive genetic correlation (r_a) is estimated at +.99, common environmental correlations (r_c) at 1.00, and the specific environmental correlation (r_e) at +.53. However, the proportion of variance in liability to the two disorders accounted for by common environment is minuscule (≤1%). In models 2, 3, and 4, we set to 0 each of the correlations in turn. The model deteriorates badly when either r_a (model 3) or r_e is set to 0 (model 4). However, the fit of the model is hardly altered when r_c is set to 0 (model 2), and the AIC of model 2 is substantially more negative than that for model 1.

Working from model 2, then, we set each of the two remaining correlations to unity in turn. While the fit deteriorates badly when r_e is set to 1 (model 6), the fit is nearly unaltered and the AIC becomes more negative when r_a is set at 1 (model 5).

Working from model 5, we then try to eliminate the other variables from the twin model. C can be eliminated from both MD (model 7) and subsequently from GAD (model 8), with no change in fit and with the AIC taking on a yet larger negative value. No further improvements could be made. The results of model 8, the best-fitting model, are seen in Fig 2, bottom. The estimate of r_e was +.51. The phenotypic correlation between GAD and MD can now be "decomposed" according to the best-fitting model, with 53% resulting from genes that predispose to both disorders and 47% resulting from subject-specific environmental factors that increase risk for both disorders.

Model Fitting: One-Month GAD With Hierarchy

As seen in Table 3, the full model fit reasonably well (χ^2=9.50, df=5, P>.10), and Fig 3, top, estimates the common environmental component for both depression and GAD to be 0. As expected, the estimates for both r_a (+.83) and r_e (+.23) are lower than those found when examining 1-month GAD without hierarchy. The results obtained in the model fitting are, nonetheless, similar to those found in the previous analysis. The r_c, but neither r_a nor r_e,

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Model	Variables for		Correlations			χ^2	df	AIC
	GAD	MD	r_a	r_c	r_e			
1 mo Without Hierarchy								
1	ACE	ACE	F	F	F	6.00	5	−4.00
2	ACE	ACE	F	0	F	6.04	6	−5.96
3	ACE	ACE	0	F	F	15.34	6	+3.34
4	ACE	ACE	F	F	0	54.54	6	+42.54
5	ACE	ACE	1	0	F	6.15	7	−7.85
6	ACE	ACE	F	0	1	42.90	7	+28.90
7	ACE	AE	1	0	F	6.18	8	−9.82
8	AE	AE	1	0	F	6.62	9	−11.38
1 mo With Hierarchy								
1	ACE	ACE	F	F	F	9.50	5	−0.50
2	ACE	ACE	F	0	F	9.50	6	−2.50
3	ACE	ACE	0	F	F	17.54	6	+5.54
4	ACE	ACE	F	F	0	17.16	6	+5.16
5	ACE	ACE	1	0	F	10.20	7	−3.80
6	ACE	ACE	F	0	1	70.60	7	+56.60
7	ACE	AE	1	0	F	10.32	8	−5.68
8	AE	AE	1	0	F	10.38	9	−7.62
6 mo Without Hierarchy								
1	ACE	ACE	F	F	F	2.05	5	−7.95
2	ACE	ACE	F	0	F	2.20	6	−9.80
3	ACE	ACE	0	F	F	4.60	6	−7.40
4	ACE	ACE	F	F	0	17.88	6	+5.88
5	ACE	ACE	1	0	F	2.20	7	−11.80
6	ACE	ACE	F	0	1	16.80	7	+2.80
7	ACE	AE	1	0	F	2.20	8	−13.80
8	AE	AE	1	0	F	3.95	9	−14.05

*GAD indicates generalized anxiety disorder (diagnosed with or without hierarchy); MD, major depression; r_a, additive genetic correlation; r_c, common environmental correlation; r_e, individual-specific environmental correlation; AIC, Akaike's Information Criterion[24]; A, additive genetic factors; C, common or familial environmental factors; E, individual-specific environmental factors; F, free (variable free to take any value); and 0 or 1, variable fixed at 0 or 1.

can be set to 0 (models 2 through 4). The r_a, but not r_e, can be set to unity (models 5 and 6). The common environment for both MD and GAD can be eliminated (models 7 and 8). Parameter estimates for the best-fitting model (model 8) are seen in Fig 3, bottom. The main difference between these results and those seen in Fig 1 is the lower environmental correlation. The phenotypic correlation between MD and 1-month GAD with hierarchy can be "decomposed" into 69% resulting from shared genes and 31% from shared subject-specific environmental factors.

Model Fitting: Six-Month GAD

As seen in Table 3, the full model fit well ($\chi^2=2.05$, $df=5$,) and, like the analysis with 1-month GAD without hierarchy, estimates both r_a and r_c to be unity (Fig 4, top). Unlike the previous analyses, estimates of C for GAD are nontrivial. Nonetheless, the fit of the model, as measured by the AIC, is improved when r_c is set to 0 but deteriorates when either r_a or r_e is set to 0. As with the previous analyses, r_a, but not r_e, can be set to unity (models 5 and 6), and the common environment for both MD and GAD can be eliminated (models 7 and 8). Parameter estimates for the best-fitting model (model 8) are seen in Fig 4, bottom. The estimate for r_e (+.38) was in between those obtained in the previous two analyses. The phenotypic correlation between MD and 6-month GAD can be decomposed according to the best-fitting model into 57%

resulting from shared genes and 43% from shared nonfamilial environmental factors.

We repeated our model fitting, defining GAD as a three-category multiple threshold model without hierarchy: unaffected, affected for 1 to 6 months, and affected for 6 months or longer. As noted previously,[6] this multiple-threshold model fit well, and the results obtained were similar to those found above, with model 8 fitting best, with estimates of r_a and r_e of 1.00 and +.47, respectively.

COMMENT

Using data from an epidemiologic sample of twins, we applied the method of bivariate twin analysis to determine the underlying causes for the high rate of comorbidity between GAD and MD. The major findings, which we will discuss in turn, were similar for all three definitions of GAD employed.

Genes, MD, and GAD

In our previous analysis of cross-sectional self-report symptoms, we found that genes appeared to act largely by predisposing to general distress rather than specifically to
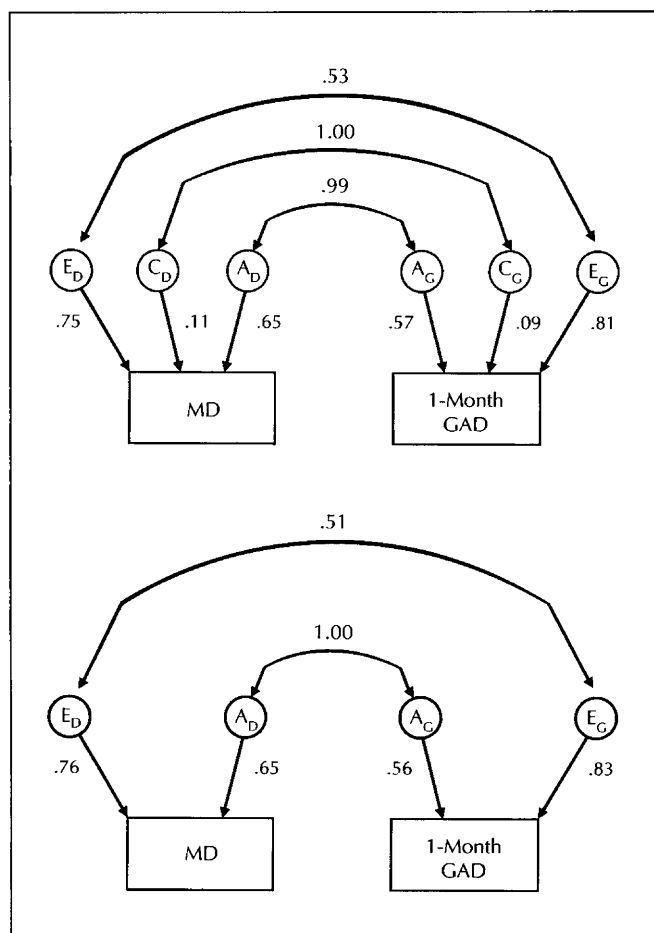
Fig 2.—*The results of bivariate model fitting for major depression (MD) and 1-month generalized anxiety disorder (GAD), diagnosed without hierarchy. Top, Results of the full model (depicted in Fig 1); bottom, results of the best-fitting submodel (model 8 in Table 3).*
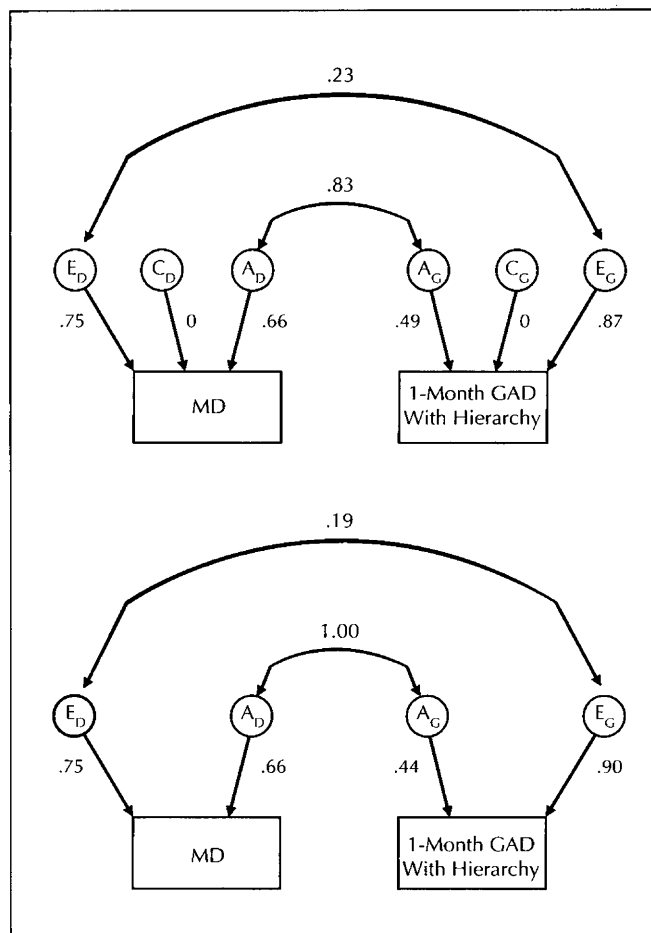

Fig 3.—*The results of bivariate model fitting for major depression (MD) and 1-month generalized anxiety disorder (GAD), diagnosed with hierarchy so that a subject only making criteria for GAD during episodes of MD would not receive the diagnosis of GAD. Top, Results of the full model (depicted in Fig 1); bottom, results of the best-fitting submodel (model 8 in Table 3).*

symptoms of either anxiety or depression.[13] Our present analysis of lifetime psychiatric disorders, assessed at personal interview, yields a similar finding. Within the power of our design, our results suggest that the same genetic liability influences risk to both MD and GAD. All the genes that influence the vulnerability to MD appear to have a similar effect on the vulnerability to GAD, and vice versa.

Of the four previous studies that found evidence that a shared liability to MD and GAD "ran in families,"[2,11,12,25] our results are particularly similar to those of Merikangas,[25] who found in a large case-controlled family study that depression and anxiety disorders were "manifestations of the same underlying transmissible factors." Our results are, by contrast, difficult to reconcile with those of Noyes et al.[5] In a nonblind family study, which included 20 probands with GAD, they found that the rate of affective disorder was similar in relatives of probands with GAD (7.3%) and in relatives of controls (7.1%).[5] Differences in sample composition, assessment instruments, or diagnostic conventions all could be responsible for this disparity of results.

Since genes are expressed through physiologic pathways, our findings suggest that there is a common, genetically influenced neurobiologic diathesis to both GAD and MD. Results from both biologic and pharmacologic treatment studies of depression and anxiety[26-29] provide further evidence that the two disorders share a biologic substrate.

The Environment, MD, and GAD

Although the same genetic factors appear to influence the liability to MD and GAD, this was not the case for environmental factors. While r_a was estimated at unity in all our best-fitting models, estimates of r_e were much lower, ranging from +.19 to +.51. Furthermore, for all the definitions of GAD, it was possible to reject models in which r_e was set to unity.

These results suggest that although some of the environmental risk factors for MD and GAD are shared in common, a substantial proportion of such factors are unique to each disorder. That is, there must be nonfamilial environmental experiences that are depressogenic without being anxiogenic and vice versa. This finding is consistent with the life-event literature, which suggests that there is partial differentiation of the kinds of life events that predispose to depression vs anxiety states.[30-33]

Consistent with results of the univariate analyses,[4,6] common or familial environment played no role in the etiology of MD or GAD and therefore could not plausibly influence their co-occurrence. According to our results,
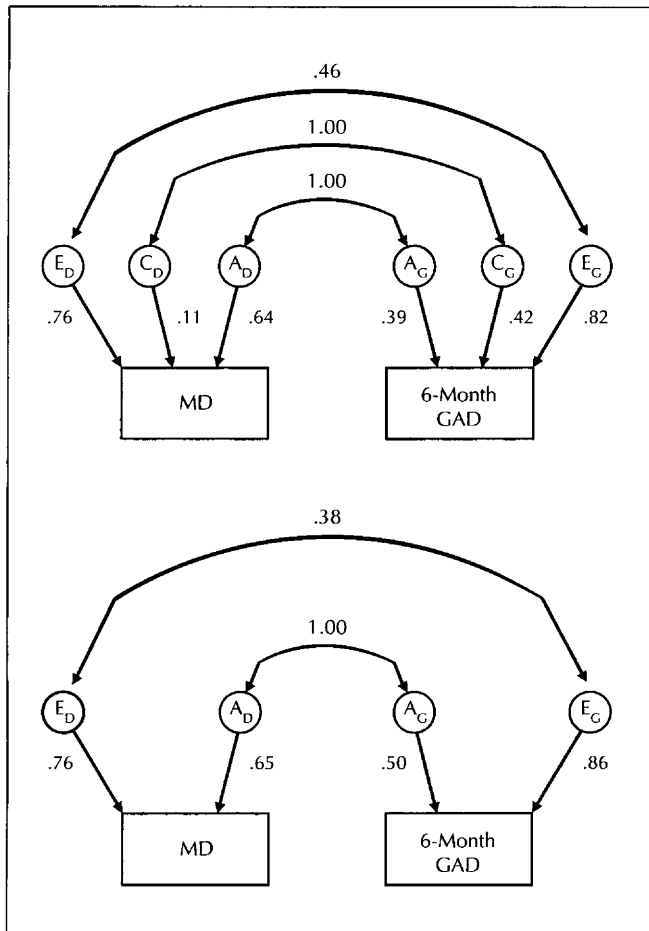
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Fig 4.—*The results of bivariate model fitting for major depression (MD) and 6-month generalized anxiety disorder (GAD), diagnosed without hierarchy. Top, Results of the full model (depicted in Fig 1); bottom, results of the best-fitting submodel (model 8 in Table 3).*

individual-specific environmental risk factors are solely responsible for the differentiation between MD and GAD. Within the power of our statistical analysis, it appears that the only reason why a vulnerable woman would suffer MD rather than GAD, or GAD rather than MD, is as a result of her environmental experiences.

Limitations

These results should be interpreted in the context of several potentially important limitations. First, our results are only relevant for women. Given differences in base rates for MD and GAD in men and women,[34] as well as evidence for substantial differences in patterns of comorbidity in men and women for other psychiatric disorders such as alcohol and drug abuse,[35] it cannot be assumed that the causes of comorbidity would be similar in men and women.

Second, this study does not address all possible causes of comorbidity such as overlapping criteria sets. Tiredness, difficulty sleeping, and problems with concentration are symptomatic criteria for both MD and GAD in *DSM-III-R*. The contribution of these overlapping symptoms to the observed patterns of comorbidity is unknown.

Third, even with our relatively large sample size, our estimates of genetic and environmental correlations have relatively large SEs. It is, for example, unlikely that we would have statistical power to discriminate a genetic correlation of +.70 between MD and GAD from unity. Our finding of a genetic correlation of unity between MD and GAD may, therefore, be interpreted more conservatively as finding a high genetic correlation between the two disorders, which did not, in our sample, differ significantly from unity.

Fourth, our bivariate model has certain assumptions that deserve mention. The comorbidity between MD and GAD may not result from shared risk factors but rather from the presence of one disorder directly increasing the risk for the other disorder. Such a "causal" model can be tested in the twin design[23] but is not powerful when, as in the case of MD and GAD, the proportions of variance in liability due to genetic and environmental factors are similar. With these two disorders, the best fitting of the possible causal models did not fit as well as the best-fitting standard bivariate models discussed above.

Fifth, we are unable, in our current data set, to incorporate unreliability of assessment into our models. This would require separate lifetime assessments for psychiatric disorders at two points in time. When treating single disorders, such unreliability of measurement, if uncorrelated in twin pairs, would lead to an overestimation of the individual-specific environment and underestimation of heritability. In bivariate models, the potential effects are subtler. If the "self-report bias" within a subject is substantially correlated for disorders assessed at the same interview, but not highly correlated within twins, then this bias would lead to an overestimation of the individual-specific environmental correlation between the two disorders.

Sixth, we were unfortunately working with an older version of the Structured Clinical Interview for *DSM-III-R*, which did not include, as a criterion for GAD, the need to be worried about "two or more life circumstances." Thus, we probably diagnosed GAD in some cases that would not meet the full *DSM-III-R* criteria because their anxiety focused on only a single life circumstance.

Seventh, as reviewed previously,[4,6] the prevalences for MD and GAD, while higher than those found in the Epidemiologic Catchment Area study,[34] are similar to or lower than those found in other recent population-based surveys.[19,36-38] We used a clinician-based instrument with added reminders to assist in long-term recall, used mental health professional interviewers, and demonstrated our high interrater reliability.

Finally, this bivariate analysis is only part of a larger picture of the interrelationship of the genetic and environmental risk factors for common disorders in women that we are seeking to clarify in this project. It will be of particular interest to determine whether the comorbidity between MD and the two other anxiety disorders assessed at interview, panic disorder and phobia, are likewise the result of the same genes and (partly) different environments. Preliminary analyses of MD and phobias suggest that this may not be the case.

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