Advances In Measurement Modeling: Bringing Genetic Information Into Preventive Interventions And Getting The Phenotype Right

Bengt Muthen, UCLA
bmuthen@ucla.edu

Modeling The Influence On A Person's Behavior

Source of Influence	**Psychometric Sophistication (Measurement Modeling)**
Environment	High (Latent variable and multilevel models)
Genes	Low (Phenotype is a latent variable)
Genes x Environment	Low

Limitations Of Conventional Analyses For Diagnosis And Genetic Analysis

- Substantively-Based Approach: "x out of y" criteria fulfilled (categorical), sum of criteria (dimensional)
    - Limited support from data analysis
    - Assumes unidimensionality and relevance of equal weighting

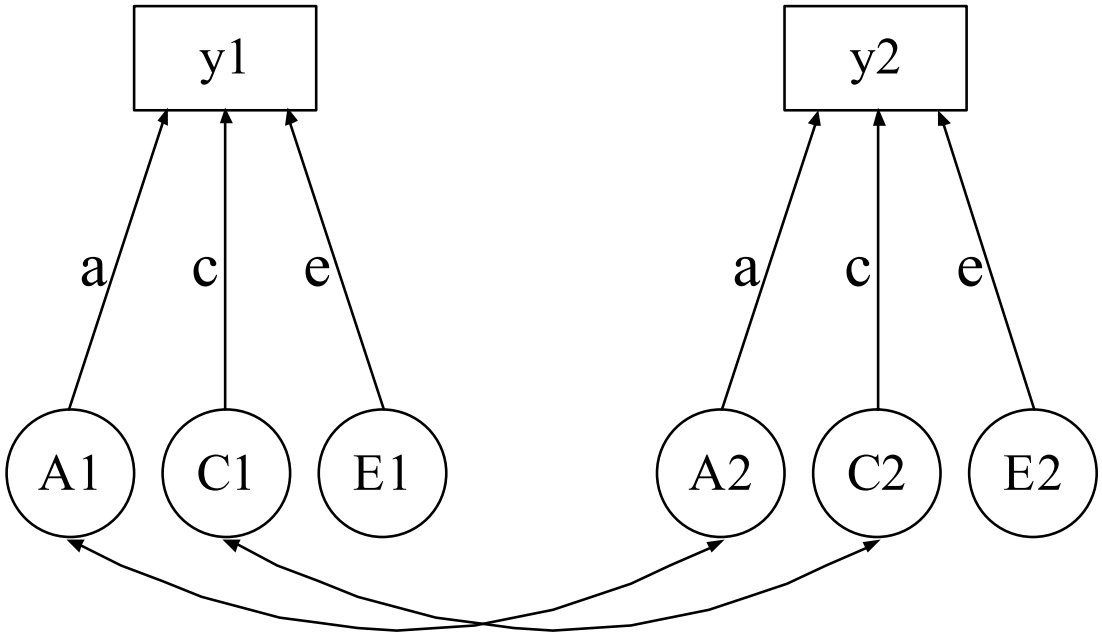
- Categorical Analysis Approach: Latent Class, Latent Transition Analysis
    - Ignores continuous within-category heterogeneity
    - Lower power for genetic linkage analysis

- Dimensional Analysis Approach: Factor Analysis, Growth Modeling
    - No model-derived classification
    - Difficulty choosing cut points
    - Ignores heterogeneity in the form of subtypes

Genetic Modeling

- Genetic information by design
  - Example: Twin analysis

- Genetic information by DNA
  - Example: QTL (Quantitative Trait Locus) linkage and association analysis using pair-specific information on alleles shared Identical By Descent

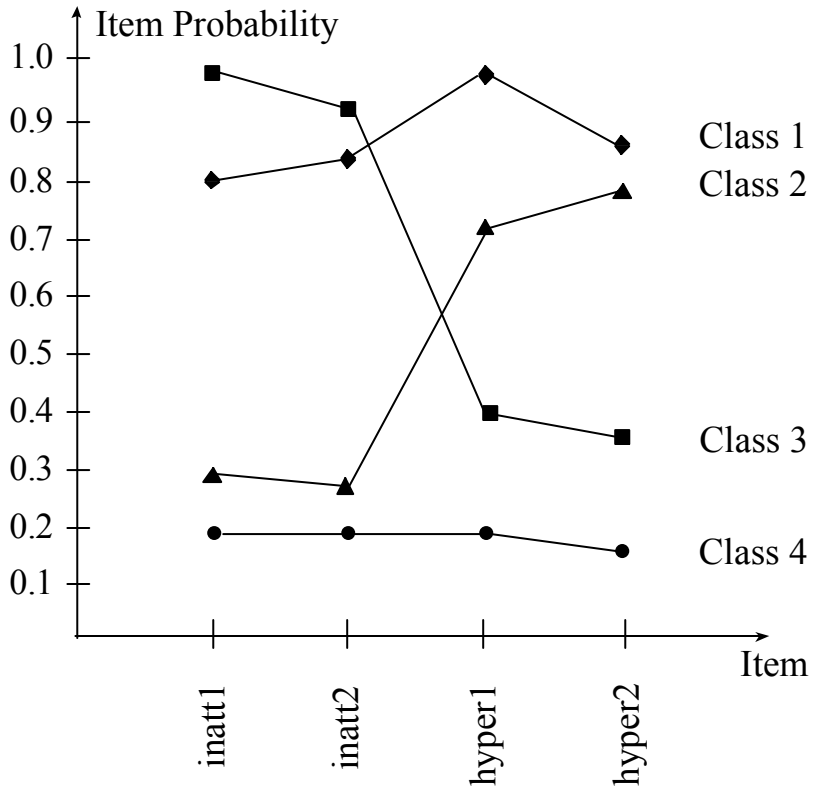

y1
y2
a
c
e
a
c
e
A1
C1
E1
A2
C2
E2

Phenotype As A Latent Variable

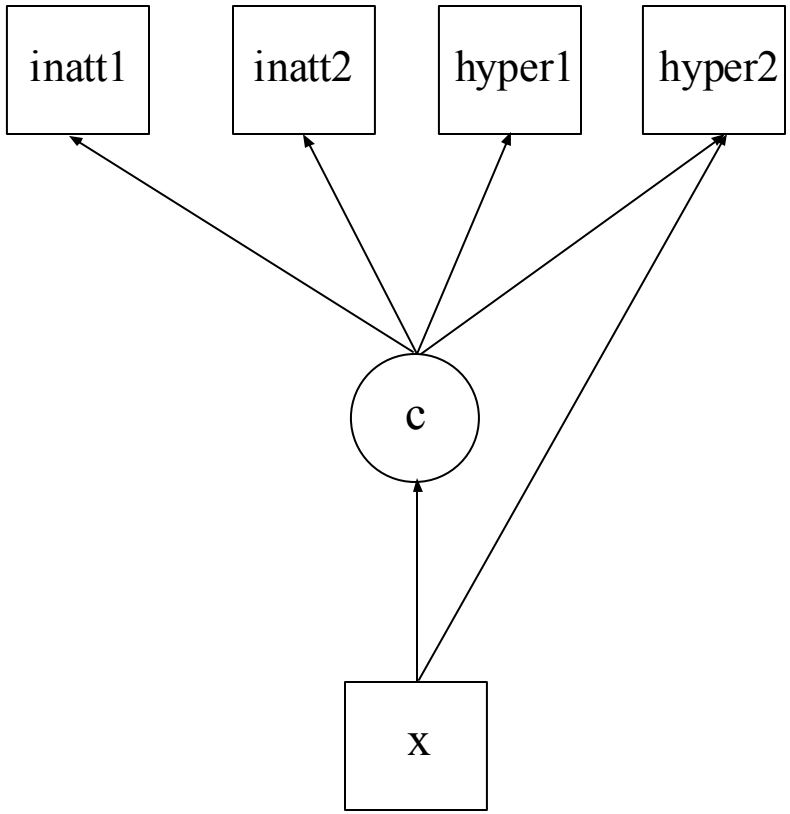
- Categorical latent variable: Latent Class Analysis
- Continuous latent variable: Factor Analysis
- Hybrids

Latent Class Analysis

a. Item Profiles



b. Model Diagram

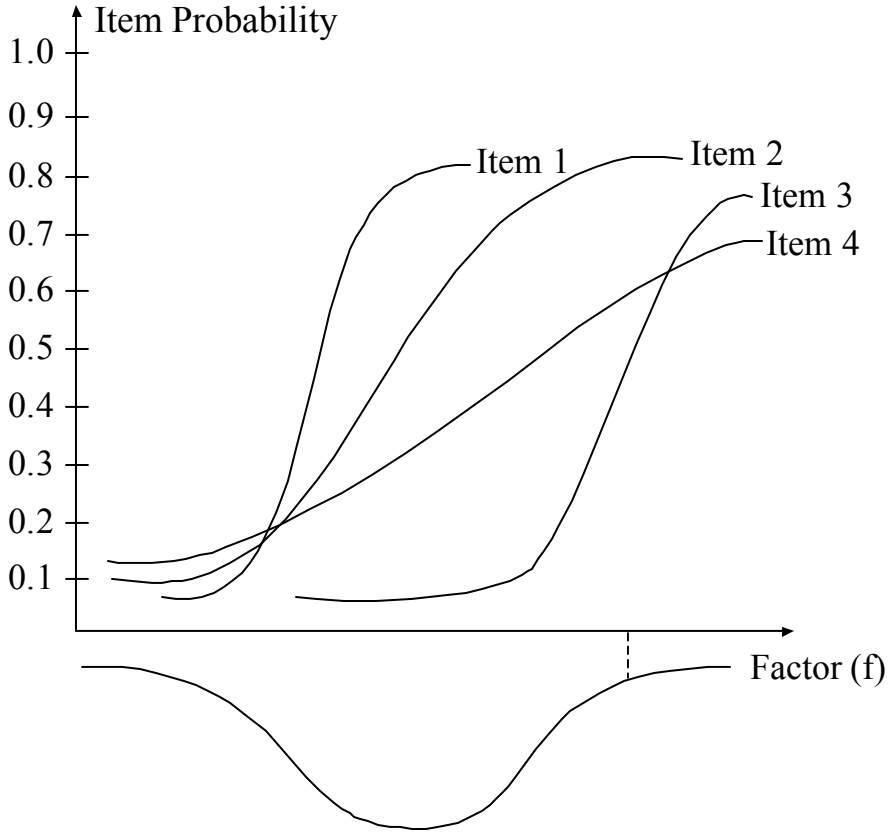


Examples Of LCA Applications To Health

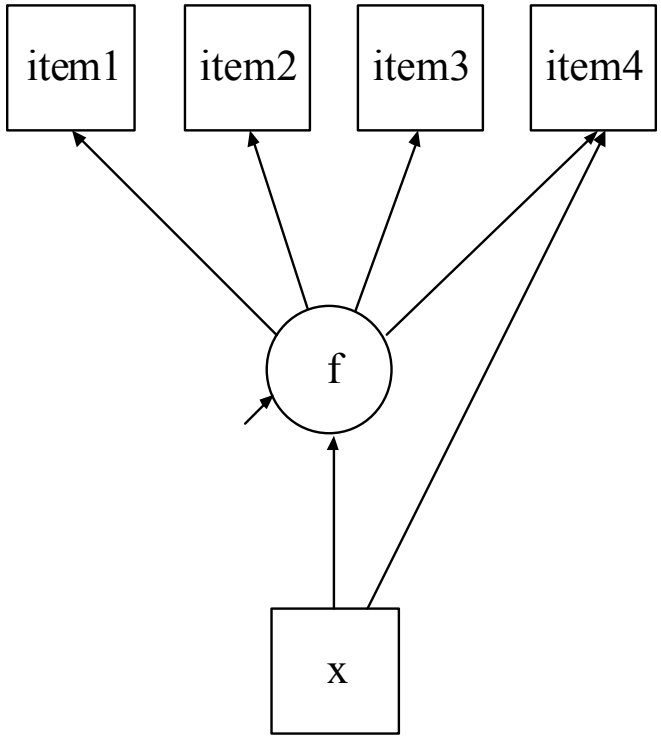
- Schizophrenia: Nestadt et al (1994)
- Alcohol: Bucholz et al (1996), Muthén (2001)
- Aging (physical disability): Bandeen-Roche et al (1997)
- Antisocial behavior: Muthén & Muthén (2000)
- Cancer tumors: Albert et al (2001)
- ADHD: Rasmussen et al (2002)

Factor Analysis (IRT, Latent Trait)

a. Item Response Curves



b. Model Diagram



DSM-IV Criteria In A National Sample Of 13,067 Male Current Drinkers

Alcohol Dependence

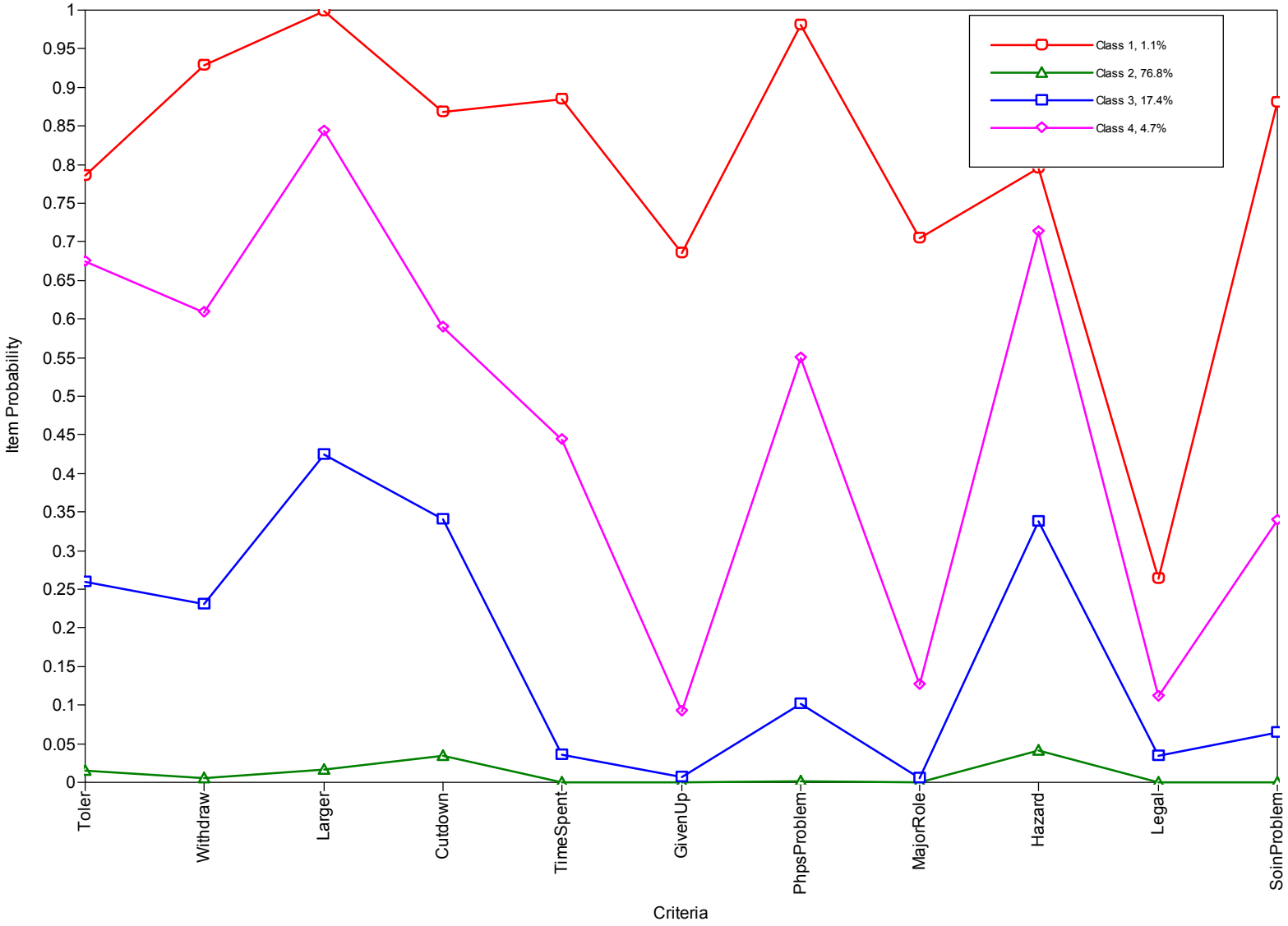
- Tolerance
- Withdrawal
- Drinking in larger amounts over a longer period of time than intended
- Persistent desire or unsuccessful efforts to cut down or control drinking
- Great deal of time spent in activities to obtain alcohol, to drink, or to recover from its effects
- Important social, occupational, or recreational activities given up or reduced in favor of drinking
- Continued to drink despite knowledge of having a persistent or recurrent physical or psychological problem caused or exacerbated by drinking

DSM-IV Criteria In A National Sample Of 13,067 Male Current Drinkers (Continued)

Alcohol Abuse

- Recurrent drinking resulting in failure to fulfill major role obligations at work, school, or home
- Recurrent drinking in situations where alcohol use is physically hazardous
- Recurrent alcohol-related legal problems
- Continued drinking despite persistent or recurrent social or interpersonal problems caused or exacerbated by drinking

Item Profiles: Latent Class Analysis (4 Classes)



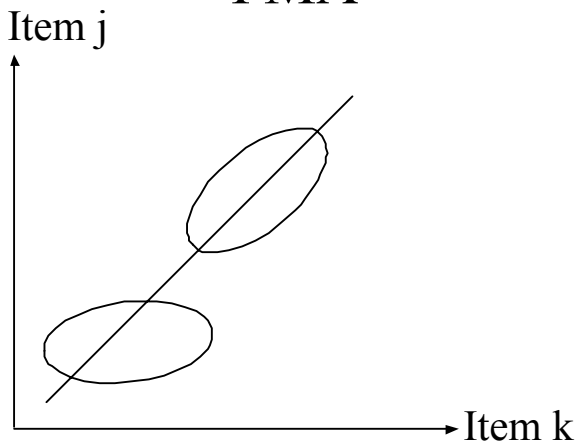
Model Testing For 11 Alcohol Criteria
Male Current Drinkers

	logL	#par's	BIC
• Latent class analysis:			
• 4 classes	-24,989	47	50,424
• Factor analysis:			
• 1 dimension	-25,032	22	50,274

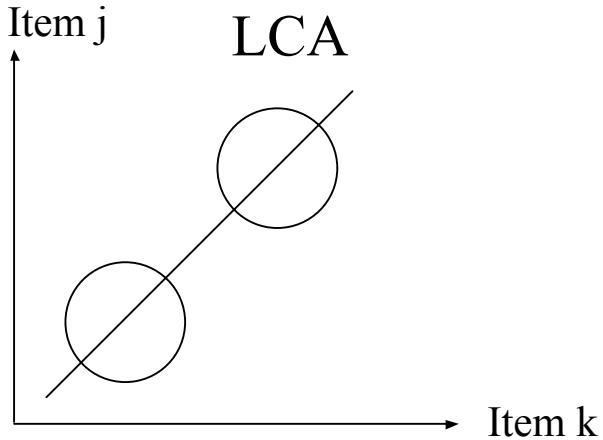
Factor Mixture Analysis

a. Cluster Types

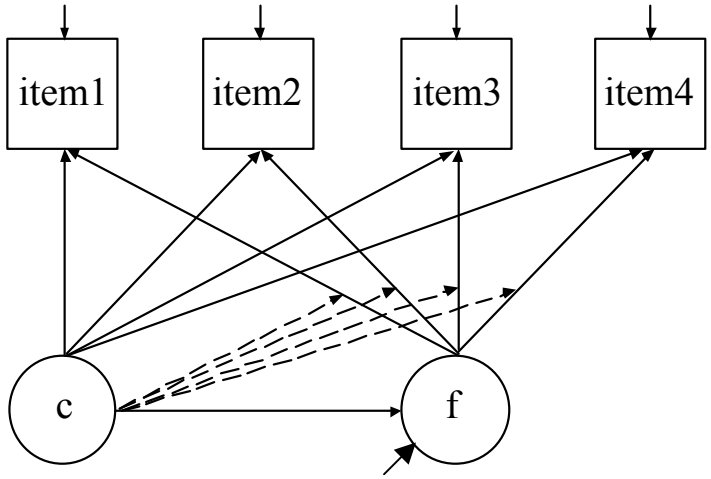
FMA



LCA



b. Model Diagram for FMA



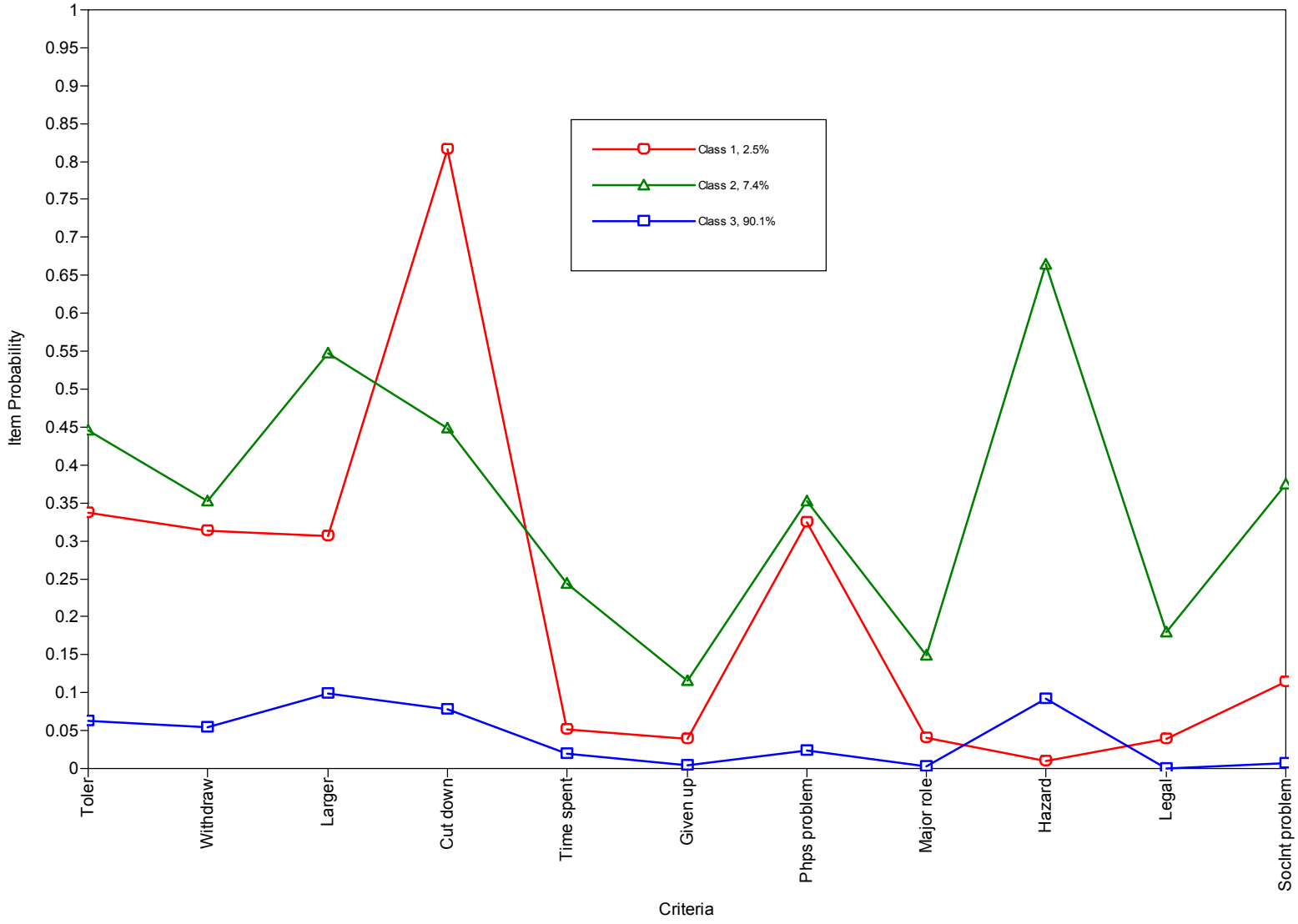
- Generalized latent class and factor analysis
- Categories and dimensions

Model Testing for 11 Alcohol Criteria

	logL	#par's	BIC
• Latent class analysis:			
• 4 classes	-24,989	47	50,424
• Factor analysis:			
• 1 dimension	-25,032	22	50,274
• **Factor mixture analysis:**			
• **3 classes, 1 dimension**	**-24,876**	**68**	**50,396**

7% (highest overall), 2% (high Cutdown), 90% (low)

Item Profiles: Factor Mixture Analysis



Conclusion I: Psychometric Modeling

New types of measurement models need to be applied to research on

- Environment
- Genes
- Genes x Environment

Conclusion II:
Design Implications for Preventive Interventions (Randomized, Longitudinal Studies)

Different aims:

- Candidate gene
  - DNA data from parents (and siblings)
  - Phenotype data from parents (and siblings)
  - Better measures of environment interacting with genes
- Genome-wide SNP array (Affymetrix 500K chip)