The Structure of Genetic and Environmental Risk Factors for Common Psychiatric and Substance Use Disorders in Men and Women

Kenneth S. Kendler, MD; Carol A. Prescott, PhD; John Myers, MS; Michael C. Neale, PhD

Background: Patterns of comorbidity suggest that the common psychiatric and substance use syndromes may be divisible into 2 broad groups of internalizing and externalizing disorders. We do not know how genetic and environmental risk factors contribute to this pattern of comorbidity or whether the etiologic structure of these groups differs in men and women.

Methods: Lifetime diagnoses for 10 psychiatric syndromes were obtained at a personal interview in more than 5600 members of male-male and female-female twin pairs ascertained from a population-based registry. Multivariate twin modeling was performed using the program Mx.

Results: We first fit models to the following 7 syndromes: major depression, generalized anxiety disorder, phobia, alcohol dependence, drug abuse/dependence, adult antisocial behavior, and conduct disorder. The full model, which could be constrained to equality in male and female subjects, identified 2 genetic factors. The first had strongest loadings on alcohol dependence, drug abuse/dependence, adult antisocial behavior, and conduct disorder. The second, on major depression, generalized anxiety disorder, and phobia. Alcohol dependence and drug abuse/dependence had substantial disorder-specific genetic risk factors. Shared environmental factors were most pronounced for conduct disorder and adult antisocial behavior. No clear internalizing/externalizing structure was seen for the unique environmental common factors. We then fit models to 5 internalizing syndromes. The full model, which could also be constrained to equality in men and women, revealed one genetic factor loading most heavily on major depression and generalized anxiety disorder and another loading most strongly on animal and situational phobia.

Conclusions: The underlying structure of the genetic and environmental risk factors for the common psychiatric and drug abuse disorders in men and women is very similar. Genetic risk factors predispose to 2 broad groups of internalizing and externalizing disorders. Within the internalizing disorders, 2 genetic factors are seen that predispose to disorders dominated by anxious-misery and fear. Substance use disorders have disorder-specific genetic risks. The externalizing disorders of conduct disorder and adult antisocial behavior are significantly influenced by the shared environment. The pattern of lifetime comorbidity of common psychiatric and substance use disorders results largely from the effects of genetic risk factors.

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IGH LEVELS of comorbidity are consistently seen for psychiatric and substance use disorders.1,2 Such a pattern suggests that many risk factors for psychopathology are not disorder specific, a contention supported by numerous studies.3-5 This observed pattern of comorbidity indicates that the broad array of common psychiatric disorders may be explained more parsimoniously by a small number of underlying factors. Recently, 3 large epidemiological studies have suggested that the most important of these factors reflect the broad groupings of internalizing and externalizing disorders6-8 (although 2 of these studies7,8 suggest that the internalizing factor might itself be divisible into subfactors).

These important studies, however, were observational and did not address the risk factors responsible for this pattern of comorbidity. By contrast, multivariate studies of genetically informative designs can decompose patterns of comorbidity into those due to genetic vs environmental risk factors. Furthermore, such studies can clarify the level of diagnostic specificity of major genetic and environmental risk factors.

Many such studies have now been published that include 2 or 3 diverse disorders9-11 or multiple disorders within
1 diagnostic class.12-14 These studies have demonstrated substantial sharing of genetic and, to a lesser extent, environmental risk factors across disorders. We are, however, aware of only 2 reports that have applied such methods to a wide array of psychiatric and drug abuse disorders.15,16 Both studies found evidence of broad genetic/familial factors that predisposed to a range of disorders. One of these studies was restricted to women and included only a single externalizing disorder (alcohol dependence).15 The other examined only nuclear families and could not discriminate genetic from shared environmental effects.16

Most psychiatric and drug abuse disorders show substantial sex differences in prevalence.17,18 Less is known about similarities or differences in patterns of comorbidity.7,19 We are unaware of any systematic examination of the similarities in the underlying genetic and environmental risk factors for common psychiatric and drug abuse disorders in both men and women.

In this study, we apply multivariate genetic analyses to the following 10 psychiatric syndromes as assessed in more than 5600 members of male-male (MM) and female-female (FF) twin pairs ascertained from a population-based registry: major depression, generalized anxiety disorder, phobia, panic disorder, animal phobia, situational phobia, alcohol dependence, drug abuse/dependence, adult antisocial behavior, and conduct disorder.

Because of computational limitations, our analyses focus on 7 disorders, chosen to balance internalizing and externalizing syndromes. We then follow up these results by examining 5 internalizing disorders. We sought answers to the following questions:

1. Can we uncover, from the pattern of comorbidity observed among common psychiatric and drug abuse disorders, evidence of the effects of a small number of genetic and environmental risk factors? Is there a pattern that reflects the broad groupings of the internalizing and externalizing disorders, and, if so, is this due to the effects of genetic or environmental factors?

2. Given differences in prevalence, how similar is the underlying pattern of genetic and environmental risk factors for common psychiatric and drug abuse disorders in men and women?

### METHODS

#### SAMPLE AND ASSESSMENT PROCEDURES

The twins in this study derive from the population-based Virginia Twin Registry.17 Female-female twin pairs, from the birth years 1934 through 1974, became eligible if both members previously responded to a mailed questionnaire in 1987 through 1988, the response rate to which was approximately 64%. They have been approached for 4 subsequent waves of personal interviews from 1988 to 1997, with cooperation rates ranging from 85% to 92%. The MM and male-female (MF) twin pairs, from the birth years 1940 through 1974, were ascertained in a separate study, with an initial cooperation rate of 72.4%, and have been approached for 2 waves of interviews from 1993 until 1998. Zygosity was determined by a combination of standard questions,21 photographs, and DNA analysis.22,23 The mean (SD) ages of the FF and MM/MF samples at their final interview were 36.6 (8.1) and 36.8 (9.1) years, respectively. Interviewers had a master's degree in a mental health–related field or a bachelor's degree in this area plus 2 years of clinical experience. At each wave, members of a twin pair were interviewed by different interviewers who were blind to clinical information about the cotwin. In this report, we examined only same-sex twin pairs.

### STATISTICAL METHODS

Our approach to multivariate genetic analysis has been outlined elsewhere.15,31 The models described herein are based on a liability threshold model, the strengths and limitations of which have been previously discussed.31,32 Like traditional factor analysis, multivariate genetic analysis seeks to explain covariation among multiple variables with a few factors. However, traditional exploratory factor analysis is purely descriptive, whereas multivariate genetic analysis provides insight into the sources of resemblance.

Using the software package Mx,33 we fit models by the method of maximum likelihood to data from all individual twins, including those without an interviewed co-twin. This method reduces the impact of cooperation bias and is a binary data maxi-
RESULTS

Phenotypic Patterns of Comorbidity

Table 1 depicts the lifetime prevalence rates for the 7 major psychiatric and substance use disorders in the male and female twins. The level of comorbidity between these disorders, as assessed by means of odds ratios and tetrachoric correlations, is also seen for twins from MM and FF pairs (above and below the diagonal, respectively). The pattern of phenotypic comorbidity was broadly similar in men and women.

Full Model in Men and Women

Fitting our full model to the MM and FF pairs and allowing all parameters to differ across sexes yielded the following: $-2LL = 30,242.1; df = 34,150; AIC = -38,057.9$. Constraining all parameters (except thresholds) to be equal in the 2 sexes produced a considerably better balance of parsimony and explanatory power: $\Delta LL = 38.8; df = 60; \Delta AIC = -81.2$.

The parameter estimates for this model are shown in Table 2 as path estimates and Table 1 as proportions of variance in liability. The first genetic common factor (seen on the right side of Figure 1) had substantial loadings on all 4 externalizing disorders, whereas the second genetic common factor had high loadings on all 3 of the internalizing disorders. In addition, the 2 substance use disorders—alcohol dependence and drug abuse/dependence—had substantial disorder-specific genetic loadings.

The first shared environmental common factor had substantial loadings on all 4 externalizing disorders, whereas the second shared environmental common factor had high loadings on phobia and conduct disorder. All the shared environmental-specific loadings were quite small.

The first unique environmental common factor had substantial loadings on alcohol dependence and drug abuse/dependence—alcohol dependence and drug abuse/dependence. The second unique environmental common factor also had a moderate loading on adult antisocial behavior. The second unique environmental common factor also had moderate loadings on alcoholic dependence, drug abuse/dependence, and conduct disorder. The second unique environmental common factor also had small loadings on all 5 internalizing disorders.

For computational reasons, our analyses were limited to 7 disorders. In our first analyses, we selected the following relatively common disorders, approximately balanced across internalizing and externalizing conditions: major depression, generalized anxiety disorder, (any) phobia, alcohol dependence, drug abuse/dependence, adult antisocial behavior, and conduct disorder. Despite these restrictions, the run times for these models on our 667-MHz 21264 dual-processor computer (Alpha; Microway, Inc, Plymouth, Mass) still often exceeded 1 week.

In our second series of analyses, we examined the following 5 internalizing disorders: major depression, generalized anxiety disorder, panic disorder, animal phobia, and situational phobia. After model fitting, using the SAS routine PROC FACTOR, factor loadings were rotated using Varimax criterion for the 7 disorders and Promax criterion for the 5 internalizing disorders. We used an oblique rotation for the 5 internalizing disorders because these were conceptualized as subfactors of a higher-order internalizing factor. We define a substantial factor loading in these analyses that accounts for more than 10% of the variance in the dependent variable ($\geq 0.10$ or $\geq 0.22$). We define a moderate factor loading as one that accounts for 5% to 10% of the variance in the dependent variable (ie, values of 0.22-0.31).

Table 1. Prevalence Rates and Comorbidity Between 7 Major Psychiatric and Substance Use Disorders†

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Men Prevalence, %</th>
<th>Women Prevalence, %</th>
<th>MD GAD Phobia AD DAD AASB CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD</td>
<td>28.5</td>
<td>40.4</td>
<td>...</td>
</tr>
<tr>
<td>GAD†</td>
<td>14.0</td>
<td>25.9</td>
<td>0.50 (4.14)</td>
</tr>
<tr>
<td>Phobia</td>
<td>21.8</td>
<td>30.0</td>
<td>0.26 (1.88)</td>
</tr>
<tr>
<td>AD</td>
<td>23.0</td>
<td>8.2</td>
<td>0.33 (2.84)</td>
</tr>
<tr>
<td>DAD</td>
<td>22.4</td>
<td>11.0</td>
<td>0.29 (2.36)</td>
</tr>
<tr>
<td>AASB</td>
<td>15.1</td>
<td>6.1</td>
<td>0.29 (2.69)</td>
</tr>
<tr>
<td>CD</td>
<td>19.1</td>
<td>4.4</td>
<td>0.33 (3.42)</td>
</tr>
</tbody>
</table>

Abbreviations: AASB, adult antisocial behavior; AD, alcohol dependence; CD, conduct disorder; DAD, drug abuse/dependence; GAD, generalized anxiety disorder; MD, major depression; OR, odds ratio.

†Indicates broad diagnostic criteria.

7 PSYCHIATRIC AND SUBSTANCE USE DISORDERS

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stantial loadings on major depression, generalized anxiety disorder, and alcohol dependence. All of the disorder-specific unique environmental loadings, which include measurement error, were substantial.

5 INTERNALIZING DISORDERS

Phenotypic Patterns of Comorbidity

Because our initial 7-disorder model included only 3 internalizing syndromes, we ran a second series of analyses to examine the fine structure of risk factors for internalizing disorders. Table 3 depicts the lifetime prevalence rates for these disorders in the MM and FF twins and the level of comorbidity. The pattern of phenotypic comorbidity was again broadly similar in men and women.

Full Model in Males and Females

Fitting our full model to the MM and FF pairs and allowing all parameters to differ across sexes yielded the following fit: $-2LL = 19165.5; df = 25,158; AIC = -31150.5$.

Constraining all the parameters (except thresholds) to be equal in the two sexes again produced a superior balance of parsimony and explanatory power:

$H_0: -2LL = 32.3; df = 42; AIC = -51.7$.

The parameter estimates for this full model are seen in Figure 2 and Table 4 (which contains an extra source...
of variance due to the covariance of the common factors. The 2 common genetic factors were positively correlated, the first of which had substantial loadings on major depression and generalized anxiety disorder and a more moderate loading on panic disorder. The second common genetic factor had substantial loadings on animal phobia and situational phobia. Panic disorder was the only condition with a significant disorder-specific genetic loading. No substantial loadings were seen for the 2 common shared environmental factors (which were negatively correlated) or for the disorder-specific shared environmental factors. The first and second unique environmental common factors, which were positively correlated, had substantial loadings only on generalized anxiety disorder and situational phobia, respectively. All the disorder-specific unique environmental factors had substantial loadings.

We sought in this report to determine whether the pattern of genetic and environmental risk factors for common psychiatric and substance abuse disorders was similar in men and women and then to clarify the underlying structure of those risk factors. We review these questions in turn.

SEX DIFFERENCES IN THE PATTERN OF GENETIC AND ENVIRONMENTAL RISK FACTORS

The genetic and environmental parameters in both of our analyses could easily be constrained to be the same in the MM and FF twin pairs. Despite large differences in prevalence rates for nearly all of the disorders, the same configuration of underlying risk factors accounted for the patterns of comorbidity in men and women.

We are aware of only 1 comparable finding. In a multivariate analysis of 10 disorders from the National Comorbidity Survey, Krueger7 found the same 3-factor model produced similar parameter estimates in men and women. From a genetic-epidemiological perspective, these results suggest that the most pronounced sex differences are in the level of liability required to manifest clinical illness, rather than in the underlying pattern of the risk factors themselves.

Our separate analyses in the MM and FF twins can be seen as replicate samples. In that sense, these results reflect the robustness of our findings, as the results were so similar in 2 large independent samples.

THE STRUCTURE OF GENETIC AND ENVIRONMENTAL RISK FACTORS FOR COMMON PSYCHIATRIC AND SUBSTANCE USE DISORDERS

The second goal of this report was to clarify the structure of the genetic and environmental risk factors for common psychiatric and substance use disorders. We examined this question in 2 stages, the first of which involved fitting multivariate genetic models jointly to 3 internalizing and 4 externalizing disorders.

COMMENT

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The full model identified 2 genetic common factors. The first factor had substantial loadings on all 4 of the externalizing disorders (alcohol dependence, drug abuse/dependence, adult antisocial behavior, and conduct disorder), whereas the second factor had substantial loadings on all 3 of the internalizing disorders (major depression, generalized anxiety disorder, and phobia). Substantial disorder-specific genetic factors were seen only for the 2 substance use disorders, alcohol dependence and drug abuse/dependence. These analyses identified the following 4 major sets of genetic risk factors for these 7 common disorders: (1) a broad liability to externalizing disorders, (2) a broad liability to internalizing disorders, (3) a factor specific for alcohol dependence, and (4) a factor specific for drug abuse/dependence. Some of the disorder-specific factors may reflect genetic differences in the metabolism, end-organ responsiveness, and hedonic effects of psychoactive substances.

The results showed a large shared-environment effect only on conduct disorder and a more modest effect on adult antisocial behavior. The first unique environmental common factor apparently reflected experiences that had an impact mainly on risk for adult antisocial behavior and conduct disorder. The second factor indexes exposures that influenced risk for major depression, generalized anxiety disorder, and alcohol dependence.

Of the 3 sources of variance in risk examined, the distinction between internalizing-externalizing disorders was seen clearly only for genetic factors. Nothing resembling these 2 dimensions of psychopathology was...
seen with the 2 shared environmental common factors. A variant of the internalizing-externalizing distinction was seen in the 2 unique environmental common factors, but with 2 critical differences from the structure seen with the genetic factors. The first or externalizing unique environmental factor did not load substantially on the 2 substance use disorders. The second or internalizing unique environmental factor loaded substantially on alcohol dependence but not phobia. These results suggest strongly that genetic factors are largely responsible for the pattern of comorbidity that results in the 2 frequently co-occurring clusters of internalizing and externalizing disorders. By contrast, at least some of the subgrouping within these 2 clusters may be driven by environmental experiences (eg, a set of individual-specific environmental events [E
$_{si}$ in Figure 1] that influences the risk for conduct disorder and adult antisocial behavior but not for alcohol dependence and drug abuse/dependence).

In our second analyses, we examined the structure of risk factors for internalizing disorders. The full model identified the following 2 major sources of genetic risk: (1) a common factor with substantial loadings on major depression and generalized anxiety disorder, and (2) a common factor with strong loadings on animal phobia and situational phobia. As would be expected if these 2 genetic common factors were components of a higher-order internalizing factor, they were positively correlated. Unexpectedly, panic disorder did not load strongly with the 2 phobic disorders, with its genetic risk coming largely from the first common genetic factor, and only modestly from the second common genetic factor, and disorder-specific effects. In the shared and the unique environmental common factors, there was no trace of 2 etiologic dimensions reflecting anxious-misery and fear. This pattern of results suggests that genetic factors are largely responsible for the pattern of comorbidity that results in the division of internalizing disorders into 2 frequently co-occurring subclusters reflecting anxious-misery and fear. This synthesis of the results of our 2 model-fitting efforts, a tentative model for the structure of the genetic risk factors for common psychiatric disorders in men and women is shown in Figure 3.

Synthesizing the results of our 2 model-fitting efforts, a tentative model for the structure of the genetic risk factors for common psychiatric disorders in men and women is shown in Figure 3. The picture is oversimplified because it ignores evidence of crossloadings (eg, the internalizing general genetic factor consistently loads modestly on the externalizing disorders and vice versa). The structure of these genetic risk factors bears a conspicuous resemblance to the phenotypic structure of adult psychiatric disorders proposed by Krueger et al.

Table 4. Proportion of Variance in Liability to 5 Internalizing Psychiatric Disorders From Common and Disorder-Specific Genetic and Environmental Risk Factors in MM and FF Twin Pairs

<table>
<thead>
<tr>
<th>Disorder</th>
<th>CF1</th>
<th>CF2</th>
<th>VDFC</th>
<th>Sp</th>
<th>Total</th>
<th>CF1</th>
<th>CF2</th>
<th>VDFC</th>
<th>Sp</th>
<th>Total</th>
<th>CF1</th>
<th>CF2</th>
<th>VDFC</th>
<th>Sp</th>
<th>Total</th>
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<tbody>
<tr>
<td>MD</td>
<td>0.28</td>
<td>0.00</td>
<td>0.01</td>
<td>0.00</td>
<td>0.29</td>
<td>0.06</td>
<td>0.00</td>
<td>-0.01</td>
<td>0.00</td>
<td>0.05</td>
<td>0.09</td>
<td>0.00</td>
<td>-0.01</td>
<td>0.58</td>
<td>0.66</td>
</tr>
<tr>
<td>GAD</td>
<td>0.28</td>
<td>0.01</td>
<td>-0.04</td>
<td>0.00</td>
<td>0.25</td>
<td>0.03</td>
<td>0.00</td>
<td>-0.01</td>
<td>0.00</td>
<td>0.02</td>
<td>0.45</td>
<td>0.01</td>
<td>0.04</td>
<td>0.23</td>
<td>0.73</td>
</tr>
<tr>
<td>PD</td>
<td>0.10</td>
<td>0.01</td>
<td>0.02</td>
<td>0.04</td>
<td>0.17</td>
<td>0.06</td>
<td>0.03</td>
<td>0.04</td>
<td>0.01</td>
<td>0.13</td>
<td>0.05</td>
<td>0.01</td>
<td>0.02</td>
<td>0.62</td>
<td>0.70</td>
</tr>
<tr>
<td>APH</td>
<td>0.00</td>
<td>0.20</td>
<td>0.02</td>
<td>0.00</td>
<td>0.22</td>
<td>0.03</td>
<td>0.07</td>
<td>-0.04</td>
<td>0.00</td>
<td>0.06</td>
<td>0.00</td>
<td>0.06</td>
<td>0.01</td>
<td>0.64</td>
<td>0.71</td>
</tr>
<tr>
<td>SPH</td>
<td>0.03</td>
<td>0.24</td>
<td>0.05</td>
<td>0.00</td>
<td>0.33</td>
<td>0.01</td>
<td>0.01</td>
<td>-0.01</td>
<td>0.00</td>
<td>0.01</td>
<td>0.00</td>
<td>0.49</td>
<td>-0.02</td>
<td>0.19</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Abbreviations: APH, animal phobia; CF1, first common factor; CF2, second common factor; FF, female-female; GAD, generalized anxiety disorder; MD, major depression; MM, male-male; PD, panic disorder; Sp, disorder specific; SPH, situational phobia; VDFC, variance due to factor covariance.

*Totals do not always sum to unity due to rounding.

Our results are broadly consistent with those of a prior multivariate analysis of a more restricted set of disorders in women from our group. That study found the following 3 major sources of genetic variance: (1) a common factor loading largely on major depression and generalized anxiety disorder; (2) a common factor loading largely on panic disorder, phobia, and bulimia; and (3) disorder-specific loadings for alcohol dependence. In the present larger sample, the structure of the second factor appears to be restricted to phobia subtypes. If more externalizing disorders were included in the earlier analysis with women, our current results would suggest that the genetic loadings for alcohol dependence would divide into those that are disorder specific and those that are shared with other externalizing syndromes. Our findings are also in general agreement with a previous analysis of family history data from the National Comorbidity Study, which identified 2 familial factors (for internalizing and externalizing disorders) that were transmitted across generations with reasonable fidelity and a recent study of adolescent twins from the general population that identified a highly heritable externalizing factor that included substance dependence, antisocial behavior, and a disinhibited personality style.

What intermediate phenotypes might best reflect the 3 common genetic factors identified in these analyses? It is tempting to speculate that these genetic effects on risk might be mediated through personality. Further work in genetically informative samples will be needed to test this hypothesis.

This study also produced estimates for the etiologic role of genetic and environmental factors for the 10 individual disorders examined (Tables 2 and 4). As might be expected, for most of the disorders, these results agree relatively well with previous estimates from this and other studies, although the heritability estimates for panic disorder and animal phobia are somewhat lower than previously reported.

For gene-finding studies for these common disorders, these results raise the question of whether it would be more efficient to focus on groups of disorders with shared genetic risk factors rather than on individual disorders.
LIMITATIONS

These results should be interpreted in the context of 6 potential methodological limitations. First, the sample consisted of white twins born in Virginia. How well these findings extrapolate to other ethnic groups is uncertain. Second, all of the diagnostic assessments were based on a single interview that includes substantial error variance. In multivariate models, most measurement error is confounded with true disorder-specific unique environmental effects and produces downward biases on other parameter estimates. Third, parameter estimates from such modeling ideally should be presented with confidence intervals. However, the additional computational burden required to estimate these would have made the analyses infeasible. Fourth, our twin model assumes that comorbidity results from the impact of latent genetic and environmental risk factors. Other models of comorbidity are possible, but were not examined here. Fifth, for computational reasons, we included in these analyses only same-sex twin pairs and therefore could examine only quantitative sex effects, ie, whether the magnitude of genetic and environmental effects differ in men and women. Our present analyses do not address the question of whether the same genetic and shared environmental factors have an impact on risk in men and women. Sixth, as noted previously, our lifetime prevalence rates for major depression are higher than those reported from most previous studies. We used clinical rather than lay interviewers and a semistructured rather than a highly structured interview, assessed the history for depression twice in the interview, and used multiple methods to encourage effortful responding. Our identified cases reported substantial levels of impairment, distress, and treatment seeking. Our sex-averaged 1-year prevalence estimates of major depression (9.7%) are nearly identical to those reported in the National Comorbidity Survey (10.3%), suggesting that we achieved a considerably lower ratio of last-year to lifetime cases. We may have identified milder cases than some other studies. However, previous studies have shown that heritability of depressive illness in this sample is not related to the narrowness of the definition.

The underlying structure of genetic and environmental risk factors for common psychiatric and substance use disorders is very similar in men and women. The patterns of comorbidity of these disorders (internalizing vs externalizing, and within internalizing, anxious-misery vs fear) is driven largely by genetic factors. Shared environmental risk factors (eg, family disruption, poor parental monitoring, or low social class of rearing) may contribute to comorbidity within at least a subgroup of externalizing disorders. Within syndromal groups, exposure to unique environmental experiences may explain why one disorder vs another develops in vulnerable individuals. Substantial disorder-specific genetic factors were found only for the substance use disorders.

Widiger and Clark recently wrote that the future of psychiatric nosology “rests on investigating the factors—genetic structures and environmental processes—that underlie the domain of psychopathology and determining how these factors combine to produce the range of clinically observed disorders.” We concur and hope these analyses contribute toward that goal.

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