
Advances in Behavioral Genetics Modeling Using Mplus: Applications of Factor Mixture Modeling to Twin Data

Bengt Muthén,¹ Tihomir Asparouhov,² and Irene Rebollo³

¹ Graduate School of Education & Information Studies, University of California, Los Angeles, United States of America

² Muthén & Muthén, United States of America

³ Department of Biological Psychology, Vrije Universiteit, the Netherlands

This article discusses new latent variable techniques developed by the authors. As an illustration, a new factor mixture model is applied to the monozygotic–dizygotic twin analysis of binary items measuring alcohol-use disorder. In this model, heritability is simultaneously studied with respect to latent class membership and within-class severity dimensions. Different latent classes of individuals are allowed to have different heritability for the severity dimensions. The factor mixture approach appears to have great potential for the genetic analyses of heterogeneous populations. Generalizations for longitudinal data are also outlined.

Analysis with latent variables has historically been a key part of behavior genetics modeling with its focus on genetic and environmental factors, liabilities, and phenotypes measured with error. This article gives an overview of some new latent variable modeling facilities that have recently been made available and which have great potential for extracting more information from behavioral genetics data. The new techniques are implemented in the Mplus program (Asparouhov & Muthén, 2004; Muthén & Muthén, 2006; see also the Mplus web site www.statmodel.com). The article focuses on the phenotype viewed as a latent variable that is arrived at in novel ways. The article uses the example of twin analysis with an ACE model (Neale & Cardon, 1992) where the use of traditional latent class and factor analysis (FA) measurement models is contrasted against a new factor mixture model.

The Mplus Modeling Framework

As described in the overview article by Muthén (2002), latent variable modeling has in recent years developed into a very general modeling framework that draws its flexibility from using a combination of continuous and categorical latent variables. The first implementation of such general latent variable modeling was made available when the Mplus program was introduced in 1998. The aim of Mplus is twofold: to offer analyses with an easy-to-use interface that does not require knowledge of

matrix algebra or statistical formulas, and to offer a very powerful modeling framework. The Mplus framework encompasses several traditionally different types of analyses, including structural equation modeling, latent class (finite mixture) modeling, multilevel modeling, and survival analysis. In March 2004 a significant further step in latent variable modeling generality was made by the introduction of Version 3 of the Mplus program (Muthén & Muthén, 2006), expanding the framework further to include a flexible combination of random intercepts and random slopes modeling integrated with psychometric modeling with constructs having multiple indicators, as well as freely combining this with modeling of multilevel sources of variation. These new analysis options draw on maximum-likelihood estimation using complex algorithms described in Asparouhov and Muthén (2004) and allow observed variables that are continuous-normal, censored-normal, binary, ordered and unordered polytomous, as well as counts, and also combinations of such variables. Of further interest to behavior geneticists are standard error and chi-square tests of model fit computations that are robust to violations of normality and independence of observations. Explicit modeling of outcomes showing strong floor and ceiling effects ('preponderance of zeros') is possible using two-part (semicontinuous) growth modeling¹ (Olsen & Schafer, 2001) and zero-inflated modeling such as zero-inflated Poisson modeling of counts² (Roeder et al., 1999). Version 4 of Mplus, released in February 2006, offers many further options of interest for genetic analysis. These include more flexible nonlinear parameter constraints, inequality constraints on parameters, and constraints that are functions of observed variables such as with pi-hat values in quantitative trait loci (QTL) analysis with

Received 5 December, 2005; accepted 31 January, 2006.

Address for correspondence: Bengt Muthén, Graduate School of Education & Information Studies, University of California, Los Angeles, 90095-1521, USA. E-mail: bmuthen@ucla.edu

Table 1
Alcohol Dependence and Abuse Criteria

Twin Data, <i>n</i> = 5020 twins: Endorsement probabilities for DSM-IV alcohol dependence and abuse criteria, for regular drinkers	Endorsement Probabilities (%)	
	Women	Men
Tolerance	38	55
Withdrawal	5	9
Use in larger amounts/over longer period than intended	23	29
Persistent desire/unsuccessful efforts to cut down or quit	16	27
Great deal of time using/recovering	8	17
Important activities given up	4	8
Continued use despite emotional/physical problems	14	26
Interference with major role obligations	6	14
Hazardous use	13	27
Recurrent alcohol-related arrests	1	9
Recurrent social/interpersonal problems	6	18

identical-by-descent (IBD) information and individually-varying covariance matrices.

Types of Models With a Latent Phenotype

The focus of this article is modeling with a phenotype that is a latent variable, either categorical (latent class variable) or continuous (factor). The aim is to capture not only measurement error but also heterogeneity in terms of different measurement models for different groups of individuals. This leads to models that use either continuous or categorical latent variables, or a combination of both. Latent variables enter into both cross-sectional and longitudinal modeling. This article focuses on cross-sectional models but longitudinal counterparts will be mentioned in the Discussion section. Cross-sectional data analysis of phenotypes has traditionally benefited from using latent variables in the form of latent class and FA. This article adds a third type, factor mixture analysis models (FMA). This article shows how these three cross-sectional models can be applied to capture a latent variable phenotype for genetic analysis. To simplify the discussion, twin ACE modeling is used to illustrate the genetic analysis, but other forms of genetic analysis such as linkage and association QTL analysis could also be used. Furthermore, the analyses could also be extended to longitudinal settings.

Materials and Methods

The subjects to be studied are young adult Australian male monozygotic (MZ) and dizygotic (DZ) twins, ages 24 to 36 years (Heath et al., 2001). The number of twin pairs is 842 of which 376 are DZ twin pairs and 466 are MZ twin pairs. Included in the twin measurements were *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; DSM-IV; American

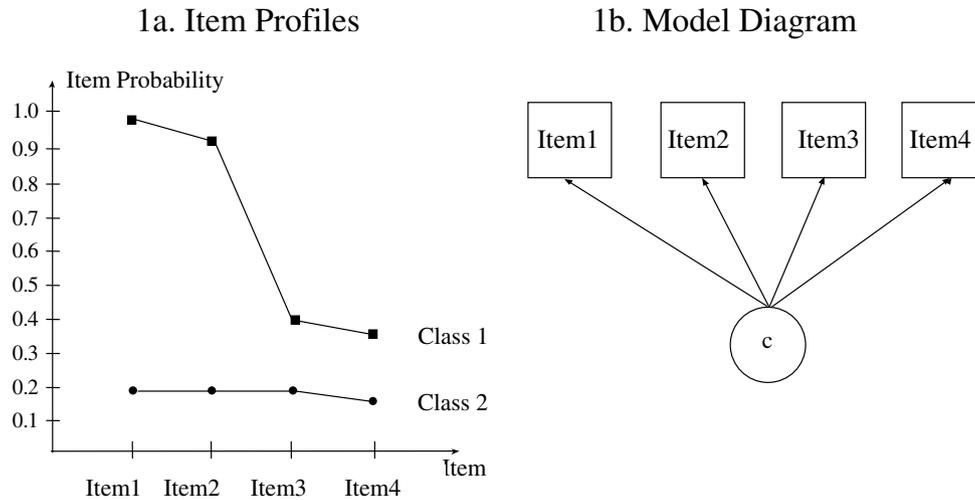
Psychiatric Association, 1994) criteria for alcohol dependence and abuse. The seven alcohol dependence criteria and the four alcohol abuse criteria are listed in Table 1. The items are dichotomously scored. Latent class analysis (LCA), FA, and factor mixture models will be used to analyze the 11 items. As a first step, the best-fitting model for the total sample is determined and, given this model, a two-group analysis of MZ and DZ twins is carried out, decomposing the variance according to the ACE model.

Latent Class Analysis

For background literature on conventional LCA, the reader is referred to Hagenaars and McCutcheon (2002) and Muthén (2001), while LCA applications in behavioral genetics include Eaves et al. (1993) and Rasmussen et al. (2002). LCA is used to uncover heterogeneous groups of individuals, thereby having the same goal as cluster analysis. Panels 1a and 1b of Figure 1 describe a LCA model. Figure 1a considers item profiles for the four items listed along the x-axis. The picture shows two latent classes (unobserved groups) of individuals who are homogeneous within classes and different across classes. Class 2 has low endorsement probabilities for all four items and the classes are further differentiated by Class 1 having considerably higher endorsement probabilities for Items 1 and 2. It is this type of class differentiation that lends an interpretation to the behavior that characterizes individuals in the two classes. In addition to the item endorsement probability parameters in each class (also referred to as conditional item probability parameters), the LCA model uses parameters to describe the prevalence of the latent classes. In a study of alcohol disorders in a general population sample, the prevalence would be the largest for the low Class 2. Figure 1b shows the model diagram for LCA where boxes represent the observed items and the circle represents the latent class variable. The latent class variable explains the dependence among the items so that the items are conditionally independent within class.

Figure 2a shows a model diagram for LCA of twins. The 11 observed alcohol criteria are labeled *ua1-ua11* for Twin a and *ub1-ub11* for Twin b. The latent class variables are labeled *ca* and *cb* for Twin a and Twin b, respectively. As indicated by the diagram, each pair of twins is analyzed together so that the data matrix consists of 842 rows (twin pairs) and 22 variables (2×11 items). The LCA modeling involves two latent class variables and is confirmatory in nature. The latent class variable *ca* does not influence the probabilities of endorsing the Twin b items and vice versa for *cb* and Twin a items. Also, all parameters for Twin a are held equal to all parameters for Twin b, both with regard to the measurement parameters (the conditional item probabilities) and the structural parameters (the latent class probabilities; the latter are restricted so that the table of joint latent class probabilities for the two twins is symmetric and have the same marginal probabilities).

Latent Class Analysis



Factor (IRT) Analysis

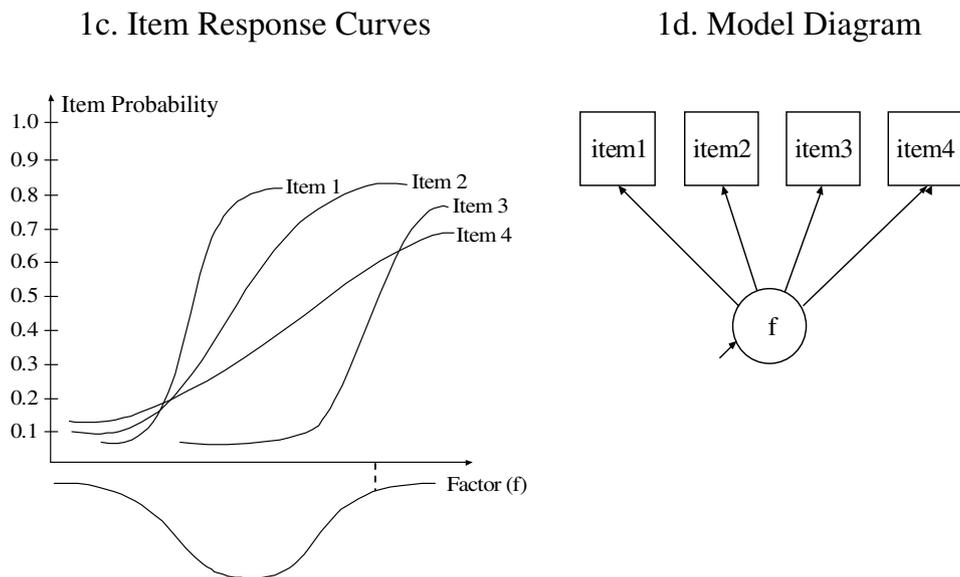


Figure 1

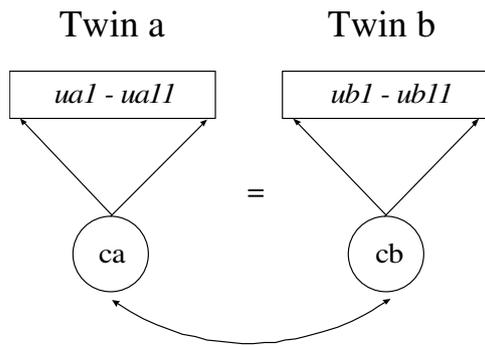
Latent class analysis and factor analysis.

In multilevel terms, the analysis implied by Figure 2a is sometimes referred to as using a multivariate approach with the hierarchical data arranged in a wide data format. LCA of twin data is often carried out in the alternative long data format where for each twin pair, a record of item responses for Twin a is followed by a record of item responses for Twin b, resulting in a data matrix with 2×842 rows and 11 columns. In many cases, the lack of independence is ignored, but may be accounted for by robust standard error and chi-square techniques or by two-level LCA modeling (Asparouhov & Muthén, 2004; Muthén & Muthén,

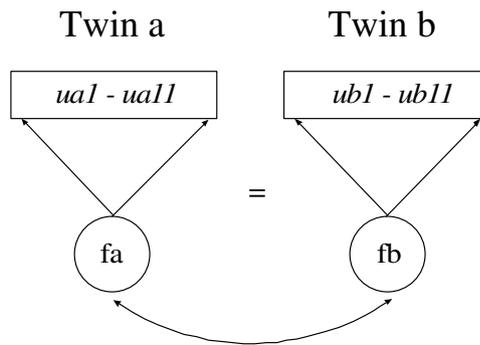
2006). In our experience, unless a two-level approach is used, the long format approach can give quite different results in terms of deciding on the number of latent classes in the LCA. The multivariate, wide approach used here is preferable to the two-level approach because it allows for a more flexible model specification. For example, full measurement or structural invariance across twins is not required and items may correlate directly and not only through the latent class variables.

It may be noted that an ad hoc three-step procedure is sometimes used when drawing on LCA for

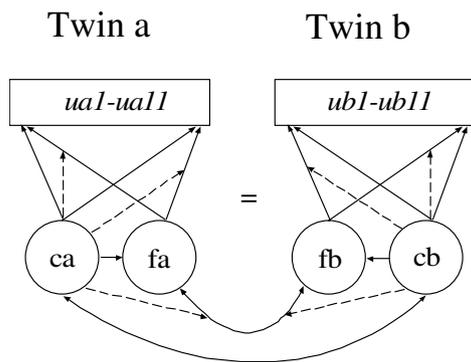
2a. Twin Latent Class Analysis



2b. Twin Factor Analysis



2c. Twin Factor Mixture Analysis



2d. Twin Factor Mixture ACE Analysis

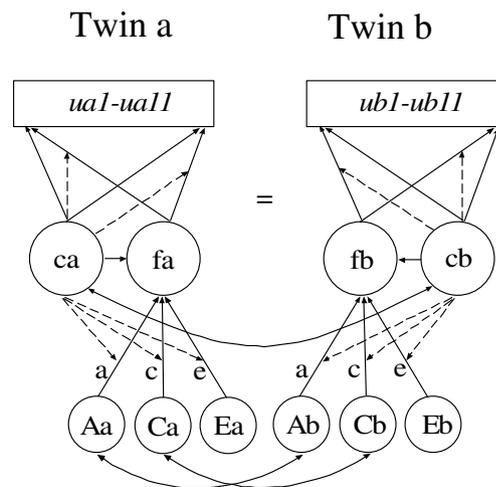


Figure 2
Twin analysis.

heritability estimation in twin samples. The first step is the LCA parameter estimation, the second step is the classification of the individuals into the most likely class based on the posterior probabilities of class membership, and the third step is to use this categorical observed variable (say using classes of ‘affected’ and ‘nonaffected’) for each twin in a liability (‘threshold’) model version of ACE analysis. The one-step approach of this article is recommended over this three-step approach. The weakness of the three-step approach is that the classification into the most likely class ignores the fractional class membership assigned by the posterior probabilities to all classes and also treats the classification as not having any sampling error. This results in biased parameter

estimates and biased, typically underestimated, standard errors.

Factor Analysis

There is a rich literature on FA of binary items, including contributions in the field of item response theory (IRT; see, for example, du Toit, 2003; Embretson & Reise, 2000) as well as in behavior genetics (Prescott, 2004). The FA model diagram in panel 1d of Figure 1 is analogous to the LCA diagram in Figure 1b, replacing the latent class variable with a continuous factor variable. With categorical items, the analysis is often referred to as latent trait analysis, or IRT (item response theory) modeling, particularly when a single factor is used. For this situation, Figure 1c shows how

the probability of endorsing an item increases as a function of the factor f . Different items have different functions, typically represented by logistic regressions with different intercepts and slopes. Below the f -axis is shown the distribution of the factor.

The twin factor (IRT) analysis is shown in Figure 2b. It is carried out using a confirmatory approach analogous to that of the above LCA using measurement and structural invariance restrictions across the two twins in a pair. The model applied here is referred to as the two-parameter logistic in IRT language. As is typically done, the factors will be assumed normally distributed.³

Factor Mixture Analysis

Figure 2c shows a twin model diagram that represents a hybrid between LCA and FA modeling called FMA. In line with LCA, the latent class variables ca and cb influence the item probabilities of the two twins. In line with FA, a continuous factor also influences the items. The factor represents within-class variation among individuals that in an alcohol use disorder context might be thought of as within-class variation in alcohol problem severity. Because of the factor influence on the items, the items are correlated within class. In contrast, LCA allows for no such within-class variation and forms clusters of individuals defined as having independence among the items (the conditional independence assumption). Using the example of severity variation within class, LCA assumes the same level of severity for all individuals within class. Substantively more meaningful clusters might be found when allowing within-class correlations among items as in FMA and this will lead to a different latent class formation. Figure 2c indicates that the item probabilities in FMA vary as a function of class membership as in LCA. In addition, as indicated by broken arrows, the item loadings of the factor are allowed to vary across classes. In this way, different items may be more representative of the severity dimension in the different classes. Furthermore, the factor variances are allowed to vary across classes indicating class differences in heterogeneity with respect to the severity. Finally, and of great interest to modeling heritability of severity, the factor covariance is allowed to vary across the classes.

FMA for continuous variables has been described in McLachlan and Peel (2001). McLachlan et al. (2004) applied FMA to cluster analysis of microarray gene expression data, arguing that FMA allows for biologically more meaningful clusters than LCA or k-means clustering. FMA for categorical variables has been studied in Asparouhov and Muthén (2004) and Muthén and Asparouhov (2005a, 2005b, in press). To our knowledge, the current analysis is the first use of FMA for twin data modeling and the estimation of heritabilities. FMA offers a more flexible modeling alternative to LCA and FA that is potentially very useful in genetic studies.

Factor Mixture Heritability Analysis

The FMA model can be applied to the simultaneous analysis of MZ and DZ twins using a two-group FMA of the two twins. The model diagram is given in Figure 2d. The FMA model presents interesting possibilities for studying genetically related similarity across twins with respect to the latent phenotypes, in this case both the latent class variables and the factors.

First, twin concordance may be studied with respect to latent class membership. This can be done in two major ways. One approach is to estimate the joint distribution of the latent class variables. In the current application, this distribution is a 2×2 table and using the estimated probabilities the concordance can be summarized by a standard odds ratio (OR; cross-product ratio). Excess twin concordance due to stronger genetic relationship can be represented by the OR for MZ twins compared to the OR for DZ twins. A second approach is to apply a liability threshold model with the latent class variables as (latent) dichotomous dependent variables. The ACE factors influencing class membership may be specified as the same as or different from the ACE factors influencing the severity dimensions. Although the second approach is possible in the Mplus framework, it will not be applied here for simplicity.

Second, for twins in the same class, the ACE model may be applied with the factors as dependent variables. Because the classes represent qualitatively different types of substance use disorder, it is important to allow for different ACE variance–covariance decomposition for the two classes, allowing for different heritability in the two classes.

As indicated in the model diagram of Figure 2d, the MZ-DZ ACE version of the twin FMA adds restrictions on the covariance matrix for the two factors in Figure 2c in the classic way. As usual in the ACE model, the diagonal variance elements of this matrix are $a^2 + c^2 + e^2$ for both factors and twin types, whereas the off-diagonal covariance element is either $a^2 + c^2$ or $.5 * a^2 + c^2$ for MZ and DZ twins, respectively. The variance component values in this covariance matrix structure are allowed to be different across the latent classes.

The modeling of the factor covariance matrix for twins that disagree in terms of class membership can be approached in different ways. An unrestricted approach lets these factor variances and covariances be freely estimated, although imposing symmetry restrictions. A restricted approach specifies that the within-class variances for a discordant twin are the same as for a concordant twin. In a further restriction, the factor covariance for a discordant twin pair can be expressed as (using the example of an AE model) $y * x * a_{11} * a_{22}$, where $y = 1$ or $.5$ for MZ and DZ twins, respectively, $0 < x < 1$ as explicated below, and a_{ij} stands for the square root of the additive variance effect a^2 in class j . The factor x allows the same ($x = 1$) or different additive genetic effects to play a role for

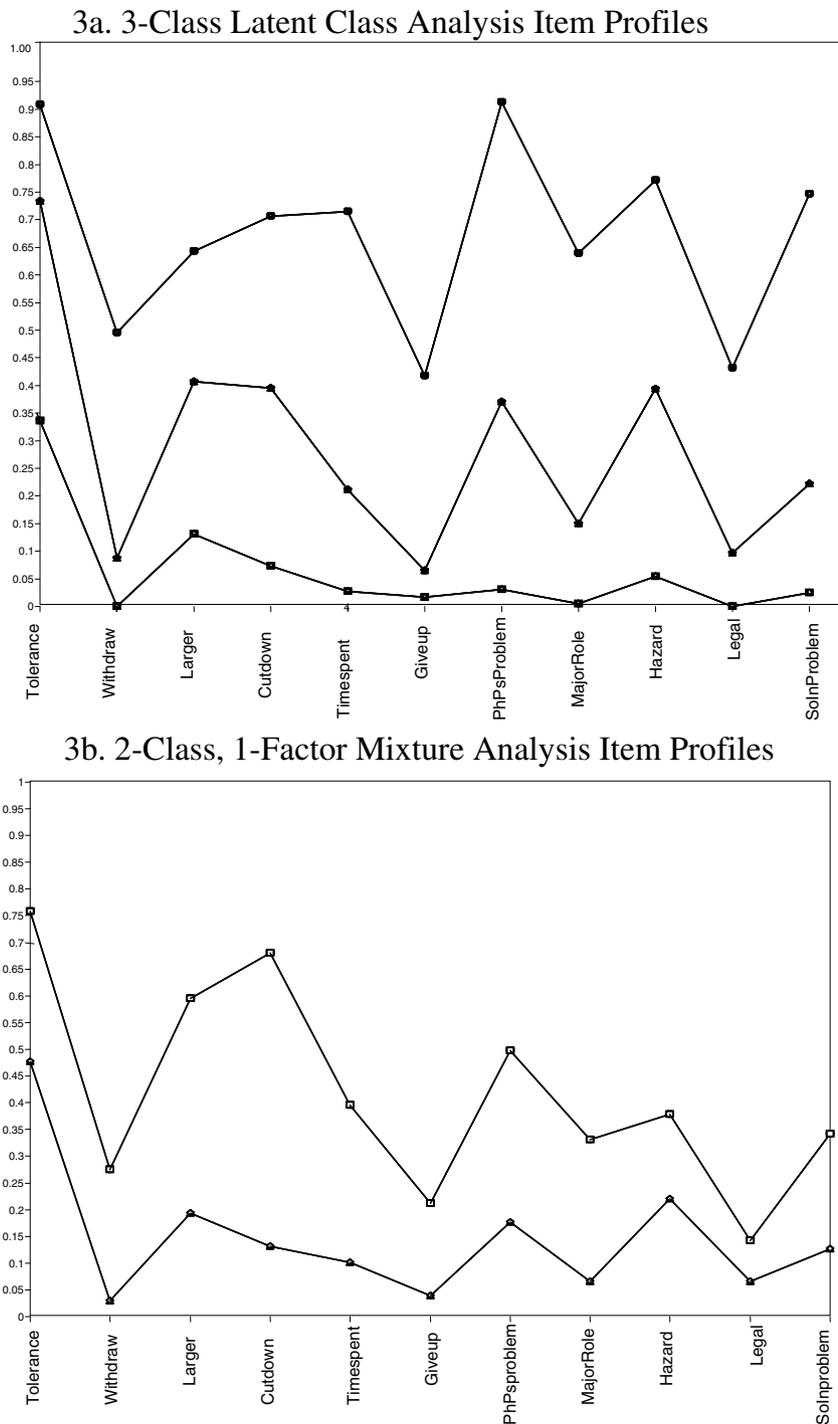


Figure 3
Item profiles from latent class and factor mixture analysis.

both concordant and discordant twins in line with sex-limitation modeling (Neale & Cardon, 1992).

Joint modeling of male and female twins as well as opposite-sex twins is also possible, either as a multiple group analysis or using gender as a covariate for both class membership and severity factors. For simplicity, such modeling will not be explored here.

Results

This section presents the results of analyzing the 22 alcohol items for the sample of 842 male twin pairs. LCA, FA, and FMA are presented without making a distinction between MZ and DZ twins. This is followed by a factor mixture heritability analysis of the

Table 2

Model Fit for Twin Data: 2 × 11 Alcohol Items

Log-likelihood	# parameters	BIC	ABIC
Approach 1: Best latent class model (3 classes)			
-7362	38	14,980	14,859
Approach 2: Best factor (IRT) model (1 factor)			
-7368	23	14,890	14,817
Approach 3: Best factor mixture model (2 classes, 1 factor)			
-7318	49	14,967	14,811

22 items where MZ and DZ twins are allowed different model structure according to the ACE model.

Latent Class Analysis

A three-class LCA was chosen based on log likelihood, number of parameters, and Bayesian Information Criterion (BIC) for two- to five-class solutions.⁴ The item profiles (estimated item probabilities conditional on class) are shown in Figure 3a. The item profiles indicate a severity ordering of the latent classes rather than profiles with distinctly different shapes. This result suggests instead using a dimensional model in the form of FA.

Factor Analysis

Preliminary exploratory FA suggested that a single factor was sufficient for each twin and that two meaningful factors could not be defined. Table 2 gives the log likelihood, number of parameters, BIC and sample-size adjusted BIC (ABIC) values for both the three-class LCA and the one-factor FA.⁵ It is seen that the LCA has a better log likelihood than the FA but at the expense of using more parameters. The BIC value is better for FA reflecting the parsimony of this model.

Factor Mixture Analysis

Applying FMA to the twin data in line with Figure 2c, parameter restrictions are imposed to represent across-twin measurement invariance analogous to those of FA and latent class symmetry analogous to those of LCA. For the Australian twin data, it was found that two classes and one factor per twin were sufficient to fit the data. Table 2 shows the resulting log likelihood results for FMA.⁶ It is seen that this FMA model clearly outperforms the LCA and FA models. The log likelihood is considerably better than for both LCA and FA while adding relatively few parameters. Although the BIC is better for FA than for FMA, the sample-size adjusted BIC (ABIC) is better for FMA and the FMA likelihood advantage outweighs the FA BIC advantage.

Figure 3b shows the resulting FMA item profiles for the two classes. It should be noted that these probabilities are marginal probabilities computed by integrating over the factor. Conditioning on different factor values, the probabilities will vary within class.

FMA reduces the three classes of the LCA solution in Figure 3a to two major types with different profiles, allowing for within-class variations on these two major themes. Figure 3b shows that the two classes do not have profiles corresponding to the DSM-IV criteria for alcohol dependence and abuse and this is further confirmed by investigating the response patterns corresponding to a classification into the two classes.⁷ Instead, the two classes show variations in probabilities for both types of criteria. A particularly marked difference in item endorsement probability across the classes is seen for the two dependence criteria 'Use in larger amounts/over longer periods than intended' and 'Persistent desire/unsuccessful effort to cut down or quit' (items 3 and 4). In the following, the high class (24%) will be alternatively referred to as Class 1 and the low class (76%) as Class 2.

Factor Mixture AE Heritability Analysis

The analyses of these Australian twin data showed that there was no significant difference for MZ and DZ twin pairs in the relationships between the two latent class variables, suggesting no effect of heritability with respect to membership in the high versus low class. When freely estimated, however, the point estimates for these ORs indicate a large degree of heritability, OR = 3.3 and 8.7 for DZ and MZ twin pairs, respectively. The insignificant difference is due to a large standard error and future analyses also involving females and opposite-sex twin pairs might provide more power and reduce this standard error. The final model holds the relationship equal across MZ and DZ twin pairs and the common OR estimate is 5.6, indicating a large degree of twin concordance.

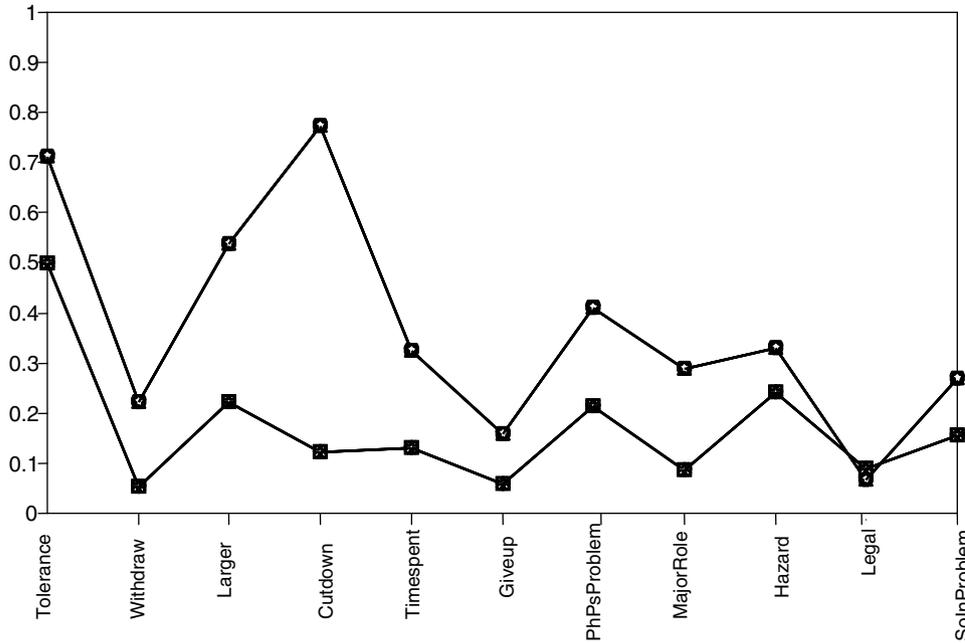
Table 3

Factor Covariance Matrix Structure for Factor Mixture Heritability Analysis

Concordant twins:			
Class 1		Class 2	
$\begin{pmatrix} a_{11}^2 + e_{11}^2 & \text{symm.} \\ x \times a_{11}^2 & a_{11}^2 + e_{11}^2 \end{pmatrix}$		$\begin{pmatrix} a_{22}^2 + e_{22}^2 & \text{symm.} \\ x \times a_{22}^2 & a_{22}^2 + e_{22}^2 \end{pmatrix}$	
Discordant twins:			
Class 1	Class 2	Class 2	Class 1
$\begin{pmatrix} a_{11}^2 + e_{11}^2 & \text{symm.} \\ x \times a_{11} a_{22} & a_{22}^2 + e_{22}^2 \end{pmatrix}$		$\begin{pmatrix} a_{22}^2 + e_{22}^2 & \text{symm.} \\ x \times a_{11} a_{22} & a_{11}^2 + e_{11}^2 \end{pmatrix}$	
Estimates (SE):			
Class 1 (high class)		Class 2 (low class)	
$a_{11} = 0.367 (0.175)$ $a_{11}^2 = 0.135 (0.128)$		$a_{22} = 1.151 (0.130)$ $a_{22}^2 = 1.325 (0.300)$	
$e_{11} = 0.699 (0.196)$ $e_{11}^2 = 0.489 (0.275)$		$e_{22} = 0.471 (0.101)$ $e_{22}^2 = 0.222 (0.095)$	
$h_1 = 0.216 (0.140)$		$h_2 = 0.858 (0.054)$	

Note: $x = .5$ for dizygotic twins
 $= 1.0$ for monozygotic twins

4a. 2-Class, 1-Factor Mixture Analysis Item Profiles



4b. Factor Mixture Estimates: 2 Classes, 1 Factor

Latent Class Distributions

		Twin b				Twin b	
Twin a	DZ	High	Low	OR = 5.6	MZ	High	Low
	High	11%	11%		High	10%	11%
	Low	11%	67%		Low	11%	68%

Within-Class Factor Covariance

		Twin a				Twin a	
Twin a	DZ	High	Low	OR = 5.6	MZ	High	Low
	High	0.07 (ns)	0.21		High	0.14 (ns)	0.43
	Low	0.21	0.66		Low	0.43	1.33

Factor Heritability: High Class (21%) = .22, Low Class (79%) = .86
(1-class, 1-factor model heritability: .65)

Figure 4
Factor mixture heritability results.

The within-class factor covariance matrices showed no evidence of the need for the C component. Because of this, the results for an AE model are reported for the factor mixture heritability analysis. The factor covariance matrix restrictions for discordant twins fitted well as measured by the log likelihood difference test against the unrestricted matrix for discordant twins. Also, the ‘y’ factor in the discordant twin covariances described above was estimated as 1, suggesting that the same additive factor is operating for both the high and the

low class. Table 3 shows the factor covariance matrix structure imposed in the modeling as well as the estimates of the A and E components of these matrices. Figure 4a shows the item probability profiles as estimated by the factor mixture heritability analysis. Figure 4b summarizes the results of the heritability analysis by comparing MZ and DZ twins both with respect to latent class agreement and with respect to within-class factor covariance.

Although there does not seem to be significant genetic influence on the probability of membership in the high class versus the low class, the within-class correlations for MZ and DZ twins at the bottom of Figure 4b show a different picture. The heritabilities are estimated as .86 and .22 for the low and high classes, respectively. The reason why twins in the latent class with a less severe alcohol use disorder profile exhibit a higher heritability is an interesting topic for further research. It may be noted that an AE analysis using a regular (one-class) factor model resulted in a heritability of .65.

Discussion

This article used three latent variable modeling techniques to model phenotypic information, LCA, FA, and FMA. FMA was found to be the best for these data and also allowed a more flexible representation of underlying heterogeneity in the population. The factor mixture model was applied to an MZ-DZ twin analysis in order to study heritability, where heritability was simultaneously studied with respect to latent class membership and within-class severity dimensions. The factor mixture approach appears to have great potential for genetic analyses of heterogeneous populations. The factor mixture analyses illustrate some of the new techniques made available by the March 2004 release of Mplus Version 3 (Asparouhov & Muthén, 2004; Muthén & Muthén, 2006). Input for all analyses shown is available at the Mplus web site (www.statmodel.com).

Although the analyses in the current article were all based on cross-sectional data, interesting extensions of the models discussed are also available for longitudinal data analysis. Two examples are briefly mentioned here. As an example of categorical latent variable modeling, latent transition modeling is used when the substantive interest is in transitions between latent states (Chung et al., 2005; Collins et al., 1997; Collins & Wugalter, 1992; Dolan et al., 2005; Reboussin et al., 1998). With a mental health measurement instrument, the latent classes of categorical latent variables represent individual latent states such as affected and nonaffected. A particularly interesting form of latent transition modeling uses a second-order categorical latent variable to represent population heterogeneity in the form of 'movers' versus 'stayers'. This model is shown in Figure 5a. To avoid inclusion of individuals who fluctuate greatly in their true states, it may be of interest for genetic analysis to focus attention on stayers, that is, the subgroup of individuals that is more likely to exhibit stability in their affected and nonaffected states. In this case the phenotype is a latent class variable of affected versus nonaffected within the stayer subgroup.⁸ Random effects heterogeneity in line with growth mixture modeling discussed below can also be added to latent transition modeling.

When development across time is instead conceptualized as continuous changes, growth modeling using

random effects to capture heterogeneity of development is commonly used (see, for example, Hedeker, 2004). In such modeling, latent continuous growth factors (intercept and slopes) would form the phenotype for genetic analysis (Neale & McArdle, 2000). As a generalization of such analysis, Muthén and Shedden (1999) and Muthén et al. (2002) introduced growth mixture modeling with a combination of latent class and random effects modeling of heterogeneity, using the latent classes to represent qualitatively different developmental trajectory types. Growth mixture modeling has been applied to achievement development and high school dropout (Muthén, 2004), alcohol misuse development (Muthén & Muthén, 2000; Muthén & Shedden, 1999), conduct disorder in classrooms and school removal (Muthén et al., 2002), as well as prostate-specific antigen development and prostate cancer (Lin et al., 2002). An example of a growth mixture model is shown in Figure 5b. Here, the graph on the right shows a quadratic growth model for an outcome (y) measured at four time points using three growth factors (i , s , and q) with one latent class variable (c) influencing the growth factors as well as a distal outcome (u). Corresponding to the three classes, the graph on the left shows three qualitatively different trajectory types indicated by three solid curves for the mean development often seen for conduct disorder data, juvenile delinquency, and heavy alcohol involvement: normative, escalating, and early onset development. Reflecting the influence of the growth factors, each class shows thinner individual curves indicating within-class variations on the major curve shape theme.⁹ In this way, the growth mixture model has features similar to FMA. The Mplus modeling framework makes it possible to expand twin heritability analysis of the factor mixture type to growth mixture modeling with longitudinal data. The phenotype may correspond to latent class as well as growth factor scores within class. The graph on the left in Figure 5b illustrates the value of using longitudinal information in genetic analysis. At about age 20 the trajectories show that it is difficult to classify an individual into the three classes while longitudinal information makes this classification feasible. Given these new latent variable techniques for genetic analysis, the rewards for collecting longitudinal data should be even greater.

Endnotes

- 1 Example 6.16 of the *Mplus Version 4 User's Guide* (Muthén & Muthén, 2006) shows how to set up a two-part growth analysis.
- 2 Example 8.5 of the *Mplus Version 4 User's Guide* (Muthén & Muthén, 2006) shows how to set up a zero-inflated Poisson growth mixture analysis.
- 3 A nonparametric representation of the factor distribution is also possible (see, for example, Muthén & Muthén, 2006, example 7.26).

5a. Mover-Stayer Latent Transition Analysis

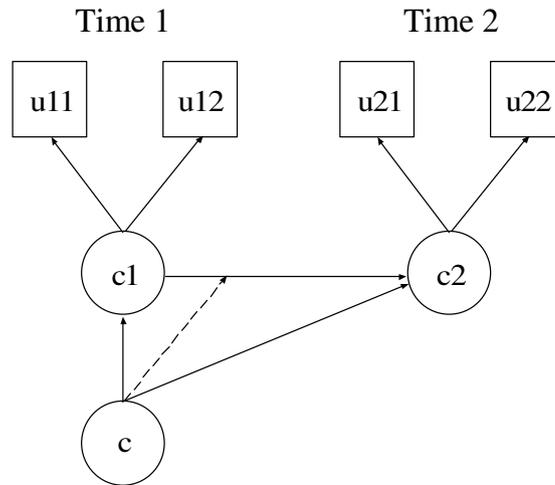
Transition Probabilities

Mover Class (c = 1)

	c2	
	1	2
1	.6	.4
2	.3	.7

Stayer Class (c = 2)

	c2	
	1	2
1	.90	.10
2	.05	.95



5b. Growth Mixture Modeling of Developmental Pathways

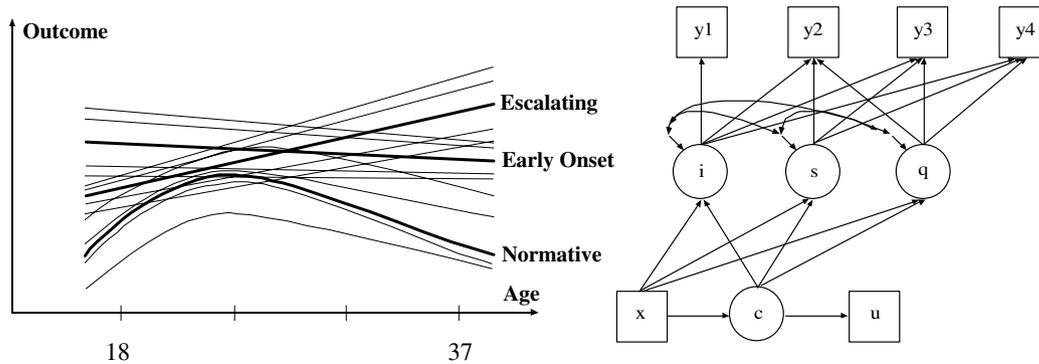


Figure 5
Longitudinal analysis.

- 4 The Mplus input for this analysis will be available on the Mplus web site www.statmodel.com
- 5 The Mplus input for this analysis will be available on the Mplus web site www.statmodel.com
- 6 The Mplus input for this analysis will be available on the Mplus web site www.statmodel.com
- 7 Muthén and Asparouhov (in press) investigates relationships between DSM-IV classification and latent variable classification of diagnostic criteria for alcohol dependence and abuse.
- 8 Example 8.14 of the *Mplus Version 4 User's Guide* (Muthén & Muthén, 2006) shows how to set up a mover-stayer latent transition analysis.

- 9 Example 8.6 of the *Mplus Version 4 User's Guide* (Muthén & Muthén, 2006) shows how to set up a growth mixture analysis with a distal outcome.

Acknowledgments

The research of the first author was supported under grant K02 AA 00230 from NIAAA. We thank Andrew Heath for kindly providing us with the Australian twin data. We thank Dorret Boomsma and anonymous reviewers for helpful comments. An earlier version of this article was presented at the July 2005 Behavior Genetics meeting in Hollywood, California.

References

- Asparouhov, T., & Muthén, B. (2004). *Maximum-likelihood estimation in general latent variable modeling*. Manuscript in preparation.
- Chung, H., Park, Y., & Lanza, S. T. (2005). Latent transition analysis with covariates: Pubertal timing and substance use behaviors in adolescent females. *Statistics in Medicine*, *24*, 2895–2910.
- Collins, L. M., Graham, J. W., Rousculp, S. S., & Hansen, W. B. (1997). Heavy caffeine use and the beginning of the substance use onset process: An illustration of latent transition analysis. In K. Bryant, M. Windle, & S. West (Eds.), *The science of prevention: Methodological advances from alcohol and substance use research* (pp. 79–99). Washington DC: American Psychological Association.
- Collins, L. M., & Wugalter, S. E. (1992). Latent class models for stage-sequential dynamic latent variables. *Multivariate Behavioral Research*, *27*, 131–157.
- Dolan, C. V., Schmittmann, V. D., Neale, M. C., & Lubke, G. H. (2005). Regime switching in the latent growth curve mixture model. *Structural Equation Modeling*, *12*, 94–119.
- du Toit, M. (2003). *IRT from SSI*. Lincolnwood, IL: Scientific Software International, Inc. (BILOG, MULTILOG, PARSCALE, TESTFACT).
- Eaves, L. J., Silberg, J. L., Hewitt, J. K., Rutter, M., Meyer, J. M., Neale, M. C., & Pickles, A. (1993). Analyzing twin resemblance in multisymptom data: Genetic applications of a latent class model for symptoms of conduct disorder in juvenile boys. *Behavior Genetics*, *23*, 5–19.
- Embretson, S. E., & Reise, S. P. (2000). *Item response theory for psychologists*. Mahwah, NJ: Erlbaum.
- Hagenaars, J. A., & McCutcheon, A. L. (2002). *Applied latent class analysis*. Cambridge, UK: Cambridge University Press.
- Heath, A. C., Howells, W., Kirk, K. M., Madden, P. A. F., Bucholz, K. K., Nelson, E. C., Slutske, W. S., Statham, D. J., & Martin, N. G. (2001). Predictors of non-response to a questionnaire survey of a volunteer twin panel: Findings from the Australian 1989 twin cohort. *Twin Research*, *4*, 73–80.
- Hedeker, D. (2004). An introduction to growth modeling. In D. Kaplan (Ed.), *Handbook of quantitative methodology for the social sciences* (pp. 215–234). Newbury Park, CA: Sage Publications.
- Lin, H., Turnbull, B. W., McCulloch, C. E., & Slate, E. (2002). Latent class models for joint analysis of longitudinal biomarker and event process data: Application to longitudinal prostate-specific antigen readings and prostate cancer. *Journal of the American Statistical Association*, *97*, 53–65.
- McLachlan, G. J., Do, K. A., & Ambrose, C. (2004). *Analyzing microarray gene expression data*. New York: Wiley & Sons.
- McLachlan, G. J., & Peel, D. (2000). *Finite mixture models*. New York: Wiley & Sons.
- Muthén, B. (2001). Latent variable mixture modeling. In G. A. Marcoulides & R. E. Schumacker (Eds.), *New developments and techniques in structural equation modeling* (pp. 1–33). Mahwah, NJ: Lawrence Erlbaum Associates.
- Muthén, B. (2002). Beyond SEM: General latent variable modeling. *Behaviormetrika*, *29*, 81–117.
- Muthén, B. (2004). Latent variable analysis: Growth mixture modeling and related techniques for longitudinal data. In D. Kaplan (Ed.), *Handbook of quantitative methodology for the social sciences* (pp. 345–368). Newbury Park, CA: Sage Publications.
- Muthén, B., & Asparouhov, T. (2005a). *Latent class factor analysis, factor mixture analysis, and non-parametric representation of latent variable distributions*. Manuscript in preparation.
- Muthén, B., & Asparouhov, T. (2005b). Item response mixture modeling: Application to tobacco dependence criteria. Forthcoming in the special issue 'Novel approaches to phenotyping drug abuse'. *Annual Review of Addictions Research*.
- Muthén, B., & Asparouhov, T. (in press). Should substance use disorders be considered as categorical or dimensional? *Addiction*.
- Muthén, B., Brown, C. H., Masyn, K., Jo, B., Khoo, S. T., Yang, C. C., Wang, C. P., Kellam, S., Carlin, J., & Liao, J. (2002). General growth mixture modeling for randomized preventive interventions. *Biostatistics*, *3*, 459–475.
- Muthén, B., & Muthén, L. (2000). Integrating person-centered and variable-centered analyses: Growth mixture modeling with latent trajectory classes. *Alcoholism: Clinical and Experimental Research*, *24*, 882–891.
- Muthén, L. K., & Muthén, B. (2006). *Mplus user's guide* (Version 4). Los Angeles, CA: Muthén & Muthén.
- Muthén, B., & Shedden, K. (1999). Finite mixture modeling with mixture outcomes using the EM algorithm. *Biometrics*, *55*, 463–469.
- Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. London: Kluwer Academic Publishers.
- Neale, M., & McArdle, J. J. (2000). Structured latent growth curves for twin data. *Twin Research*, *3*, 165–177.
- Olsen, M. K., & Schafer, J. L. (2001). A two-part random effects model for semicontinuous longitudinal data. *Journal of the American Statistical Association*, *96*, 730–745.
- Prescott, C. A. (2004). Using the Mplus computer program to estimate models for continuous and categorical data from twins. *Behavior Genetics*, *34*, 17–40.
- Rasmussen, E. R., Neuman, R. J., Heath, A. C., Levy, F., Hay, D. A., & Todd, R. D. (2002). Replication of the

latent class structure of Attention-Deficit/Hyperactivity Disorder (ADHD) subtypes in a sample of Australian twins. *Journal of Child Psychology and Psychiatry*, *43*, 1018–1028.

Reboussin, B. A., Reboussin, D. M., Liang, K. Y., & Anthony, J. C. (1998). Latent transition modeling of

progression of health-risk behavior. *Multivariate Behavioral Research*, *33*, 457–478.

Roeder, K., Lynch, K. G., & Nagin, D. S. (1999). Modeling uncertainty in latent class membership: A case study in criminology. *Journal of the American Statistical Association*, *94*, 766–776.
