

Models of Comorbidity for Multifactorial Disorders

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Summary

We develop several formal models for comorbidity between multifactorial disorders. Based on the work of D. N. Klein and L. P. Riso, the models include (i) alternate forms, where the two disorders have the same underlying continuum of liability; (ii) random multiformity, in which affection status on one disorder abruptly increases risk for the second; (iii) extreme multiformity, where only extreme cases have an abruptly increased risk for the second disorder; (iv) three independent disorders, in which excess comorbid cases are due to a separate, third disorder; (v) correlated liabilities, where the risk factors for the two disorders correlate; and (vi) direct causal models, where the liability for one disorder is a cause of the other disorder. These models are used to make quantitative predictions about the relative proportions of pairs of relatives who are classified according to whether each relative has neither disorder, disorder A but not B, disorder B but not A, or both A and B. For illustration, we analyze data on major depression (MD) and generalized anxiety disorder (GAD) assessed in adult female MZ and DZ twins, which enable estimation of the relative impact of genetic and environmental factors. Several models are rejected—that comorbid cases are due to chance; multiformity of GAD; a third independent disorder; and GAD being a cause of MD. Of the models that fit the data, correlated liabilities, MD causes GAD, and reciprocal causation seem best. MD appears to be a source of liability for GAD. Possible extensions to the models are discussed.

Introduction

General Aims

The aims of this paper are to (i) describe several models of comorbidity; (ii) derive formal mathematical models under multifactorial theory; (iii) extend these models to predict resemblance between and within disorders

across relatives of different degree; and (iv) illustrate the models with twin data on GAD and MD. For the most part, we shall address the 10 models described in Klein and Riso's (1994; hereafter referred to as KR) seminal work. Our main goal is a set of models that quantify the likelihood of observing patterns of comorbidity within and between relatives, so that the models' predictive abilities may be statistically compared.

Significance of Comorbidity

When patients have two co-occurring disorders, we refer to them as *comorbid* for these disorders (Feinstein 1970). Many studies have reported significant and substantial comorbidity for psychiatric disorders (Boyd et al. 1984; Docherty et al. 1986; Maser and Cloninger 1990; Biederman et al. 1991, 1992; Caron and Rutter 1991; Gunderson and Phillips 1991; Brady and Kendall 1992; Kendler et al. 1992b); and this is true of physical diseases as well (Carmelli et al. 1994). Some of the reported comorbidity may reflect Berkson's or other biases (Berkson 1946; discussed below), but genuine comorbidity raises several important research questions. Perhaps the most fundamental issues are at the nosological level: are the two disorders distinct, or do they reflect an arbitrary division of a single syndrome? Conversely, might persons comorbid for disorder A and B actually have a *third* disorder independent from A and B? These taxonomic questions form the basis of critical hypotheses in both research and clinical practice. For example: (i) Do "risk factors" correlate with disorder A because of comorbidity with B? (ii) Is it appropriate to give the same treatment for two disorders on the basis of their comorbidity? And (iii) what information about the etiology of the disorders can be gleaned from the study of their comorbidity? These questions identify co-occurrence of disorders as one of today's most important areas for methodological and substantive research.

One explanation for the appearance of two disorders within the same individual is simply *chance*. If the two disorders are independent, with prevalences p and q , then comorbid cases should arise with frequency pq . As will become clear, this statistical independence model is a submodel of many of the models we shall describe. Under this model, individuals with one disorder do not, on average, have any increase in risk to the second disorder. It is possible for both disorder A and disorder B to be familial within themselves, so that, for example, the

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rate of disorder A is elevated in those with relatives who have disorder A. No increase in risk for A would be seen in those with relatives with disorder B. This purely random origin of comorbidity is KR model 1.

When subjects are ascertained through hospital records or other “enriched” sources, several types of *sampling bias* may adversely affect results. Perhaps the most well-known bias is Berkson’s (Berkson 1946), whereby subjects with more than one disorder are more likely to be part of a clinical sample. This will occur when either disorder may merit clinic attendance, but not all subjects are referred. Thus, rates of comorbidity may be artifactually increased when assessed using clinically ascertained samples. A second potential source of bias—less frequently mentioned but probably quite common—is that clinical samples do not consist of a random sample of those who meet criteria within the population. Individuals with a greater number and severity of symptoms would be more likely to receive treatment and thus be part of an enriched sample. Furthermore, some symptoms (e.g., suicidal ideation or attempts) might be more likely to elicit treatment than others. To the extent that different symptoms can be differentially familial, or more or less longitudinally stable, clinical samples are not ideal for epidemiological research. Nonrandom sampling of even one of the disorders can lead to bias in the estimation of comorbid rates. While we recognize that for rare disorders there may be no alternative but to use clinical samples, and that such samples can increase power (Neale et al. 1994b), for etiological study it seems wise to use representative epidemiological samples wherever possible. A joint strategy—using both epidemiologic and clinical cases—may be beneficial (Kendler et al., in press) if the epidemiological sample is large enough to provide good estimates of population rates and a basis for comparison of the pattern of symptoms in the two samples. The methods we describe may readily be extended to cover such analyses. By restricting ourselves to studies that include epidemiological samples, we exclude sampling bias (KR model 2) as a source of comorbidity.

A third source of apparent comorbidity may be *population stratification*. The argument goes like this: if disorders A and B have non-overlapping sets of risk factors, but these risk factors both tend to be more common in certain strata of the population, then significant comorbidity may be observed across the sample as a whole. Such stratification would be expected to have effects on a classical twin study. If members of a twin pair occupied the same stratum—regardless of their zygosity—then evidence for common environmental factors (c^2) in the comorbidity between disorders should be found. That stratification can inflate the estimate of c^2 might seem to be disadvantageous. However, one might consider this finding to be informative nonetheless, because when

neither the particular risk factors nor the nature of the strata have been identified, it is not possible to directly test for their effects. Yet this method is weak because it relies on knowledge of the extent and origin of familial resemblance for the stratification variables. A much stronger approach is to measure the putative stratification variable and analyze it jointly with the disorders in question. If stratification is wholly responsible for comorbidity, there should be no comorbidity within strata. This hypothesis could be tested by splitting the sample into subgroups according to the stratification variable. Methods for fitting models to multiple groups are well known, and we have described elsewhere their application within structural equation modeling of twin data (Neale and Cardon 1992). The models we develop in this article could take advantage of measured stratification variables, should they be available.

Fourth, there is the possibility that comorbid cases are more common than would be expected by chance because of *symptom overlap*. As Klein and Riso (1994) point out, several symptoms are common to two disorders, e.g., major depression (MD) and borderline personality disorder. In this paper we shall restrict ourselves to fitting models to data at the level of diagnoses, rather than the constituent symptoms or items used to form them. However, it would seem appropriate to bring the full psychometric tool kit to bear on these more basic issues. For example, we might consider a latent-factor model with two diagnostic “traits,” which cause variation in the observed symptoms, and test for comorbidity by assessing the significance of the covariance between the factors. Alternatively, the diagnoses could be specified as dependent variables and the symptoms as independent variables. Comorbidity beyond that due to shared symptoms would then be evident in the correlation between the residuals of the diagnoses. If data on relatives are available, it is possible to discriminate between these models empirically (Neale et al. 1994a). Yet further models could be devised to match the particular method used to derive diagnoses; some discussion of the a priori relative merits may be found in Bagozzi and Hetherington (1994). Both latent-class analysis and item-response theory have been extended to exploit information collected from relatives by Eaves et al. (1987, 1993), and these methods would seem useful at the fundamental diagnostic level. Though important, these methods are outside the main focus of the present study and will not be discussed further.

Multifactorial Models of Comorbidity

In this section we develop models of comorbidity under multifactorial theory. To define the models with statistical rigor, we use some basic calculus and probability methods that some may find hard to read. As far as

Table 1

Summary of Threshold Models and Their Relationship to Those of Klein and Riso (1994)

MODEL	PRESENT ARTICLE	KLEIN AND RISO 1994	
		Model Number	Name
1	Chance	1	Chance
2	Sampling bias ^a	2	Sampling bias
3	Population stratification	3	Population stratification
4	Alternate forms	9	Alternative forms or phases
5	Random multiformity	7	Heterogeneity
6	Extreme multiformity	7	Heterogeneity of severe form
7	Submodels ^b of 3 and 4	5	One disorder encompasses the other
8	Submodels ^b of 3 and 4	6	Multiformity of one disorder
9	Three independent disorders	8	Third independent disorder
10	Correlated liabilities	11	Overlapping etiological processes
11	Causal model	10	One disorder is risk factor for the other
12	Reciprocal causation	...	Extension of KR 10

NOTE.—Models 1–3 are artifactual sources of comorbidity; 4–9 are ordered from closest to most distant relationship; and 10–12 are models in common use prior to this article.

^a Sampling bias may be excluded by design or statistically controlled.

^b Submodels where multiformity is of one disorder.

possible, we have tried to state in words and diagrams the essential features of the models so that the less technically oriented reader may still appreciate the underlying concepts without struggling through the algebra.

To help put the methods in context, we have summarized our models and their relationship to those of KR in table 1. The difference between KR models 5 (one disorder encompasses the other) and 6 (multiformity) is subtle at best, and does not yield different empirical predictions for familial or longitudinal data. As will become clear, we treat both KR 5 and 6 as restricted versions of our random and extreme multiformity models. In their full forms, our multiformity models are variants of KR model 7, heterogeneity.

The Threshold Model

Common to all the models in this paper is the idea that disease liability arises from the independent action of a large number of factors, each of small effect, which give rise to a normal distribution of liability. In the basic threshold model (Pearson and Lee 1903; Falconer 1965), individuals above an abrupt threshold have the disorder, whereas those below do not. We shall be elaborating on this model to address the alternative explanations of comorbidity. For now, we note that a normal distribution of liability may be quite closely approximated by relatively few factors (Kendler and Kidd 1986). Models for comorbidity within an individual will be presented first and followed by those for pairs of relatives.

Notation

The expressions for probabilities involve multiple integrals of the multivariate normal distribution, which

we shall write with simplified notation. In the models that follow, individuals may be at the lower (*L*), middle (*M*), or upper (*U*) part of the distribution with respect to the thresholds. Thus,

$$L = \int_{-\infty}^{t_1} \phi(R)dR \tag{1}$$

$$M = \int_{t_1}^{t_2} \phi(R)dR \tag{2}$$

$$U = \int_{t_2}^{\infty} \phi(R)dR . \tag{3}$$

For all models except extreme multiformity, $t_1 = t_2$ so $M = 0$, and we require only *L* and *U* to define the models. Subscripts A, B, and AB are used to denote the dimension being truncated. For the correlated liability models, we require joint probabilities that are computed by integrating over the bivariate normal. For example, individuals above threshold on dimension A but below threshold on dimension B would be written $UL_{A,B}$.

Models for Comorbidity within an Individual

Alternate forms.—Perhaps the closest relationship between disorders arises when there is one underlying dimension of liability, which gives rise to both disorders. Figure 1 illustrates this model in a modified path diagram. At the top is the latent liability or risk distribution *R* (normally distributed with zero mean and unit variance) which is then “filtered” through the threshold system to give rise to the phenotypes. The parameters in

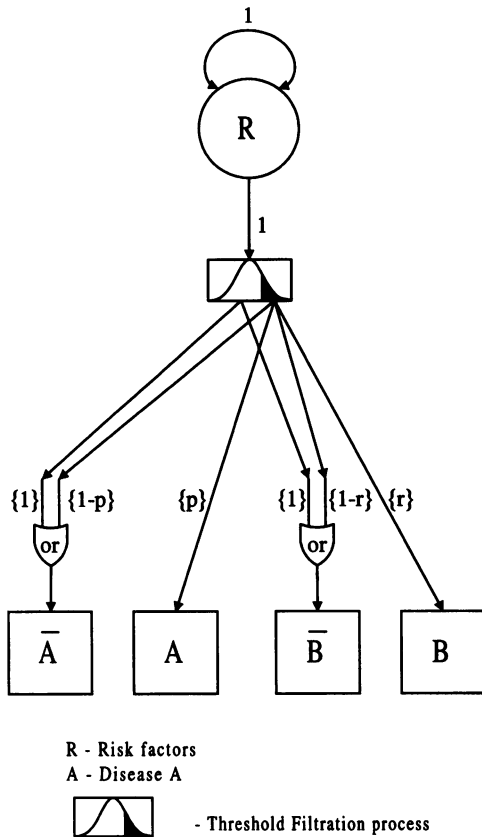


Figure 1 Alternate-forms model of individual comorbidity for diseases A and B. Individuals above threshold on R_A express disease A with probability p and disease B with probability r . Probabilities p and r are independent, so comorbid cases arise with frequency pr .

curly braces, $\{p\}$ and $\{r\}$, are not path coefficients, but represent the probability that individuals in the above-threshold part of the distribution will manifest the disorder. These probabilities may feed into the shield-shaped symbol (used in electrical engineering) which represents the “or” operation. Individuals do not display disorder A if they are (i) below threshold *or* (ii) above threshold, but asymptomatic (probability $1 - p$). Implicit in the diagram is the zero probability that those below threshold will manifest the disorder due to this particular threshold trait; the zero probability path has been omitted. We assume that the manifestation of A or B or both is entirely random, given that an individual has liability above threshold.

We make no a priori assumption about the alternation between the two disorders. They might be expressed at the same time in the same individual (e.g., agoraphobia and MD) or they might alternate (e.g., mania and depression in bipolar illness). If diagnoses were made at a particular instant in time, it would be impossible to identify any comorbidity in the latter case—individuals would express one disorder or the other but not both.

Therefore, we assume that diagnostic information covers a period of time during which both disorders have the opportunity to appear.

The probabilities of belonging to the four combinations of disease state (neither A nor B; A but not B; B but not A; and both A and B) are

$$P(\bar{A}, \bar{B}) = L + (1 - p)(1 - r)U \quad (4)$$

$$P(\bar{A}, B) = p(1 - r)U \quad (5)$$

$$P(A, \bar{B}) = (1 - p)rU \quad (6)$$

$$P(A, B) = prU, \quad (7)$$

where, e.g., $P(A, \bar{B})$ denotes the probability of individuals having A but not B; p and r are the probabilities that individuals above threshold t manifest A and B respectively; and L and U are the probabilities of being below or above threshold, as defined above. This model corresponds to KR model 9 (the pure and comorbid conditions are different phases, or expressions of the same disorder). Two disorders with a single underlying dimension of liability are very closely related indeed. This model implies that comorbid cases are no different in mean liability than those who have only one of the disorders.

Random multiformity.—Under this model, excess comorbidity occurs when some cases of B are epiphenomena of disorder A. By *epiphenomena*, we mean that having disorder A can itself generate the symptoms of disorder B. These symptoms arise because of disorder A and are entirely unrelated to liability for disorder B. We can specify this model with two independent dimensions of liability, called R_A and R_B , and allow the epiphenomenon process to be symmetric. Thus, for example, those above threshold on the MD dimension may exhibit symptoms of general anxiety disorder (GAD), and those above threshold on the GAD dimension may exhibit symptoms of MD. We call this model *random multiformity* because we assume that the probability of displaying the symptoms of disorder B as an epiphenomenon of disorder A is flat. Those who are only slightly above threshold for A have exactly the same probability of displaying disorder B’s symptoms as the most extreme cases have. This assumption will be modified in the extreme multiformity model below.

Figure 2 shows a graph of this model, which includes both the shield-shaped “or” operation and a spade-shaped “and” operation. Individuals with disorder B may be either above threshold for the pure form of B, *or* one of a proportion p of those above threshold for A who meet criteria for B. Tracing up from \bar{B} , we see that to be free of disorder B requires that one is below threshold for B *and* either below threshold for A *or*

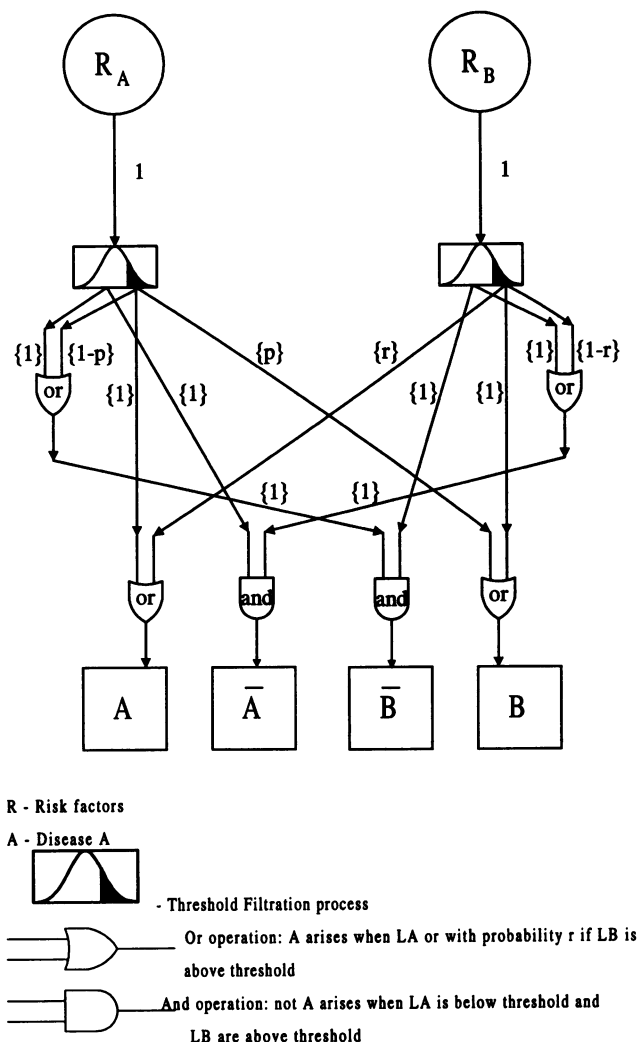


Figure 2 Random-multiformity model of liability to diseases A and B. Disorder A arises if individuals are above threshold on R_A or with probability p if they are above threshold on R_B . Disorder B arises if individuals are above threshold for R_B or with probability r if they are above threshold for R_A .

above threshold for A but not showing B as an epiphenomenon of A (probability $1 - p$).

The four possible classes of affection status with respect to these criteria have the following probabilities:

$$P(\bar{A}, \bar{B}) = L_A \cdot L_B \tag{8}$$

$$P(\bar{A}, B) = (1 - r)L_A \cdot U_B \tag{9}$$

$$P(A, \bar{B}) = U_A \cdot (1 - p)L_B \tag{10}$$

$$P(A, B) = U_A \cdot (U_B + pL_B) + rL_A \cdot U_B, \tag{11}$$

where r is the probability of expressing disorder A as an epiphenomenon of disorder B.

In its full form, this model represents a variant of KR model 7 (heterogeneity of the comorbid condition). When the probability of becoming a comorbid case is set to zero for one of the dimensions, the model is a variant of KR model 6 (multiformity), which encompasses their model 5 (one disorder is encompassed by the other). In common with the alternate-forms model, comorbid cases that arise because they are above threshold for disorder A and are part of the epiphenomenon set have the same average liability to disorder A as those with the pure form of A. However, these individuals have much lower average liability to disorder B than those with the pure form of B.

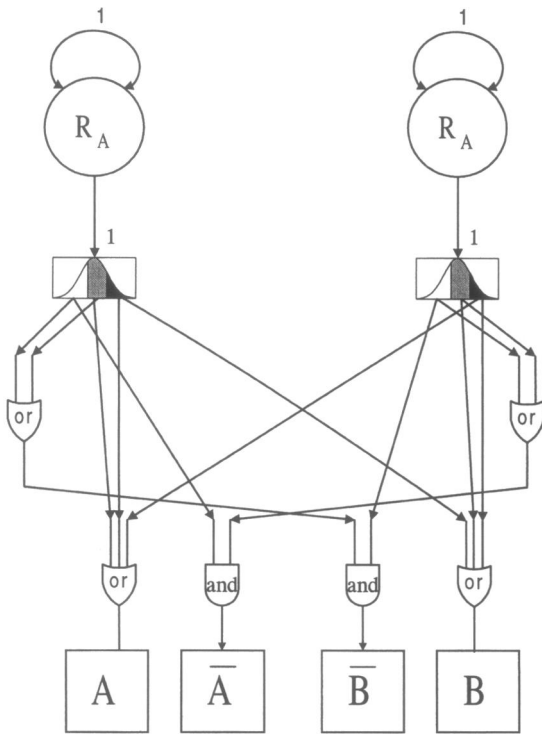
This model represents a quite novel idea about comorbidity. If an individual is affected with disorder A, then affection status per se gives rise to increased risk for disorder B. It is very different from liability models, which are *homoscedastic*; that is, the relationship between the disorders is constant across the whole range of liabilities.

Extreme multiformity.—This second variant of multiformity also models a process where some of those affected with one disorder show the symptoms of the other. In contrast to random multiformity, we suppose that the atypical form arises at the extreme of the distribution of liability, which we model by imposing two thresholds on the liability continuum. Considering the liability for A, those below the first threshold are free of risk for A from this source; those above the first but below the second threshold manifest disorder A only; and those above the second threshold manifest both A and B. We allow the same two-threshold process to operate for the liability to disorder B. Therefore, comorbid cases may arise in three distinct ways: above the second threshold on either R_A or R_B , or between the first and second threshold on both dimensions.

The model is illustrated in the modified path diagram shown in figure 3. The “or” operator in this case has three inputs; if any one is active then the outcome will be affected status. Note that we assume that the liability for A is independent of liability for B—comorbidity arises primarily from the extremes of the two dimensions. A number of submodels of this model are noteworthy: (i) if the second threshold in dimension A is set to $+\infty$, then excess (i.e., greater than chance) comorbidity arises solely from those above the second threshold in dimension B; (ii) the converse of (i), that is, excess comorbidity arises solely from those above the second threshold of A; and (iii) if t_{2A} and t_{2B} are both set to $+\infty$, then comorbid cases arise only by chance.

The probabilities of the four outcomes for an individual are

$$P(\bar{A}, \bar{B}) = L_A \cdot L_B \tag{12}$$



R - Risk factors
 A - Disease A
 - Threshold Filtration process
 Or operation: A arises when LA is above threshold 1 or if LB is above threshold 2
 And operation: not A arises when LA is below threshold 1 and LB is below threshold 2

Figure 3 Extreme-multiformity model of liability to diseases A and B. Disorder A arises if individuals are above either threshold on R_A or above the second threshold on R_B . Disorder B arises if individuals are above either threshold for R_B or if they are above the second threshold for R_A .

$$P(\bar{A}, B) = L_A \cdot M_B \quad (13)$$

$$P(A, \bar{B}) = M_A \cdot L_B \quad (14)$$

$$P(A, B) = U_A + U_B - U_A \cdot U_B + M_A \cdot M_B \quad (15)$$

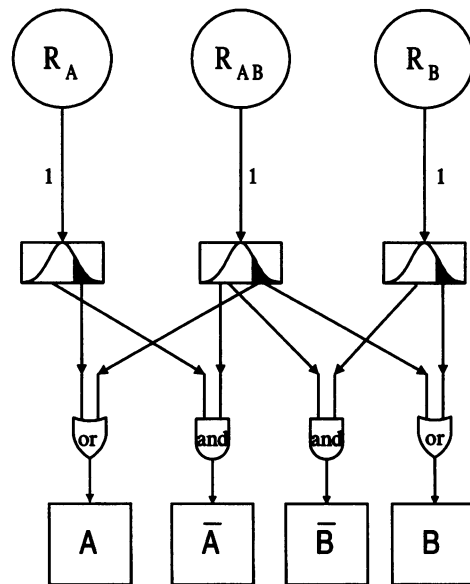
In its full form, this model is a variant of KR model 7. When the upper threshold of one of the dimensions is set to $+\infty$, no comorbid cases arise from high liability on this dimension. This asymmetric form of the model is a variant of KR model 6 (multiformity), which subsumes their model 5 (one disorder is encompassed by the other).

As with the random-multiformity model, this model

suggests that there is something about affected status that gives rise to a sharply increased risk to a second disorder. The key difference between extreme and random multiformity is that under extreme multiformity the abrupt change in risk only applies to those cases with high liability (above the second threshold). Therefore, comorbid individuals have a higher mean liability than do those with the pure form.

Three independent disorders.—Alternate forms might be regarded as the closest relationship between disorders, and three independent disorders might be regarded as the most distal. Not only are A and B entirely independent distributions, but comorbid cases arise from a third independent dimension, AB . An individual has disorder A if either R_A is above threshold or R_{AB} is above threshold. Likewise, an individual is affected with disorder B if either $R_B > t_B$ or $R_{AB} > t_{AB}$. The model is shown in figure 4; the “or” operation combines the two possibilities for affected status.

The probabilities for the four classes of affected status are



R - Risk factors
 A - Disease A
 Threshold Filtration process
 Or operation: A arises when LA or LAB are above threshold
 And operation: not A arises when LA and LAB are below threshold

Figure 4 Three-independent-disorder model for an individual's liability to diseases A and B. Disorder A arises when individuals are above threshold on either R_A or R_{AB} . Disorder B arises when individuals are above threshold on either R_B or R_{AB} . All paths below the filter process carry probability 1.

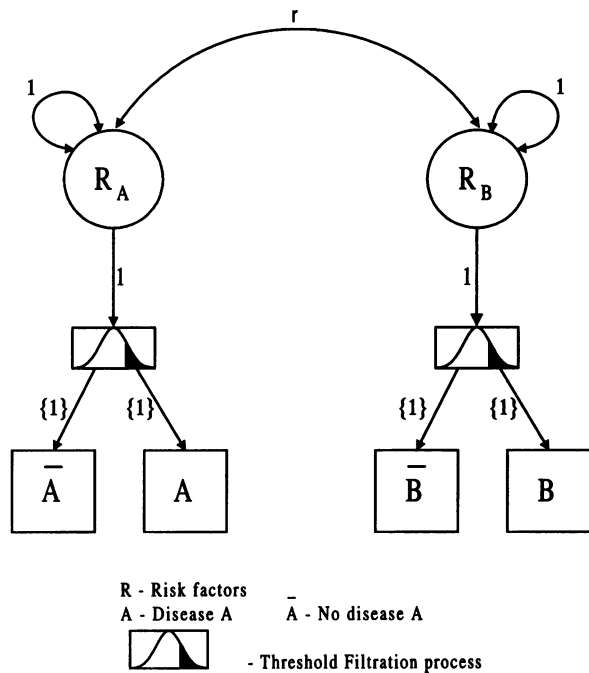


Figure 5 Correlated liability model of individual comorbidity for diseases A and B. Individuals have disease A if they are above threshold on L_A and disease B if they are above threshold on R_B . Comorbidity arises when r , the correlation between the risk factors R_A and R_B , is >0 . Paths in curly braces indicate probabilistic functions: those from the shaded portion of the filter are affected with probability 1.

$$P(\bar{A}, \bar{B}) = L_A \cdot L_{AB} \cdot L_B \tag{16}$$

$$P(\bar{A}, B) = L_A \cdot L_{AB} \cdot U_B \tag{17}$$

$$P(A, \bar{B}) = U_A \cdot L_{AB} \cdot L_B \tag{18}$$

$$P(A, B) = U_A \cdot L_{AB} \cdot U_B + U_{AB} \tag{19}$$

This model corresponds to KR model 8. Though somewhat implausible, it is the only model that specifies that excess comorbidity is due to some quite separate process from those that give rise to the pure forms.

Correlated liability.—Finally, we consider comorbidity that arises because the liability (or risk factors) correlate, as illustrated in figure 5. Given two states, with (A) and without (\bar{A}) disorder, there are four possible combinations for any person, with respect to two disorders, A and B. If the liabilities (R) to these disorders have a joint distribution function $\phi(R_A, R_B)$, then the probability of the four states may be written

$$P(\bar{A}, \bar{B}) = LL_{A,B} \tag{20}$$

$$P(\bar{A}, B) = LU_{A,B} \tag{21}$$

$$P(A, \bar{B}) = UL_{A,B} \tag{22}$$

$$P(A, B) = UU_{A,B} \tag{23}$$

The correlation in liability is the key feature of this model; it corresponds to KR model 9, correlated risk factors. Under certain circumstances (described below in the section “Models for genetically informative data”) pairs of relatives may give information to resolve a special form of this model, where one disorder causes the other (KR model 10). The chance model is a submodel of correlated liability, where the correlations are fixed at zero.

We assume that ϕ , the joint liability to disorders A and B, is bivariate normal, and that there is an abrupt threshold above which individuals are affected. These assumptions reflect an arbitrary choice of model and could be replaced by other distributions and other relationships between liability and disorder.

Models for Pairs of Relatives

Given cross-sectional data collected from unrelated individuals, there is almost no information to discriminate between different models of comorbidity (e.g., the one-, two-, and three-disorder variants shown in figs. 1–5). However, when we extend these models to data from relatives, the information on comorbidity rates across family members may resolve the different origins of comorbidity. Therefore, in this section we derive analogous formulas for pairs of relatives, in whom there are 16 possible combinations of affected and unaffected status for the two disorders. For notation we refer to relatives as 1 or 2, so that the pair status $A1B1A2\bar{B}2$ would indicate that relative 1 is comorbid for A and B but relative 2 has only disorder A. Fortunately, this 4×4 table is symmetric across the diagonal (e.g., $P(A1B1\bar{A}2\bar{B}2) = P(\bar{A}1\bar{B}1A2B2)$), so we only need derive and compute 10 integrals.

We shall not offer proofs of the equations that follow, as this would add much tedium in return for little insight. The reader who wishes to check the predicted frequencies may do so with a little applied logic, which we illustrate in appendix A.

Notation for pairs.—We expand the L, M, U notation to deal with pairs of relatives. When considering one liability dimension with one threshold, pairs may be concordant for being below threshold (LL), discordant (LU or UL) or concordant for being above threshold (UU). For the extreme multiformity model, there are nine possible configurations of pairs, being every pairwise combination of L, M and U with L, M and U . In the present treatment, the thresholds are set equal for the first and second relative, so only six of these combinations are distinct:

$$LL_A = \int_{-\infty}^{t_1^1} \int_{-\infty}^{t_1^1} \phi(R_{A1}, R_{A2}) dR_{A2} dR_{A1} \quad (24)$$

$$LM_A = \int_{-\infty}^{t_1^1} \int_{t_1^1}^{t_2^1} \phi(R_{A1}, R_{A2}) dR_{A2} dR_{A1} \quad (25)$$

$$LU_A = \int_{-\infty}^{t_1^1} \int_{t_2^1}^{\infty} \phi(R_{A1}, R_{A2}) dR_{A2} dR_{A1} \quad (26)$$

$$MM_A = \int_{t_1^1}^{t_2^1} \int_{t_1^1}^{t_2^1} \phi(R_{A1}, R_{A2}) dR_{A2} dR_{A1} \quad (27)$$

$$MU_A = \int_{t_1^1}^{t_2^1} \int_{t_2^1}^{\infty} \phi(R_{A1}, R_{A2}) dR_{A2} dR_{A1} \quad (28)$$

$$UU_A = \int_{t_2^1}^{\infty} \int_{t_2^1}^{\infty} \phi(R_{A1}, R_{A2}) dR_{A2} dR_{A1} \quad (29)$$

where $\phi(R_{A1}, R_{A2})$ is the bivariate normal probability density function. In all models other than extreme multiformity $t_1 = t_2$, and $LM_A = MM_A = MU_A$, so the probabilities may be expressed using LL_A , LU_A , and UU_A alone.

Alternate forms in pairs.—This model is based on a single underlying dimension of liability combined with probabilistic expression of A or B or both. The liabilities of a pair of relatives may correlate, so we require double integration to express the probabilities of observing each pair type. No subscript is needed for the $LL/LU/UU$ notation, because there is only one dimension per individual. The pairwise probabilities are

$$P(\bar{A}1, \bar{B}1, \bar{A}2, \bar{B}2) = LL + 2(1 - p)(1 - r)UL + (1 - p)^2(1 - r)^2UU \quad (30)$$

$$P(\bar{A}1, \bar{B}1, \bar{A}2, B2) = r(1 - p)LU + (1 - p)^2r(1 - r)^2UU \quad (31)$$

$$P(\bar{A}1, \bar{B}1, A2, \bar{B}2) = p(1 - r)LU + p(1 - p)(1 - r)^2UU \quad (32)$$

$$P(\bar{A}1, \bar{B}1, A2, B2) = prLU + p(1 - p)r(1 - r)UU \quad (33)$$

$$P(\bar{A}1, B1, \bar{A}2, B2) = (1 - p)^2r^2UU \quad (34)$$

$$P(\bar{A}1, B1, A2, \bar{B}2) = p(1 - p)r(1 - r)UU \quad (35)$$

$$P(\bar{A}1, B1, A2, B2) = p(1 - p)r^2UU \quad (36)$$

$$P(A1, \bar{B}1, A2, \bar{B}2) = p^2(1 - r)^2UU \quad (37)$$

$$P(A1, \bar{B}1, A2, B2) = p^2r(1 - r)UU \quad (38)$$

$$P(A1, B1, A2, B2) = p^2r^2UU \quad (39)$$

Under this model, the concordant disorder-free pairs comprise several types, whereas only one configuration leads to concordant comorbid pairs.

Random multiformity in pairs.—When we examine a disorder with heterogeneous comorbidity in pairs of relatives, the predicted probabilities become more complex. This is because there are alternative processes that may give rise to the disorders. The pair of relatives is the unit of observation, so the total number of alternatives is the product of the number of alternatives for the two relatives. The probabilities under this model are

$$P(\bar{A}1, \bar{B}1, \bar{A}2, \bar{B}2) = LL_A \cdot LL_B \quad (40)$$

$$P(\bar{A}1, \bar{B}1, \bar{A}2, B2) = LL_A \cdot (1 - r)LU_B \quad (41)$$

$$P(\bar{A}1, \bar{B}1, A2, \bar{B}2) = (1 - p)LU_A \cdot LL_B \quad (42)$$

$$P(\bar{A}1, \bar{B}1, A2, B2) = LU_A \cdot (pLL_B + LU_B) + LL_A \cdot rLU_B \quad (43)$$

$$P(\bar{A}1, B1, \bar{A}2, B2) = LL_A \cdot (1 - r)^2UU_B \quad (44)$$

$$P(\bar{A}1, B1, A2, \bar{B}2) = (1 - p)LU_A \cdot (1 - r)LU_B \quad (45)$$

$$P(\bar{A}1, B1, A2, B2) = (1 - r)LU_A \cdot (pLU_B + UU_B) + LL_A \cdot rLL_B \quad (46)$$

$$P(A1, \bar{B}1, A2, \bar{B}2) = (1 - p)^2UU_A \cdot LL_B \quad (47)$$

$$P(A1, \bar{B}1, A2, B2) = UU_A \cdot (p(1 - p)LL_B + (1 - p)LU_B) + (1 - p)LU_A \cdot rLU_B \quad (48)$$

$$P(A1, B1, A2, B2) = p^2UU_A \cdot LL_B + 2pUU_A \cdot LU_B + UU_A \cdot UU_B + LU_A \cdot 2rUU_B + 2pLU_A \cdot rLU_B + LL_A \cdot r^2UU_B \quad (49)$$

Concordant comorbid pairs are thus a heterogeneous collection of various ways to become affected, whereas the concordant normal pairs are of a single type. This is the reverse of the situation for alternate forms.

Extreme multiformity in pairs.—Expressions for the extreme multiformity model are complicated by the two-threshold model. For a single individual, we can cross-tabulate the three possible locations (below first threshold, between first and second, and above second threshold) on the A dimension with the three locations on the B dimension, giving nine possible types. Cross-tabulating these with the nine possible types to which a relative may belong yields 81 possibilities, which are then partitioned and summed to form the probabilities for the pair types. This model offers several ways for an individual to be comorbid; concordant comorbid pairs arise from 36 of the 81 cells. Although it would be simple to obtain this last cell by subtraction, we prefer to compute it to verify that the probabilities of the 16 pair types sum to unity. The probabilities are

$$P(\bar{A}1, \bar{B}1, \bar{A}2, \bar{B}2) = LL_A \cdot LL_B \quad (50)$$

$$P(\bar{A}1, \bar{B}1, \bar{A}2, B2) = LL_A \cdot LM_B \quad (51)$$

$$P(\bar{A}1, \bar{B}1, A2, \bar{B}2) = LM_A \cdot LL_B \quad (52)$$

$$P(\bar{A}1, \bar{B}1, A2, B2) = LU_A \cdot (LL_B + LM_B + LU_B) + LM_A \cdot (LM_B + LU_B) + LL_A \cdot LU_B \quad (53)$$

$$P(\bar{A}1, B1, \bar{A}2, B2) = LL_A \cdot MM_B \quad (54)$$

$$P(\bar{A}1, B1, A2, \bar{B}2) = LM_A \cdot LM_B \quad (55)$$

$$P(\bar{A}1, B1, A2, B2) = LU_A \cdot (LM_B + MM_B + MU_B) + LM_A \cdot (MM_B + MU_B) + LL_A \cdot MU_B \quad (56)$$

$$P(A1, \bar{B}1, A2, \bar{B}2) = MM_A \cdot LL_B \quad (57)$$

$$P(A1, \bar{B}1, A2, B2) = MU_A \cdot (LL_B + LM_B + LU_B) + MM_A \cdot (LM_B + LU_B) + LM_A \cdot LU_B \quad (58)$$

$$P(A1, B1, A2, B2) = UU_A + UU_B - UU_A \cdot UU_B + MU_A \cdot (LM_B + LU_B) + MM_B + MU_B + MU_B + LU_A \cdot (LU_B + MU_B)$$

$$+ MU_A + MM_A \cdot (MM_B + MU_B + MU_B) + LM_A \cdot MU_B + LU_A \cdot (LU_B + MU_B) + LM_A \cdot MU_B. \quad (59)$$

The constitution of the different pair types is similar in pattern to the random multiformity model.

Three independent disorders in pairs of relatives.—This model is similar to the multiformity models in that only two-dimensional integrals are required to specify comorbidity across pairs of relatives. However, complexity arises when one or both of the individuals is comorbid for A and B, because of the two possible causes of comorbidity—being above threshold on both A and B or being above threshold on AB.

The probabilities are

$$P(\bar{A}1, \bar{B}1, \bar{A}2, \bar{B}2) = LL_A \cdot LL_{AB} \cdot LL_B \quad (60)$$

$$P(\bar{A}1, \bar{B}1, \bar{A}2, B2) = LL_A \cdot LL_{AB} \cdot LU_B \quad (61)$$

$$P(\bar{A}1, \bar{B}1, A2, \bar{B}2) = LU_A \cdot LL_{AB} \cdot LL_B \quad (62)$$

$$P(\bar{A}1, \bar{B}1, A2, B2) = L_A \cdot LL_{AB} \cdot LL_B + LU_A \cdot LL_{AB} \cdot LU_B \quad (63)$$

$$P(\bar{A}1, B1, \bar{A}2, B2) = LL_A \cdot LL_{AB} \cdot UU_B \quad (64)$$

$$P(\bar{A}1, B1, A2, \bar{B}2) = LU_A \cdot LL_{AB} \cdot LU_B \quad (65)$$

$$P(\bar{A}1, B1, A2, B2) = L_A \cdot LU_{AB} \cdot U_B + LU_A \cdot LL_{AB} \cdot UU_B \quad (66)$$

$$P(A1, \bar{B}1, A2, \bar{B}2) = UU_A \cdot LL_{AB} \cdot LL_B \quad (67)$$

$$P(A1, \bar{B}1, A2, B2) = L_A \cdot LU_{AB} \cdot L_B + UU_A \cdot LL_{AB} \cdot LU_B \quad (68)$$

$$P(A1, B1, A2, B2) = UU_{AB} + UU_A \cdot LL_{AB} \cdot UU_B + 2U_A \cdot LU_{AB} \cdot U_B. \quad (69)$$

There are several ways to become a concordant comorbid pair under this model, and only one way to be a concordant normal pair.

Correlated liabilities in pairs.—Under the correlated liability model for an individual, the liability to A correlates with the liability of B, so the likelihood involves two-dimensional integration. When we extend the model to cover pairs of relatives, we must integrate over four dimensions: the liabilities for A and B in both members

of the twin pair. Assuming multivariate normality, we can express each of the 16 cells of the contingency table as a quadruple integral, with only the limits of the integrals changing from one cell to the next. For example,

$$\begin{aligned}
 &P(A1, B1, A2, B2) \\
 &= UUUU_{A1,B1,A2,B2} \\
 &= \int_{t_A}^{\infty} \int_{t_B}^{\infty} \int_{t_A}^{\infty} \int_{t_B}^{\infty} \phi(R_{A1}, R_{B1}, R_{A2}, R_{B2}) \\
 &\quad \times dR_{B2}dR_{A2}dR_{B1}dR_{A1}
 \end{aligned}
 \tag{70}$$

is the probability that both relatives are comorbid.

Perhaps the most striking aspect of this model is its simplicity; it makes very few assumptions about the nature of comorbidity and familiarity. Liability to the two disorders in pairs of relatives is assumed to be multivariate normal, which is most commonly assumed when analyzing familial resemblance for either qualitative or quantitative traits. Despite this simplicity, the model is able to predict a wide variety of patterns of comorbidity. This predictive power comes from varying the four correlations: within-person across traits; across relatives within trait A; across relative within trait B; and across relatives across traits. One drawback is that it is tedious to compute with current hardware and software.

Models for Genetically Informative Data

We note that every liability dimension is amenable to variance partitioning when genetically informative data are available. Thus in a classical twin or adoption study we can partition trait variance into additive genetic (G), common environment (C) and specific environment (E) components (Neale and Cardon 1992). This partitioning is achieved through appropriate parameterization of the model so that, for example, additive genetic variance makes MZ pairs correlate twice as highly as DZ pairs, whereas common environment variance increases MZ and DZ resemblance equally. Specific environmental factors are unique to each individual (and subsume measurement error) and thus contribute only to within-person variance. A large proportion of specific environment variance implies low twin correlations. Figure 6 shows path diagrams for MZ and DZ twin resemblance on the basis of this simple structural equation model. The model is fitted to both data groups simultaneously, a procedure that we have described in detail elsewhere (Heath et al. 1989; Neale and Cardon 1992).

The alternate-forms model specifies a single dimension of liability, so the correlation between liabilities in pairs of MZ or DZ twins relatives can be derived from a simple univariate model. In the multiformity models there are two dimensions (for liability to A and B) but they are independent of each other, so two univariate

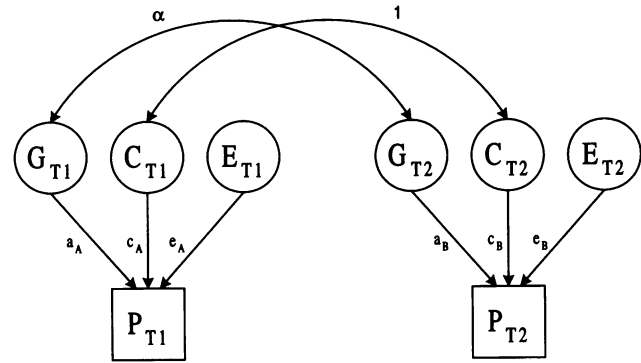


Figure 6 Path diagram of a univariate model of resemblance for MZ and DZ twins, T1 and T2. Variation in the observed phenotypes (P_{T1} and P_{T2}) is caused by additive genetic factors (G), environmental factors shared by members of a twin pair (C), and environmental factors unique to each twin (E). Parameter α is fixed at 1.0 for MZ twin pairs and at .5 for DZ.

models can be used for genetically informative data from relatives. Similarly, the liabilities in the three-disorders model are assumed to be independent so three univariate models are needed.

Only in the correlated liabilities model do we need apply a bivariate model of resemblance between relatives. Such bivariate genetic analysis would typically be carried out using summary statistics such as polychoric correlations and their asymptotic weight matrices (Browne 1984; Jöreskog and Sörbom 1989; Neale and Cardon 1992). However, we cannot use that approach for the other models described in this paper, so we use this more computationally intensive method to obtain fit statistics on the same scale. Another advantage of our chosen method is that it is, in principle, simple to modify for nonrandom samples, such as relatives of probands.

Figure 7 shows some of the possible bivariate models for genetically informative data. The most general of these is the Cholesky or triangular factor model, in which the latent variables for trait A also affect liability for trait B. This model is equivalent to allowing the latent factors of trait A to correlate with their counterparts for trait B (e.g., C_A correlates with C_B). Of special note are direction-of-causation models (Neale and Cardon 1992; Heath et al. 1993; Duffy and Martin 1994; Neale et al. 1994c), in which one disorder may be specified as a cause of the other, or the two may reciprocally interact. Some caution is required with these models because they can produce seriously biased results if the diagnostic instruments have markedly unequal reliabilities (Heath et al. 1993). If the reliabilities are equal, or if estimates of the reliabilities are available, then these direction-of-causation models may be used to assess the fit of KR model 10.

Model Identification

For the reader who has data on relatives, but not from different classes of relative, most of the models presented

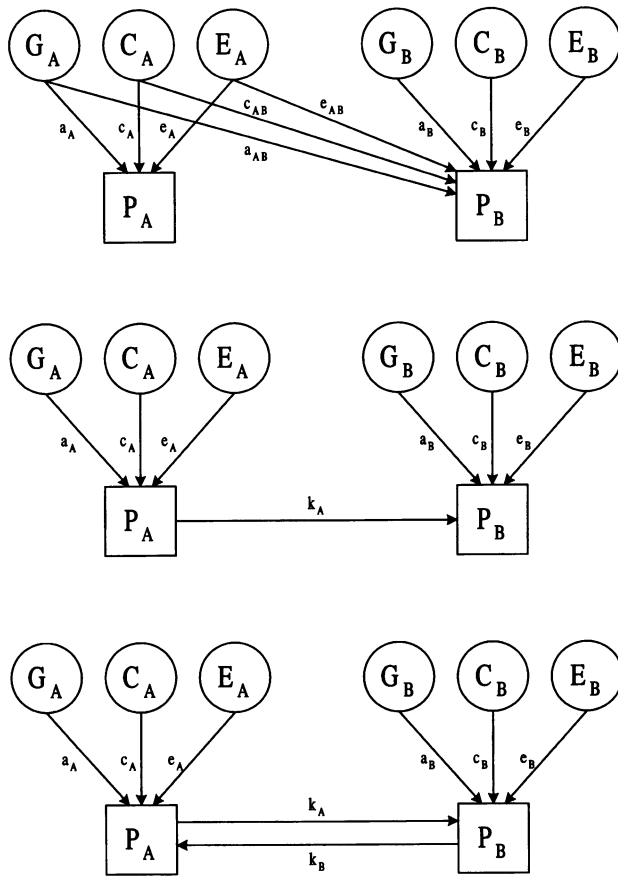


Figure 7 Three models for correlated liability that may be resolved with data from twins. *Top*, triangular decomposition or “Cholesky” factor model for additive genetic (G), common environment (C), and specific environment (E) components of phenotypic variation (P) in two traits (subscripts A and B). *Middle*, causal model in which A is a cause of B. *Bottom*, reciprocal causation model in which A and B are causes of each other in a feedback loop.

here could be used in a simplified form. Perhaps easiest would be to fix additive genetic effects at zero, in which case the common environment component would reflect both genetic and shared environmental factors.

It is not simple to prove identification algebraically when complex nonlinear functions of parameters are used to form predicted statistics. This problem applies to structural equation modeling in general and is especially true in the models used here. Under these circumstances, support for the hypothesis that the model is identified may be obtained using the following procedure:

1. Select a random set of values of the parameters, θ_1
2. Generate predicted frequencies under the model using θ_1
3. Use the predicted frequencies from step 2 as data, and begin optimization from a different set of parameter values, θ_2

If optimization starting at θ_2 yields estimates that equal

θ_1 (and therefore a perfect fit to the data) this is support for identification of the model. If this procedure yields a different set of parameters, but they fit the data equally well, the hypothesis of identification is rejected. We carried out this procedure several times for each of the models described in this article, and obtained support for the hypothesis that they are all identified.

Practical Model Fitting

A useful feature of these models is that the probabilities of the 16 possible pairwise patterns of affected status on disorders A and B may be reduced to 10 equations because of symmetry. In the same way, the observed frequencies may be expressed as 16 patterns and then reduced to 10. Ordinarily, such a strategy would not be recommended, because it ignores the asymmetry across replicate statistics, which might indicate failure of the statistical assumptions of the model. In this case, however, we are likely to be faced with relatively low cell frequencies, which can cause departures from the expected behavior-of-fit statistics. We judge this latter problem to be more important than the minor loss of information incurred by combining equivalent observations.

The possibility of low observed cell frequencies also guides our choice of fit statistic. Suitable fit statistics include the negative log-likelihood, and minimum χ^2 . We might opt for the likelihood statistic because of its well-known advantageous properties of minimum variance, invariance to transformation, and robustness (Fisher 1925). Comparisons between models and sub-models would be performed with the likelihood-ratio test given by twice the difference in the negative log-likelihood, which is asymptotically distributed as χ^2 . However, the approach to asymptote is slow when sample sizes are small, and minimum χ^2 has superior performance in this respect (Agresti 1990). Therefore we compute the function:

$$F = \sum_{i=1}^{10} \frac{(O_i - E_i)^2}{E_i},$$

where O_i is the observed cell frequency, E_i is the expected cell frequency (computed as NP_i where $N = \sum_{i=1}^{10} O_i$ and P_i is the predicted probability according to the model in question). Although there is no built-in fit function of this type in Mx, it is easy to custom-design such functions in this package (Neale 1994). A sample script to fit the extreme multiformity model is given in appendix B. Scripts for this and the other models are available through the Internet (anonymous ftp to opal.vcu.edu and look in ~ftp/pub/mx/comorb).

Application: GAD and MD

Subjects and Measures

As outlined in detail elsewhere (Kendler et al. 1992*b*), as part of a longitudinal study of the genetic and environmental risk factors for common psychiatric disorders in women, we personally interviewed 2,163 female twins from the population-based Virginia Twin Register with a mean age (+SD) of 30.1 + 7.6 years, including both members of 1,033 pairs. The refusal rate during the personal interviews phase of this project, conducted by interviewers with Master’s degrees in Social Work or at least 2 years clinical experience, was 8%. All individuals were interviewed by an individual blind to the psychopathologic status of their co-twin. Zygosity was determined by an algorithm based on questionnaire responses, photographs, and, where these sources were ambiguous, DNA polymorphisms, and yielded 590 MZ pairs, 440 DZ pairs, and 3 pairs of unknown zygosity.

Lifetime diagnoses, using DSM-III-R criteria (American Psychiatric Association 1987) were made by one of us (K.S.K.) on blind review of the interview protocols, which included adapted sections of the SCID interview (Spitzer et al. 1987) for MD and GAD. For MD, all analyses conducted here use the DSM-III-R criteria. For GAD, we modified the DSM-III-R criteria in two important ways. First, we reduced the required minimum duration of illness from 6 mo to 1 mo, as originally proposed in DSM-III (American Psychiatric Association 1980). Second, we eliminated criterion C (“The disturbance does not occur only during the course of a mood disorder or a psychotic disorder”) so that GAD was diagnosed without a diagnostic hierarchy. The full DSM-III-R criteria for GAD were not used, because they produced very low prevalence rates in our sample, with resulting low statistical power. In addition, multiple threshold analyses suggested that 1-mo and 6-mo GAD could be conceptualized as disorders on a single continuum of liability (Kendler et al. 1992*a*). Furthermore, the change from a 1-mo minimum duration of illness in DSM-III (American Psychiatric Association 1980) to 6-mo in DSM-III-R (American Psychiatric Association 1987) was made without strong empirical support, and one previous study (Breslau and Davis 1985) suggests that this change may have confounded rather than improved the category’s validity.

Results

The observed frequencies of the 16 cells of the contingency table of GAD and MD diagnoses within MZ and within DZ twin pairs are shown in table 2. Frequencies in row and column *ij* were added to those of cell *ji* for analysis, as described above. The data reflect the somewhat high lifetime rates of GAD and MD in our sample, and show substantial comorbidity.

Table 2

Observed Frequencies for Pairwise Diagnostic Data on MD and in MZ and DZ Female Twins

		TWIN 1			
		No MD		MD	
TWIN 2		No GAD	GAD	No GAD	GAD
A. MZ Twins					
No MD	No GAD	282	25	54	29
No MD	GAD	19	3	3	9
MD	No GAD	31	10	8	18
MD	GAD	36	6	9	28
B. DZ Twins					
No MD	No GAD	155	20	38	34
No MD	GAD	22	4	1	9
MD	No GAD	38	8	11	13
MD	GAD	42	6	21	18

Table 3 shows the goodness-of-fit χ^2 , df, probability, and Akaike’s information criterion ($AIC = \chi^2 - 2df$) for 13 models that we fitted to the data. These models do not form an exhaustive set; we did not seek “better” submodels by fixing parameters to equal zero. The model with the largest negative AIC may be regarded as the most parsimonious explanation of the data (Williams and Holahan 1994), although the differences here are not large, and their confidence intervals overlap.

Model 1, chance (no comorbidity within or between relatives other than by chance), is strongly rejected by these data, which show considerable aggregation of GAD and MD. The simple alternate-forms model (model 2) fits somewhat poorly (the probability level indicates that the observed frequencies significantly depart from those predicted by the model at the .05 level), but by AIC it is ranked fifth and is not far behind the best. Random multiformity (model 3) fits the data slightly worse than model 2 and uses more parameters, so it is considerably poorer by AIC. Its first submodel (model 4), in which a random subset of those with MD may exhibit the symptoms for GAD, but not vice versa, fits the data almost as well, with one fewer parameter, and is slightly more parsimonious. The converse model (model 5; excess comorbid cases arise because those with GAD exhibit MD) fits poorly. This same general pattern is repeated for the extreme multiformity models (models 6–8), except that they all fit better than their random multiformity counterparts, and the full extreme multiformity model (model 6) fits substantially better than the multiformity of MD alone (model 7). The three-independent-disorders model (model 9) is rejected by the data; by AIC it is one of the worst.

Table 3

Fit Statistics Obtained for Various Models of Comorbidity Applied to Data on GAD and MD in Adult Female Twins

MODEL NUMBER AND NAME	FIT STATISTIC			
	χ^2	df	<i>p</i>	AIC
1 (Chance)	412.54	12	.00	388.54
2 (Alternate forms)	23.74	13	.03	-2.26
3 (Random multiformity)	25.59	10	.04	5.59
4 (Random multiformity of MD)	26.19	11	.06	4.19
5 (Random multiformity of GAD)	40.89	11	.00	18.89
6 (Extreme multiformity)	16.51	10	.08	-3.49
7 (Extreme multiformity of MD)	21.76	11	.03	-.24
8 (Extreme multiformity of GAD)	37.02	11	.00	15.02
9 (Three independent disorders)	39.77	9	.00	21.77
10 (Correlated liabilities)	12.23	9	.20	-5.77
11 (MD causes GAD)	14.79	11	.19	-7.21
12 (GAD causes MD)	21.09	11	.03	-.91
13 (Reciprocal causation)	12.29	10	.27	-7.71

The model of correlated liabilities (model 10) fits best by the χ^2 measure, but it is not the most parsimonious according to AIC. MD as a cause of GAD (model 11) fits somewhat less well, but uses two fewer parameters to describe the relationship between the disorders and is better by AIC. The converse hypothesis, that GAD causes MD (model 12), fits much worse than the other correlated liability models and is statistically rejected. Allowing for reciprocal causation (model 13) improves the fit, uses one fewer parameter than the correlated liabilities model, and is thus superior by AIC.

Table 4 shows the parameter estimates for 13 models and submodels that we fitted. Note that throughout model fitting, we fixed the random environment parameters e_A and e_B to unity. We did that because there is no information to estimate both the threshold and the underlying variance of the distribution when we are fitting to binary data. Our approach was to fix the random environment parameters, estimate the additive genetic and common environment parameters, and then standardize the predicted covariance matrix. The estimates we report are standardized to unit variance.

The findings of moderate heritable variance for GAD and MD and no shared environment are in accord with our previously published results by using other methods (Kendler et al. 1992b). The strong genetic correlation between these variables is also reproduced in the present paper. In general, thresholds for GAD are higher than those for MD, reflecting the lower rate of GAD in the present sample. Perhaps the most counterintuitive finding is the negative path from GAD to MD in the reciprocal interaction model. It is hard to conceive of high liability to GAD causing reduced risk for MD in the presence of such strong comorbidity.

Discussion

Methodological Approach

The method we devised for comparing the alternative models of comorbidity has several things to recommend it. Model fitting has numerous inherent advantages, which are at least partly responsible for its rapid growth in many areas of science (Bollen 1989). First, there is a measure of overall fit, in this case the χ^2 statistic, which may be used to give a broad indication of whether a set of data supports or rejects the model in question. Other derived fit indices, such as AIC, are valuable tools for assessing the relative efficiency with which different models account for a set of data. The AIC has recently been shown to be better than many other methods for selecting the true model when the data were simulated covariances derived from a structural equation model (Williams and Holahan 1994). These results may extend to the types of model and data summaries used in the present study, but a simulation study is needed to test this hypothesis. A second advantage of model fitting is that the parameter estimates can be used to make predictions about other data sets, not necessarily of the same type. The estimates of heritability and common environment effects allow us to predict comorbidity patterns for other classes of relatives. Data on such pair types as parents and offspring, spouses, cousins, adoptees, and so on, would test the assumptions of our model of familial resemblance. In the event that the new data cause the model to fail, it could be revised to include other factors such as nonadditive genetic effects. Taken at face value, the approach allows us to make tentative predictions about the nature of covariance between disorders and putative risk factors. For example, if we found support for the three-disorders model, then we would not expect treatment of either disorder to substantially reduce the rate of comorbid cases. On the other hand, if disorder A appeared to be a cause of disorder B then we would expect treatment of A to have benefits for A, B, and comorbid cases, whereas treatment of B would likely be beneficial for B alone. Any approach that discriminates between such models would have the benefit of enabling such predictions to be made; the advantage of the modeling approach used in the present study is that the predictions can be *quantified*. Thus we should be able to predict how much effect different treatments should have on each of the two disorders. In reality, treatment effects may be nonspecific, in which case these predictions would fail. Nevertheless, the potential to establish whether treatments or risk factors are disorder specific is a useful one.

Previous work on comorbidity has focused on the relative rates of disorder in various combinations of proband and relative classes. Thus, Klein and Riso (1994) tabulated the diagnosis in relatives against the ordering

Table 4

Parameter Estimates Obtained for Various Models of Comorbidity Applied to Data on GAD and MD in Adult Female Twins

	MODEL												
	1	2	3	4	5	6	7	8	9	10	11	12	13
a_{MD}^246	—	.45	.43	.40	.50	.42	.41	.40	.43	.46	.30	.46
c_{MD}^200	—	.00	.00	.00	.00	.00	.00	.00	.18	.00	.01	.00
a_{GAD}^237	—	.25	.25	.25	.38	.34	.34	.22	.00	.06	.42	.00
c_{GAD}^200	—	.09	.05	.05	.00	.00	.00	.02	.05	.02	.00	.06
a_{DA}^2	—	.55	—	—	—	—	—	—	.42	.32	—	—	—
c_{DA}^2	—	.01	—	—	—	—	—	—	.00	.01	—	—	—
e_{DA}^2	—	.44	—	—	—	—	—	—	.58	.05	—	—	—
MD→GAD	—	—	—	—	—	—	—	—	—	—	.73	—	.62
GAD→MD	—	—	—	—	—	—	—	—	—	—	—	.67	-.32
ρ	—	.68	.41	.45	(0)	—	—	—	—	—	—	—	—
r	—	.52	.16	(0)	.60	—	—	—	—	—	—	—	—
t_{1MD}43	.09	.52	.48	.81	.67	0.48	.36	.82	.48	.48	.48	.48
t_{1GAD}61	—	1.12	1.21	.71	.68	1.20	.81	1.06	.71	.71	.71	.71
t_{2MD}	—	—	—	—	—	1.24	1.06	∞	—	—	—	—	—
t_{2GAD}	—	—	—	—	—	1.72	∞	1.06	—	—	—	—	—
t_{MA}	—	—	—	—	—	—	—	—	1.21	—	—	—	—

NOTE.—Parameters a , c , and e subscripted DA (for “Depression-Anxiety”) refer to either model 2, the variance components for the single liability distribution in the alternate-forms model; model 9, the variance components of the liability to be comorbid in the three-disorders model; or model 10, the paths from the latent variables of MD to the liability of GAD in the Cholesky model. All estimates are standardized to unit variance. Parameters e_{MD}^2 and e_{GAD}^2 may be obtained by subtraction, for example, $e_{MD}^2 = 1 - a_{MD}^2 - c_{MD}^2$. A dash (—) indicates parameter not used in this model.

of proband groups. Although this method can be a useful heuristic device to get a sense of the different patterns of proband and relative status under certain well-defined conditions, it has its limitations. Most important, changing one or more of the parameters of the model can change the patterns of rates in the proband groups. For example, Klein and Riso report that under the heterogeneity model, the highest rates of A only would be among relatives of probands with A only, then AB comorbid, then probands with B only, who should be as frequent as control probands (C) with neither disorder. Although true for certain rates of disorders A and B, certain rates of heterogeneity, and certain levels of familial correlation for the two underlying traits, the pattern is not always the same when the thresholds or correlations in liability are varied. Identifying such patterns seems to be of limited use. In contrast, the model-fitting procedure we have developed is not subject to these assumptions or limitations but is appropriate for all rates of disorder and degrees of familiarity.

Extensions of the models.—In principle, it is possible to extend the methods in several different directions, although practical constraints make some extensions easier than others. First, a true multivariate model would be valuable when there are a number of simultaneously comorbid conditions, such as is the case with MD, GAD, phobias, bulimia, and alcoholism (Kendler et al. 1995b). In practice, we need faster hardware and software to

handle the higher dimension normal distribution integration. For the alternate, multiformity, and three-independent-disorder models we could add two more disorders—requiring four-dimensional integration—and fit models within a reasonable amount of time. The correlated liability models would take longer; even one more disorder would require a large amount of CPU time to assess. If the relationship between the fit statistics obtained using asymptotic weight matrices and those used to fit directly to the contingency tables were known precisely, then the correlated liability models could be fit using this more efficient approach.

Another way to extend the models would be to allow for multiple thresholds within each disorder, e.g., unaffected, mild, and severe forms. We could expect considerably increased complexity in the equations to describe the greater number of cell types. Some automatic method of generating the equations would be very useful. A limitation with this approach would be the decrease in average cell frequency incurred with a constant sample size, which could lead to inappropriate fit statistics. Samples might need to be quite large to circumvent this problem.

Designs that use pairs of relatives are only a start in the genetic epidemiological study of any phenotype. Many convenient samples contain larger groups of relatives than pairs, but these would be difficult to handle correctly with the current methods, as the number of

dimensions of integration and the possible constellations of joint affected status would increase. Instead, we might select pairs of relatives that are independent of one another, and fit the different pair types in a series of separate groups, just as we did for the MZ and DZ twins in this article, but with a wider variety of pair types. This approach would be statistically correct but would be wasteful of data. The other extreme would be to use all possible pair types and recognize that the statistical precision of parameter estimates obtained this way would be overestimated.

The astute reader will have already noticed that there is a more general type of multiformity model possible than the two variants we used here. The random multiformity model says, "My chance of displaying symptoms of disorder B is zero if I am below threshold and p if I am above it." The extreme multiformity model says that my chances of spuriously displaying B are zero until I pass a second threshold on the A dimension, where my chance suddenly leaps to unity. We could imagine other functional forms for the relationship between liability to A and the chance of spuriously displaying B, e.g., a smooth exponential. These functions could have parametric forms, and we might be able to estimate parameters describing their shape, as long as they are kept relatively simple.

We have not considered the information that might be obtained through multiple occasions of measurement. Formally, pairs of relatives might be seen as equivalent to pairs of measurement occasions, in which case the models here could be used without modification. However, it seems likely that the valuable invariance of the model parameters that may be assumed for pairs of relatives (e.g., the comorbidity rate is the same for both relatives) could not generally be made for one individual measured on two occasions. Structural models for repeated measures are well known (Collins and Horn 1991), and these could be implemented for the correlated liability model. The alternate forms, multiformity, and three-disorder models are less obvious. Predictions will vary according to the assumptions that we make about which parameters of the model change over time. Perhaps most informative would be the joint analysis of data collected from relatives on more than one occasion of measurement. Such models are beyond the scope of the present article.

A valuable addition to the method would be to include measured covariates. If these were continuous and normally distributed, then modeling them would require extending the integrand to include the covariates, but no further dimensions of integration would be required. Since the measured covariate would render each pair unique, it would be necessary to compute a separate integral for each pair in the sample, but for all but the largest of samples the method would remain practical.

Some modification of the Mx software is needed to implement this extension. One form of measured covariate would be genotypes assessed through DNA polymorphisms. Indeed, a form of genetic association analysis could be performed with the alternate-forms model, if the presence of a particular genotype were substituted for one of the disorders. We could investigate major gene effects on comorbidity if the model were extended to multiple disorders.

Mx (Neale 1994) could be used to fit models to more than two disorders at the same time. To extend the alternate-forms model to multiple disorders would be straightforward and would not be computationally demanding. The same is true of the multiformity and independent-disorders models, but the correlated-liability model would become increasingly intractable as the number of dimensions of integration depends on the number of disorders analyzed. Some "hybrid" models for comorbidity across multiple disorders could be devised, e.g., correlated liability for some disease pairs, and multiformity for others. A limitation to this approach stems from the statistical properties of sparse contingency tables. With low cell frequencies, such goodness-of-fit statistics as minimum χ^2 or maximum likelihood can be substantially biased. The number of cells in the contingency table of disorder status for k disorders is 2^{2k} , (16 in the bivariate case), which rapidly increases with more disorders. The large number of cells for $k > 2$ will lead to a low average cell frequency for a given sample size. Investigation into the amount of bias and the development of alternative-fit functions for low cell frequencies would be useful.

Limitations.—Our methods are predicated on the linearity and additivity assumptions inherent in the threshold model. Clearly, these assumptions will be more appropriate for some disorders than for others, but often they will serve as a reasonable approximation. Note also that the assumptions are not strictly necessary; further models that employ a "soft" threshold whereby affected status is not a step function of the underlying liability distribution (see, e.g., Martin and Wilson 1982; Neale and Martin 1989) could be implemented. Similarly, not all risk factors for a disorder would be expected to act additively. As nonadditive effects of specified risk factors become evident, the comorbidity models could be fit to subgroups consisting of subjects (or pairs) homogeneous for the risk factors. This would allow examination of, for example, comorbidity for alcoholism and depression in those who have experienced parental separation versus those who have not. Quite possibly, the effects of other environmental factors may be moderated by such major environmental—or major genetic—effects.

The account given in this article does not allow for sex

differences in thresholds, as we have taken advantage of symmetry in several places to simplify the formulas and their computation. Extension to allow for sex differences presents no practical problems, merely careful re-specification of the equations.

A more difficult problem is variable age at onset. In common with the vast majority of genetic analyses of diagnoses, we have assumed that everyone has passed the age of risk for first onset. If this is not the case, some bias in the parameter estimates may occur if age at onset is correlated between relatives. Although we have described methods elsewhere for handling variable age at onset (Neale et al. 1989), adapting them to the models for comorbidity would appear difficult at best. Some insight into the severity of the problem might be obtained by age banding the sample and looking for systematic changes of the parameter estimates with age.

Etiology of GAD and MD

Our analysis of MD and GAD in this paper was primarily for illustrative purposes, but it shed new light on the relationship between these disorders. It seems that there is genuine comorbidity between the conditions and that they are best represented by two correlated-liability distributions. Their correlation is quite substantial, so that a model of alternate forms of a single underlying dimension gives a much better fit than one that specifies three independent disorders, MD, GAD, and MD with GAD. Of course, a more complex explanation is possible—such as three correlated disorders, but Occam's razor would seem to cut these from consideration at this time, when the data do not reject the simpler models. These results vindicate the treatment that we and others have used in the bivariate genetic analysis of depression and anxiety symptoms (Jardine et al. 1984) and diagnoses (Kendler et al. 1992*b*, 1995*a*, 1995*b*; Roy et al., in press).

A possibility that was not tested in earlier articles is that liability to MD is a risk factor for GAD. This model gives the best fit of those tested in this paper, although caution should be exercised because the differences in fit were slight and the confidence intervals on the fit statistics have considerable overlap. The superior fit of models that placed MD as a cause of GAD rather than the reverse was also found in the multiformity models. Again, care must be taken with these results because they may be influenced by the relative reliabilities of the diagnoses of MD and GAD. As a rule, there is bias toward giving greater support to a model in which the more reliable variable is a cause of the less reliable one than to the reverse (Heath et al. 1993). GAD is less frequent than MD, and we know that the reliability of tetrachoric correlations decreases as the thresholds become more extreme (Neale et al. 1994*b*), so it is inherently less reliable. The extent of this prevalence effect

could be explored with simulated data. If diagnoses are made using some threshold on a quasi-continuous scale, selecting broader or narrower forms of one of the disorders to compensate for the difference in prevalence may be helpful. However, it would incur the risk that the disorder redefined in this way would not be a good indicator of the true disorder. Our diagnosis of GAD even when it occurred during an episode of MD (ignoring the diagnostic hierarchy of DSM-III) generated a higher prevalence of GAD than would normally be the case. In the context of relative reliabilities, this procedure might somewhat bias the results toward GAD causes MD rather than the reverse. Yet reanalyses including the diagnostic hierarchy (not reported here) show very little change from the pattern of results reported here.

These considerations notwithstanding, our results suggest that the liability factors that give rise to depression—both genetic and environmental—increase liability to anxiety. If the MD-causes-GAD model is correct, the increased risk is transmitted via the underlying continuous liability to depression. That is, the same increased risk to GAD occurs right across the range of liability to depression. Diagnosis of depression does not imply a sudden jump in the risk to GAD. Furthermore, treatment of depression would seem likely to alleviate anxiety to a greater extent than vice-versa. Clearly, treatments are not often disorder specific, and perhaps especially not for psychiatric disorders, but, if our model is correct, it would be difficult to find a treatment for depression that did not simultaneously reduce risk for GAD. These conclusions remain tentative at this point, because the difference in fit between the extreme multiformity model and the causal model is not great. Replication with other samples would be valuable.

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Appendix A

Method Used to Derive Predicted Proportions

Here we illustrate a method to obtain the predicted proportion of pairs where both have disease B and where neither have disease A, i.e., $P(A1\bar{B}1A2\bar{B}2)$ under the alternate forms model (fig. 1). We recall from probability theory that the probability of X and Y equals the probability of X given Y multiplied by the probability of Y, which we write as:

$$P(X, Y) = P(X|Y)P(Y) . \tag{71}$$

Second, $P(X, Y)$ can be “factored” with respect to another variable, so that

$$P(X, Y) = P((X, Y)|Z)P(Z) + P((X, Y)|\bar{Z})P(\bar{Z}) . \tag{72}$$

We can apply this factorization for liabilities that may be above or below threshold. Hence,

$$P(A, \bar{B}) = P((A, \bar{B})|U)P(U) + P((A, \bar{B})|L)P(\bar{U}) \tag{73}$$

$$= P(A|U)P(\bar{B}|U)P(U) + P(A|L)P(\bar{B}|L)P(L) \tag{74}$$

$$= (1 - p)rU + 0 \cdot 1 \cdot L \tag{75}$$

$$= (1 - p)rU . \tag{76}$$

For the second relative, the same individual probabilities hold, so the joint probability of the pair is

$$P(A1\bar{B}1A2\bar{B}2) = U_1(1 - p)r \cap U_2(1 - p)r \tag{77}$$

$$= UU(1 - p)^2r^2 , \tag{78}$$

where UU is the integral of the bivariate normal, $\int_t^\infty \int_t^\infty \phi(x_1, x_1)dx_2dx_1$.

Appendix B

Mx Script for the Random Multiformity Model

The following is available through the Internet (anonymous ftp to opal.vcu.edu and look in ~ftp/pub/mx/comorb):

```
G1 Calculation of MZ Correlation matrix for A factor
DA CALC NG=6
MATRICES
A Lo 1 1 Free
C Lo 1 1 Free
I id 1 1
begin algebra;
X = A*A' ;
Y = C*C' ;
end algebra;
COMPUTE I|X+Y_
  X+Y|I ;
Option RS
End
```

```
G2 Calculation of DZ Correlation matrix for A factor
DA CALC
MATRICES
A Lo 1 1 =A1
C Lo 1 1 =C1
H fu 1 1
```

```
I id 1 1
begin algebra;
X = A*A' ;
Y = C*C' ;
end algebra ;
COMPUTE I|H@X+Y_
  H@X+Y|I ;
Matrix H .5
Option RS
End
```

```
G3 Calculation of MZ Correlation matrix for B factor
DA CALC
MATRICES
A Lo 1 1 Free
C Lo 1 1 Free
I id 1 1
begin algebra;
X = A*A' ;
Y = C*C' ;
end algebra;
COMPUTE I|X+Y_
  X+Y|I ;
Option RS
End
```

```
G4 Calculation of DZ Correlation matrix for B factor
DA CALC
MATRICES
A Lo 1 1 =A3
C Lo 1 1 =C3
H fu 1 1
I id 1 1
begin algebra;
X = A*A' ;
Y = C*C' ;
end algebra ;
COMPUTE I|H@X+Y_
  H@X+Y|I ;
Matrix H .5
Option RS
End
```

```
Fit model to MZ Anxiety/Depression data
Data NI=1 NO=1
Matrices
A Full 2 2 =%E1 ! Corr between A factors as computed in Group 1
B Full 2 2 =%E3 ! Corr between B factors as computed in Group 3
I Iden 1 1
N Full 1 1 ! The scalar 2.0
O Full 10 1 ! observed data
P Full 1 1 free ! probability of being comorbid given A
R Full 1 1 free ! probability of being comorbid given B
T Full 1 2 ! Threshold for A
U Full 1 2 ! Threshold for B
W Zero 1 2 ! + + These are to control integral type
X Zi 1 2 ! + -
Y Full 1 1 ! for sample size
Z Unit 1 2 ! - -
Begin Algebra;
D = \mulin((A_T_T_Z)) ; ! LL_A obtained by calling multivariate normal function
E = \mulin((A_T_T_X)) ; ! LU_A
F = \mulin((A_T_T_W)) ; ! UU_A
G = \mulin((B_U_U_Z)) ; ! LL_B
H = \mulin((B_U_U_X)) ; ! LU_B
J = \mulin((B_U_U_W)) ; ! UU_B
Q = I - P ;
S = I - R ;
K = D.G _ ! put all expected proportions into a vector
  N.D.H.S _
  N.E.Q.G _
  N.(E.(P.G + H) + D.H.R) _
```

```

D.J.S.S _
N. E.Q.H.S _
N. (E.S.(P.H + J) + D.J.R.S) _
F.Q.Q.G _
N. (F.(P.Q.G + Q.H) + E.H.R.Q) _
F.(P.P.G + N.P.H + J) + N.E.H.P.R + N.R.E.J + R.R.D.J ;
L = Y@K ; ! multiply expected proportions by total sample size
end algebra;
compute \sum((L-O).(L-O)%L) ; !_\sum(K)+\sum(L);
Matrix O File=admz.frq
Matrix Y File=admz.n
Option func=1.e-7 ! set the function precision to mulnor accuracy
Option user-defined RS
End

```

```

Fit model to DZ A/D data
Data NI=1 NO=1
Matrices
A Full 2 2 =%E2 ! Corr between A factors of DZ as computed in Group 2
B Full 2 2 =%E4 ! Corr between B factors of DZ as computed in Group 4
I Idem 1 1
N Full 1 1 =N5 ! The scalar 2.0
O Full 10 1 ! observed data
P Full 1 1 =P5 ! probability of being comorbid if you are A
R Full 1 1 =R5 ! probability of being comorbid if you are B
T Full 1 2 =T5 ! Threshold for A
U Full 1 2 =U5 ! Threshold for B
W Zero 1 2 ! + + These are to control integral type
X Zi 1 2 ! + -
Y Full 1 1 ! for sample size
Z Unit 1 2 ! - -
Begin Algebra;
D = \muln((A_T_T_Z));
E = \muln((A_T_T_X));
F = \muln((A_T_T_W));
G = \muln((B_U_U_Z));
H = \muln((B_U_U_X));
J = \muln((B_U_U_W));
Q = I - P ;
S = I - R ;
K = D.G _
N. D.H.S _
N. E.Q.G _
N. (E.(P.G + H) + D.H.R) _
D.J.S.S _
N. E.Q.H.S _
N. (E.S.(P.H + J) + D.J.R.S) _
F.Q.Q.G _
N. (F.(P.Q.G + Q.H) + E.H.R.Q) _
F.(P.P.G + N.P.H + J) + N.E.H.P.R + N.R.E.J + R.R.D.J ;
M = \sum(K);
L = Y@K ;
end algebra;
compute \sum((L-O).(L-O)%L) ; !_\sum(K)+\sum(L);
Matrix O File=addz.frq
Matrix N 2
Matrix P .4
Matrix R .3
Specify T 8 8
Specify U 9 9
Matrix T .5 .5
Matrix U 2 2
Matrix Y File=addz.n
Bound -.5 .95 1 2 3 4
Bound .01 .99 5 6
Bound 0 3 7 8
Option func=1.e-7 nd=7 ldiff=.001
Option user-defined RS mu
End

```

```

! save current solution to binary file
Save biepiece.mxs

```

```

! Now drop a parameter to fit multiformity of MD only
Drop 6
End

```

```

! read the full model solution back in again
Get biepiece.mxs
! Now drop a parameter to fit multiformity of GAD only
Drop 5
End

```

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