Phenomics

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Boulder Workshop
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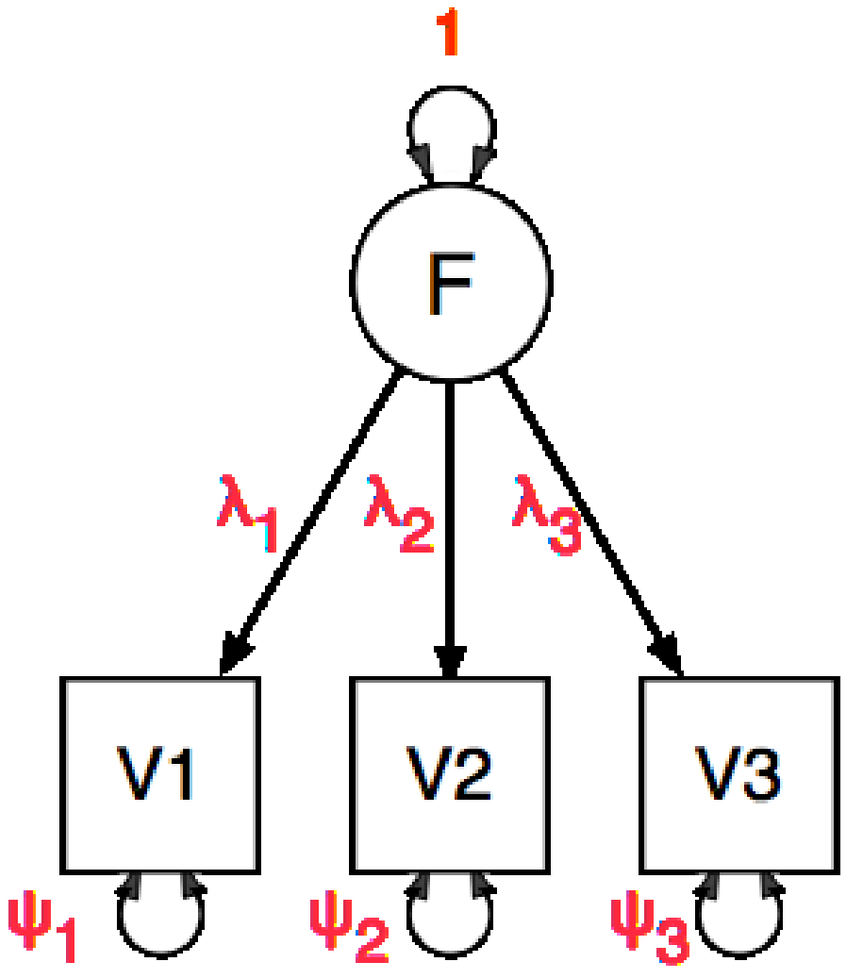
Outline

- Measuring Complex Traits
- Drug factors vs. Symptom factors
- Genomewide Structural Equation Modeling
- Testing Hypotheses about Gene Action: FTND
- Obligate Missingness
- Developmental Issues
- Future Directions including GREML

Measurement Invariance: Factor Model



Usually want to know about F, the latent factor!

Indirect measurement

Correlations across Substances: Add Health

	Stimulants	Tranquilizers	Marijuana
Stimulants	1		
Tranquilizers	0.74	1	
Marijuana	0.63	0.66	1
Factor Loadings	0.84	0.87	0.75

Medland & Neale (2010) An integrated phenomic approach to multivariate allelic association. European Journal of Human Genetics18:233–239

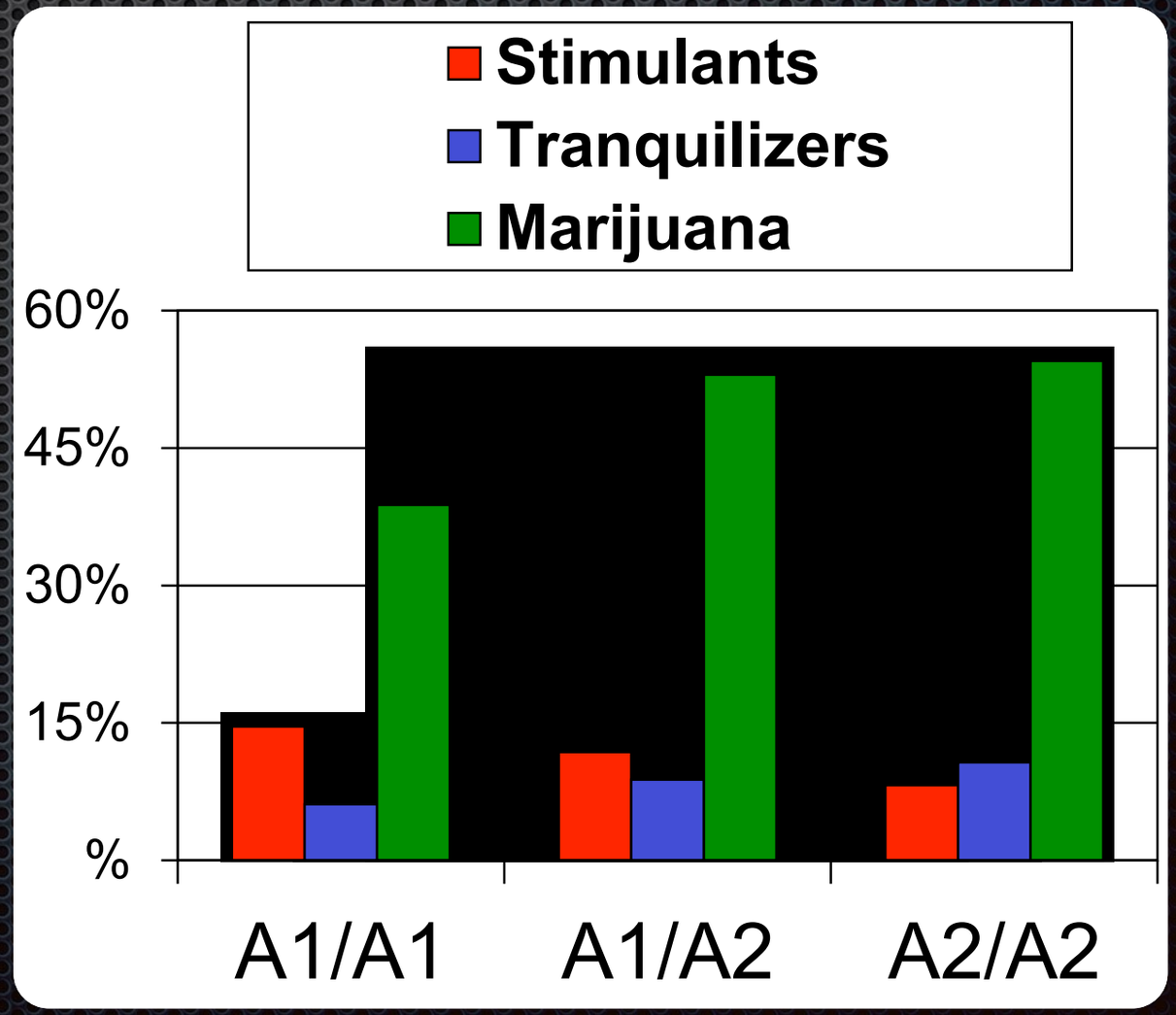
DRD2 Association Results (Add Health)

- Univariate associations
  - Stimulants: χ^2=3.88, β= -.18, p < .05
  - Tranquilizers: χ^2=1.65, β= .13, NS
  - Marijuana: χ^2=2.60, β= .11, NS
- Factor level association
  - χ^2=0.65, kF= .06, NS
- Item level association
  - χ^2=13.91 (3df; p < 0.005)

$\beta_{Stimulants}$ = -0.19

$\beta_{Tranquilizers}$ = 0.14

$\beta_{Marijuana}$ = 0.11

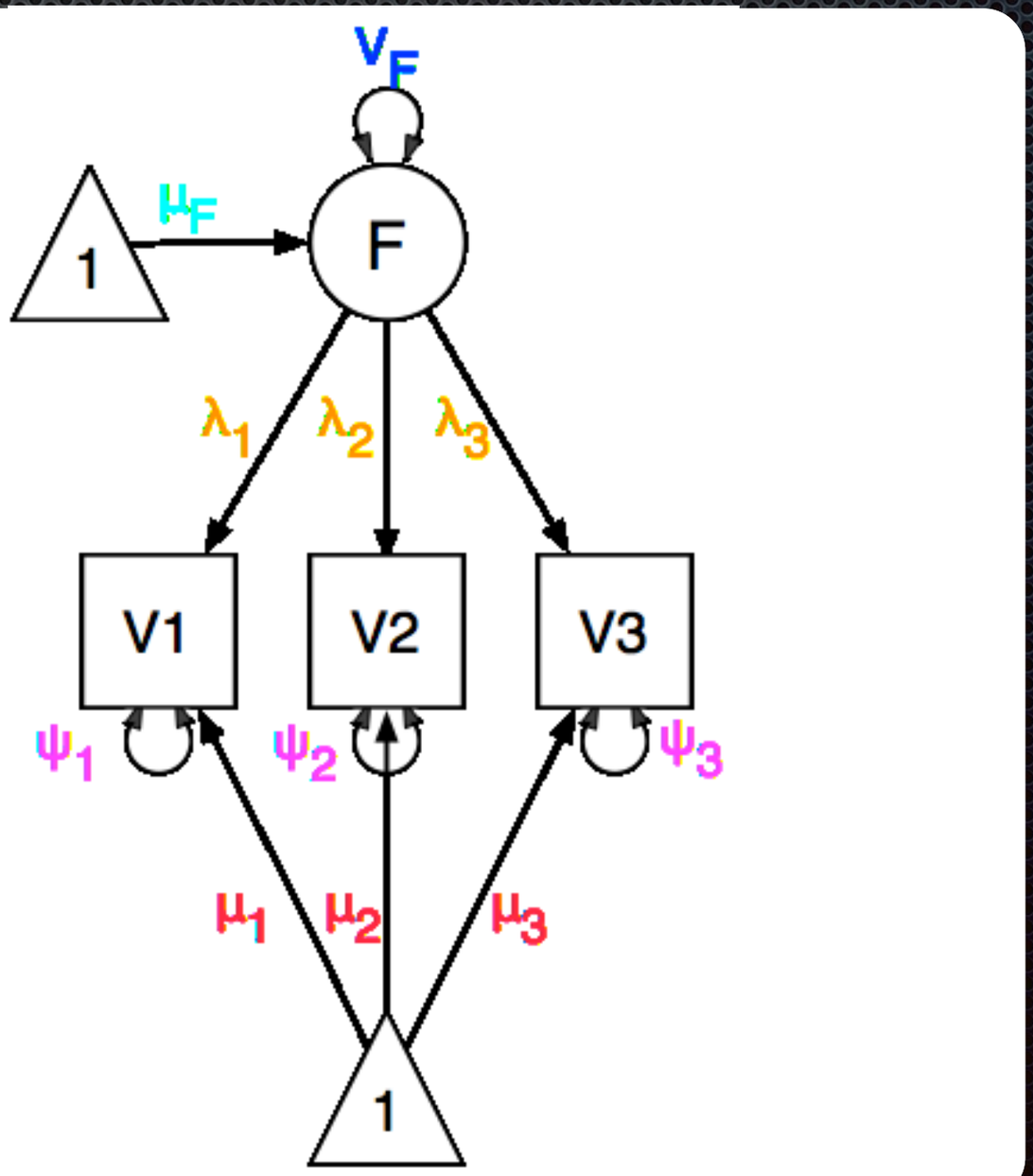


MNI Causes Errors of Inference

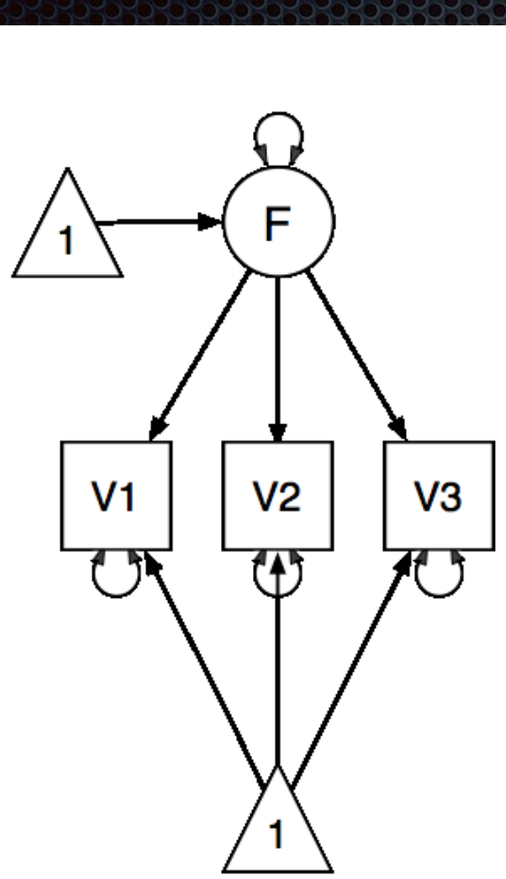
- Sum Scores & Factor Scores Depend on Model
- Item-level Differences May:
  - Invalidate Group Mean Tests (Association even)
  - Invalidate Group Variance Tests
- MI Still Rarely Tested

Invariance: Five Potential Types of Difference

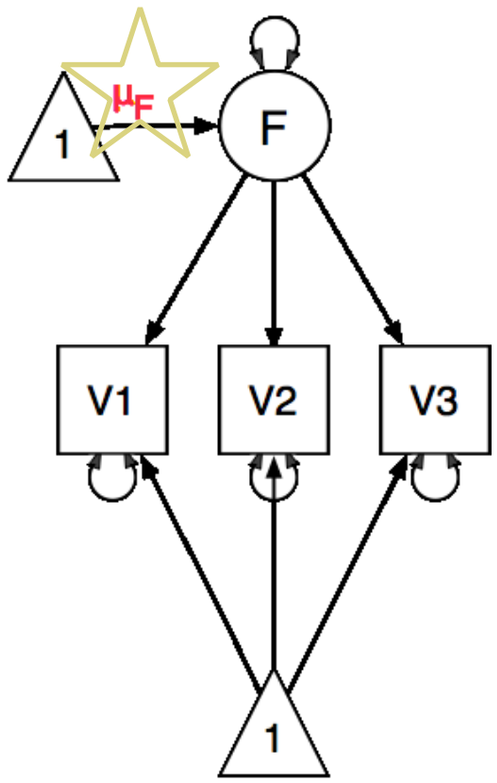
- Factor Variances
- Factor Means
- Factor Loadings
- Item Variances
- Item Means



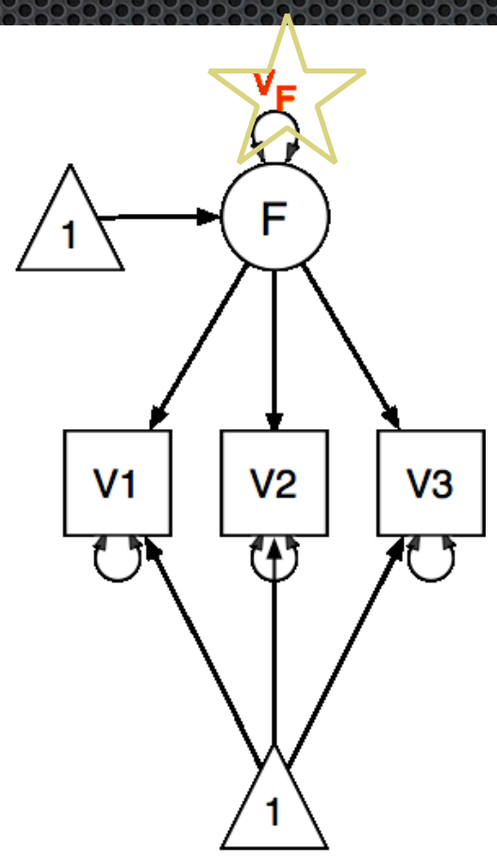
Invariance Models of Factor-Level Effects



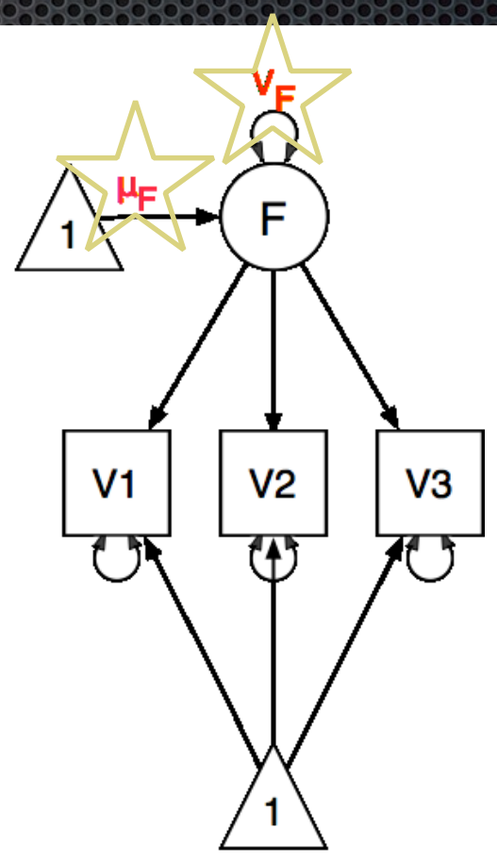
1. No Covariates



2. Age/Sex on Factor Mean



3. Age/Sex on Factor Variance



4. Age/Sex on Factor Mean and Variance

MI Application: National Survey of Drug Use in Households (NSDUH)

- Substance Abuse and Mental Health Services Administration (SAMSA) regular data collection
- ~50,000 persons per assessment
- Face-to-face Interviews(!)
- Audio-Computer-Assisted Testing

Map Items to DSM-IV Substance Abuse and Dependence Criteria

- A1 During the past 12 months, did using marijuana or hashish cause you to have serious problems like this either at home, work, or school?
- A2 During the past 12 months, did you regularly use marijuana or hashish and then do something where using marijuana or hashish might have put you in physical danger?
- A3 During the past 12 months, did using marijuana or hashish cause you to do things that repeatedly got you in trouble with the law?
- A4 Did you continue to use marijuana or hashish even though you thought it caused problems with family or friends?

DSM-IV Dependence Criteria

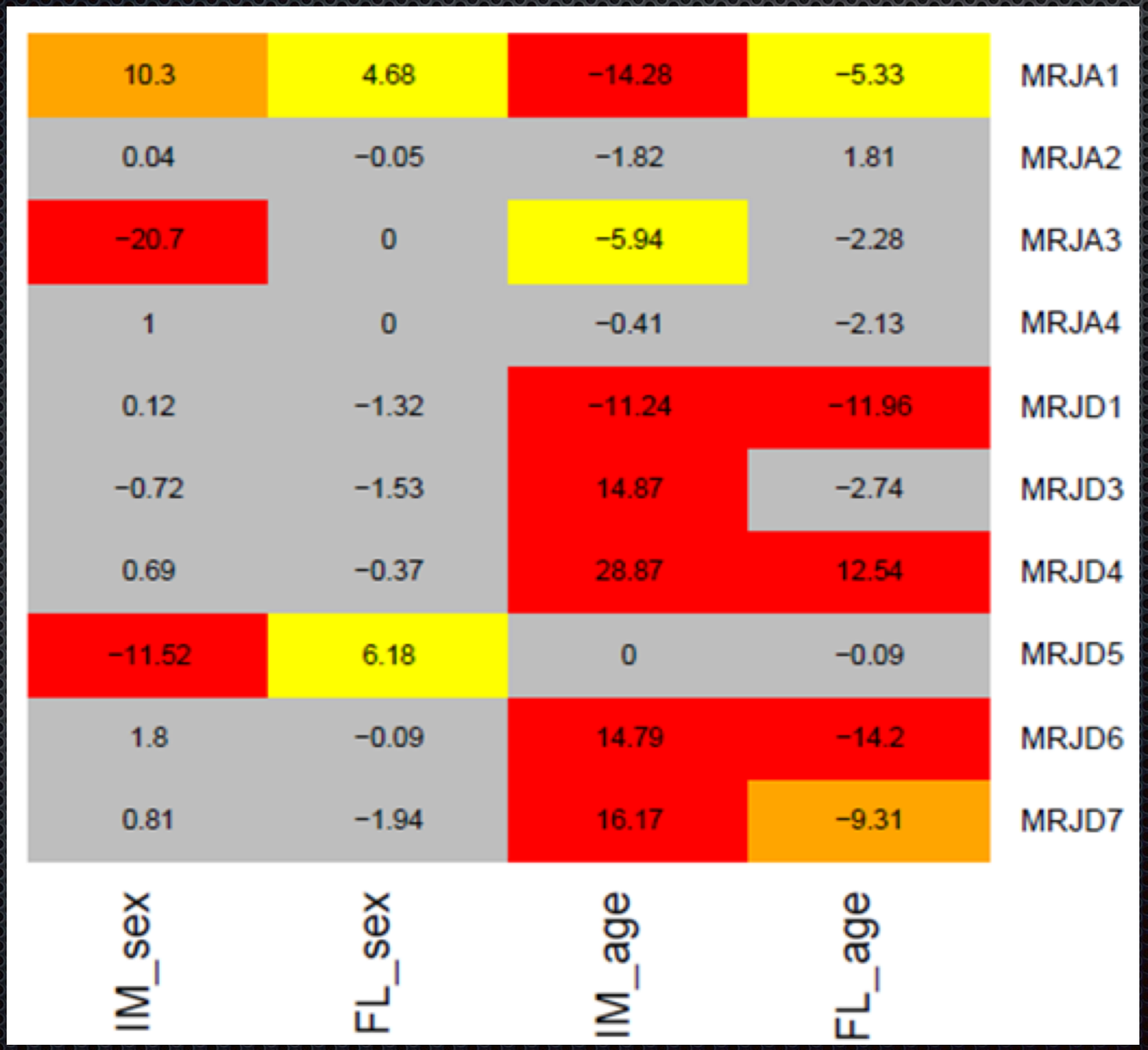
- D1 During the past 12 months, did you need to use more marijuana or hashish than you used to in order to get the effect you wanted?
- D3 Were you able to keep to the limits you set, or did you often use marijuana or hashish more than you intended to?
- D4 During the past 12 months, did you want to or try to cut down or stop using marijuana or hashish?
- D5 During the past 12 months, was there a month or more when you spent a lot of your time getting or using marijuana or hashish?
- D6 This question is about important activities such as working, going to school, taking care of children, doing fun things such as hobbies and sports, and spending time with friends and family.
  - During the past 12 months, did using marijuana or hashish cause you to give up or spend less time doing these types of important activities?
- D7 Did you continue to use marijuana or hashish even though you thought it was causing you to have physical problems?

Test of Item Mean Invariance: Marijuana in NSDUH

- Strong evidence of MNI with respect to age and sex
- Examine individual items
  - Four column heatmap for significance of effects
    - Item Means & Factor Variances
    - Sex and Age
  - Compare across self-reported race

-2lnL Likelihood Ratio Test Statistics: Marijuana Item Means & Factor Loadings

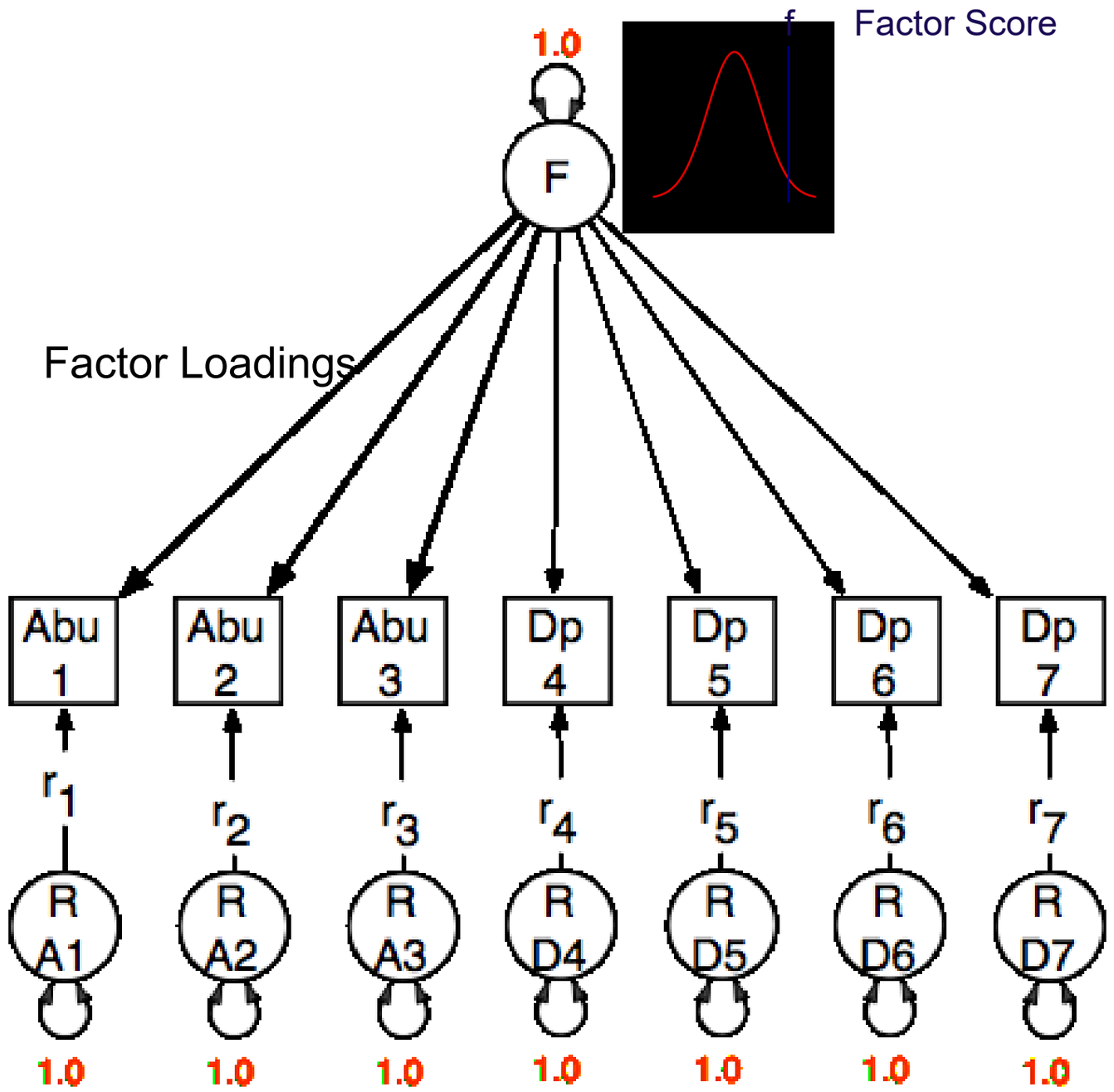
Entire Sample



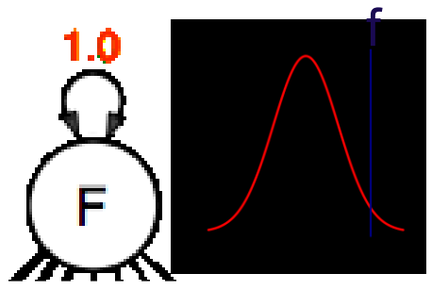
+/- sign denotes direction

Work
Danger
Law
Friends
Tol
>Intend
TryCut
TimeGet
TimeOther<
PhysProb

Estimating Factor Scores



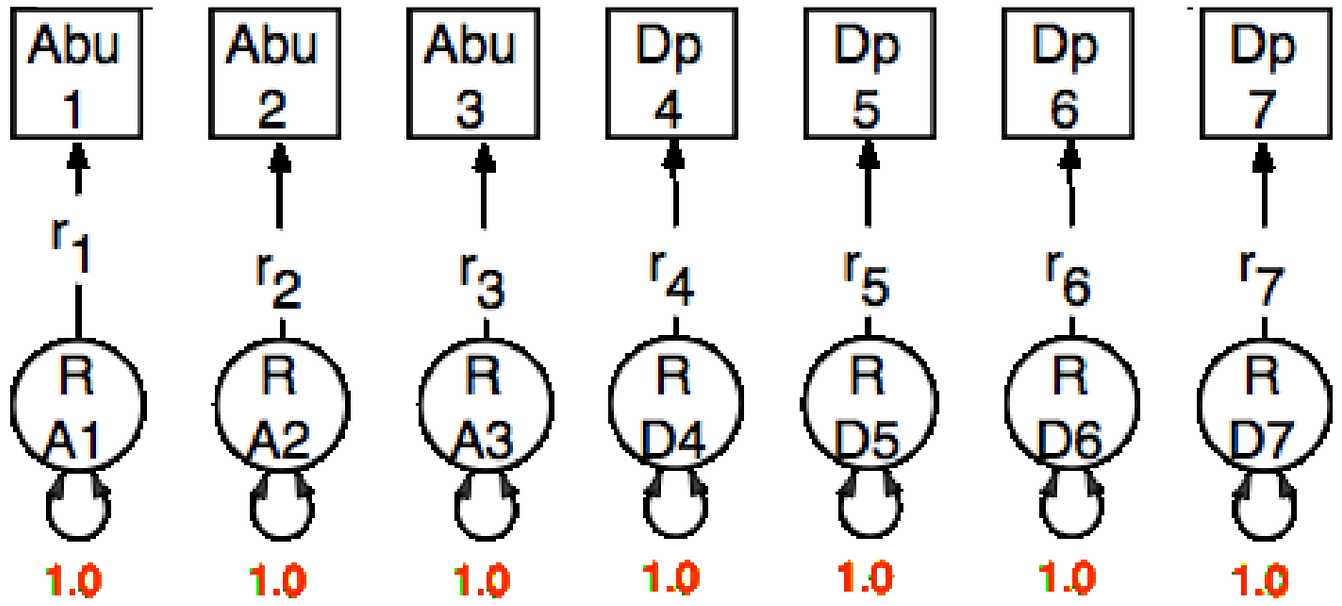
ML Estimation of Factor Scores

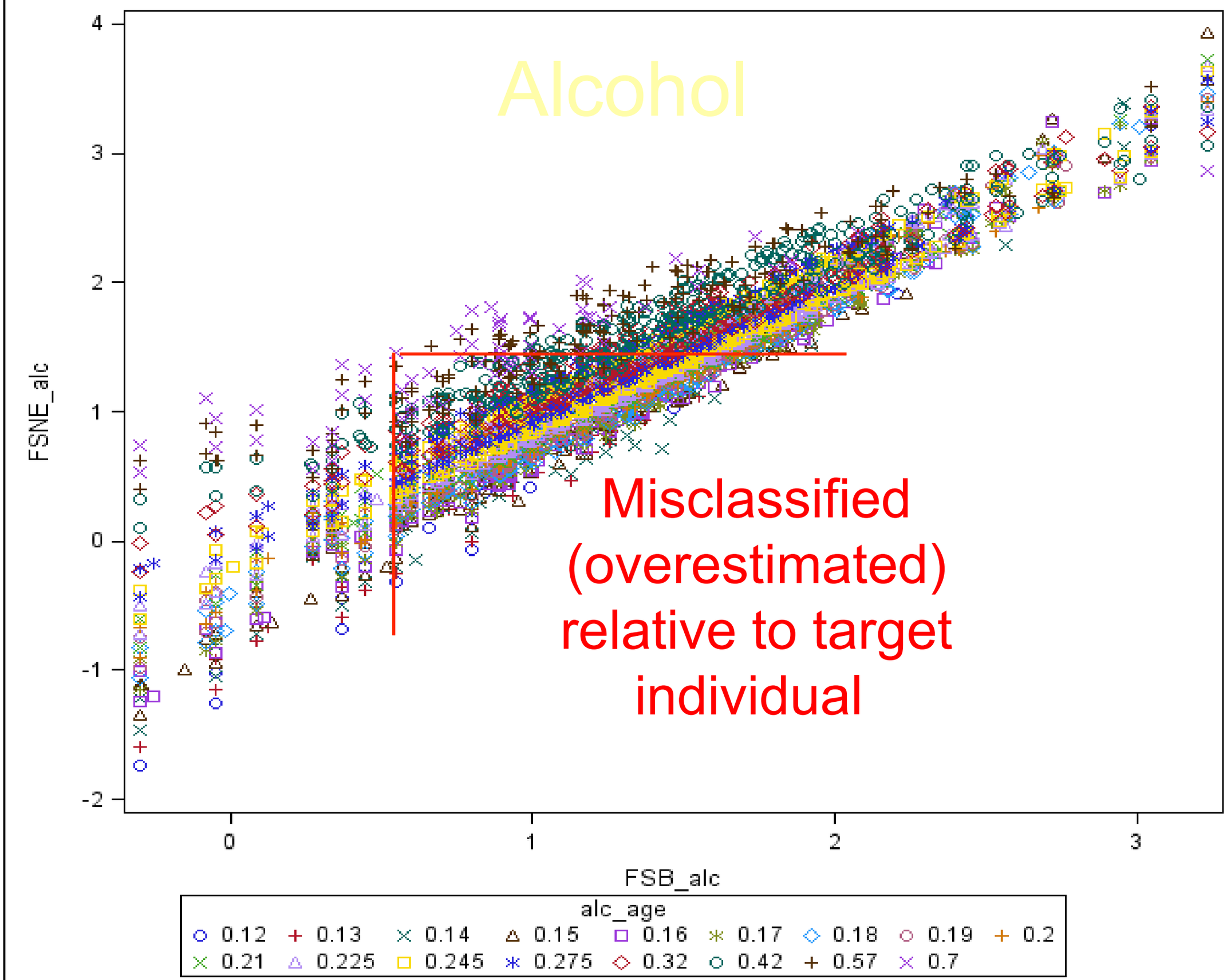


Factor Score

Factor Score * Likelihood of items conditional on factor score

Items independent conditional on factor score:
Means and variances change according to size of factor loadings



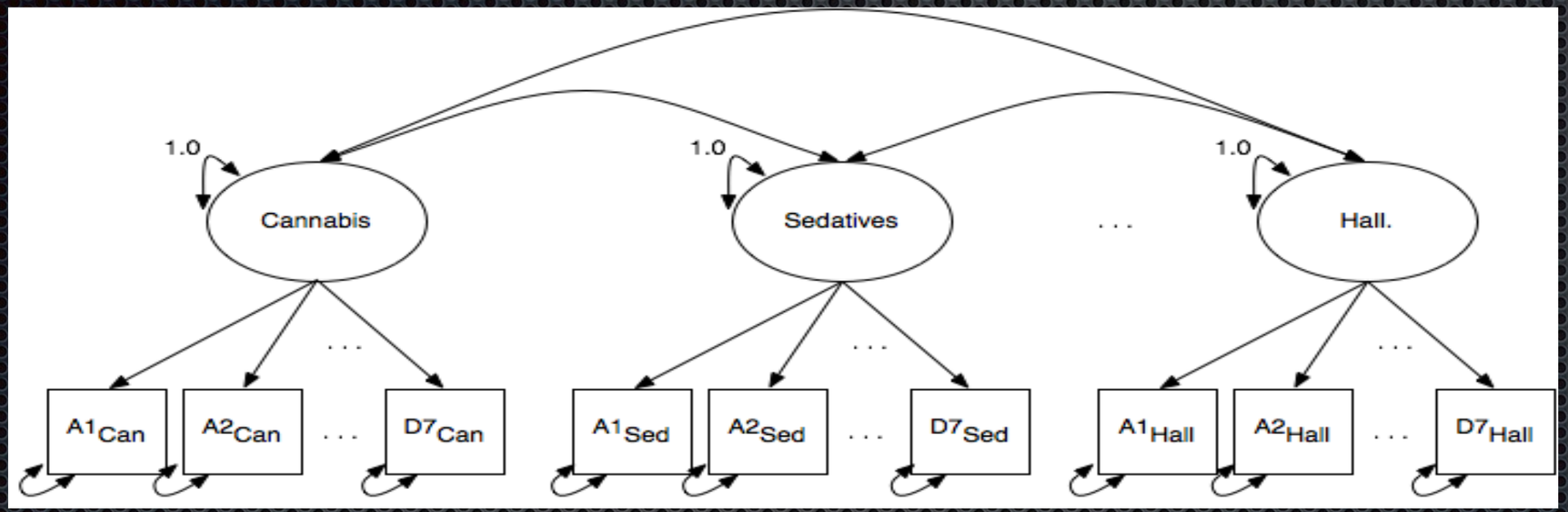

Comparison Plot of Base and MNIE Adjusted Alcohol Problem Factor Scores (Age)
Alcohol
Misclassified (overestimated) relative to target individual
FSNE_alc
FSB_alc
4
3
2
1
0
-1
-2
0
1
2
3
alc_age
0.12 0.13 0.14 0.15 0.16 0.17 0.18 0.19 0.2
0.21 0.225 0.245 0.275 0.32 0.42 0.57 0.7

Drug vs Symptom Factors

- DSM III-R/IV drug abuse and dependence symptoms for cannabis, sedatives, stimulants, cocaine, opioids and hallucinogens
- 13 misuse symptoms measured across six illicit substance categories (78 items)
- 4179 males born 1940–1970 from the population-based Virginia Adult Twin Study of Psychiatric and Substance Use Disorders
- Confirmatory factor analyses tested specific hypotheses regarding the latent structure of substance misuse

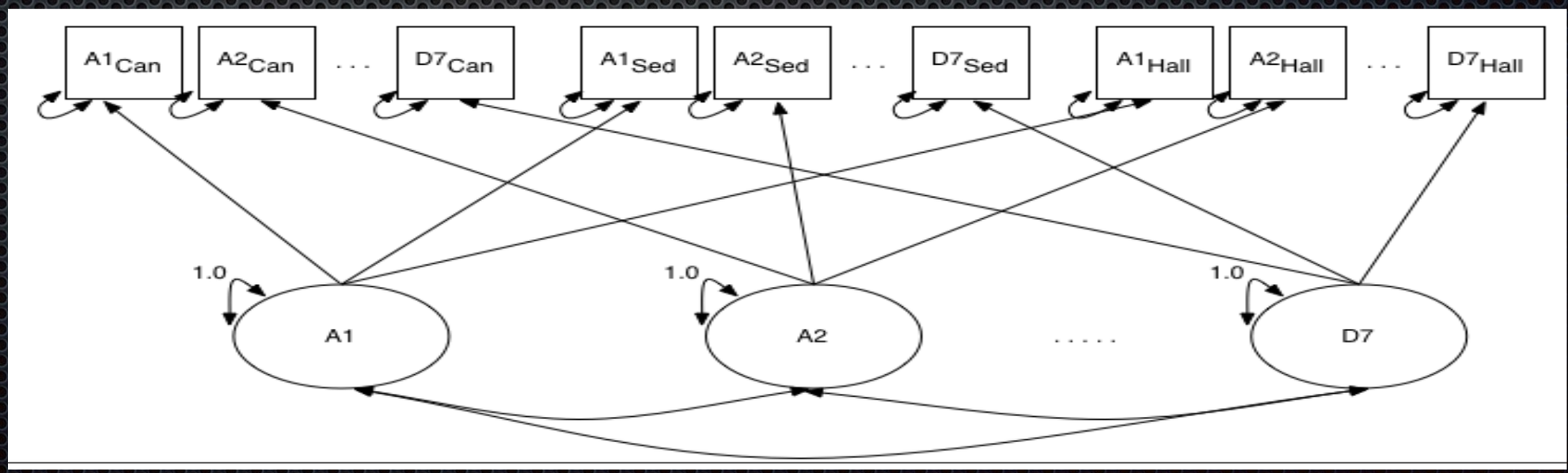
Drug vs Symptom Factors

A.



B.

Clark, S. L., Gillespie, N. A., Adkins, D. E., Kendler, K. S., and Neale, M. C. (2016). Psychometric modeling of abuse and dependence symptoms across six illicit substances indicates novel dimensions of misuse. *Addict Behav*, 53:132–40. PMCID: PMC4679450.



Drug vs Symptom Factors

Model	χ^2	DF	*p*-Value	CFI	RMSEA
M1: Drug factors only	4175	2910	<0.001	0.78	0.017
M2: Misuse characteristic factors only	3647	2847	<0.001	0.86	0.013
M3: Drug and misuse characteristic factors	2966	2754	<0.001	0.96	0.007
M4: General liability factor	4598	2925	<0.001	0.71	0.019
M1 vs. M3	1209	156	<0.001		
M2 vs. M3	681	93	<0.001		

- Adding symptom factors dramatically improves fit
- Majority of variance in many Sx due to *symptom* not *drug* factor

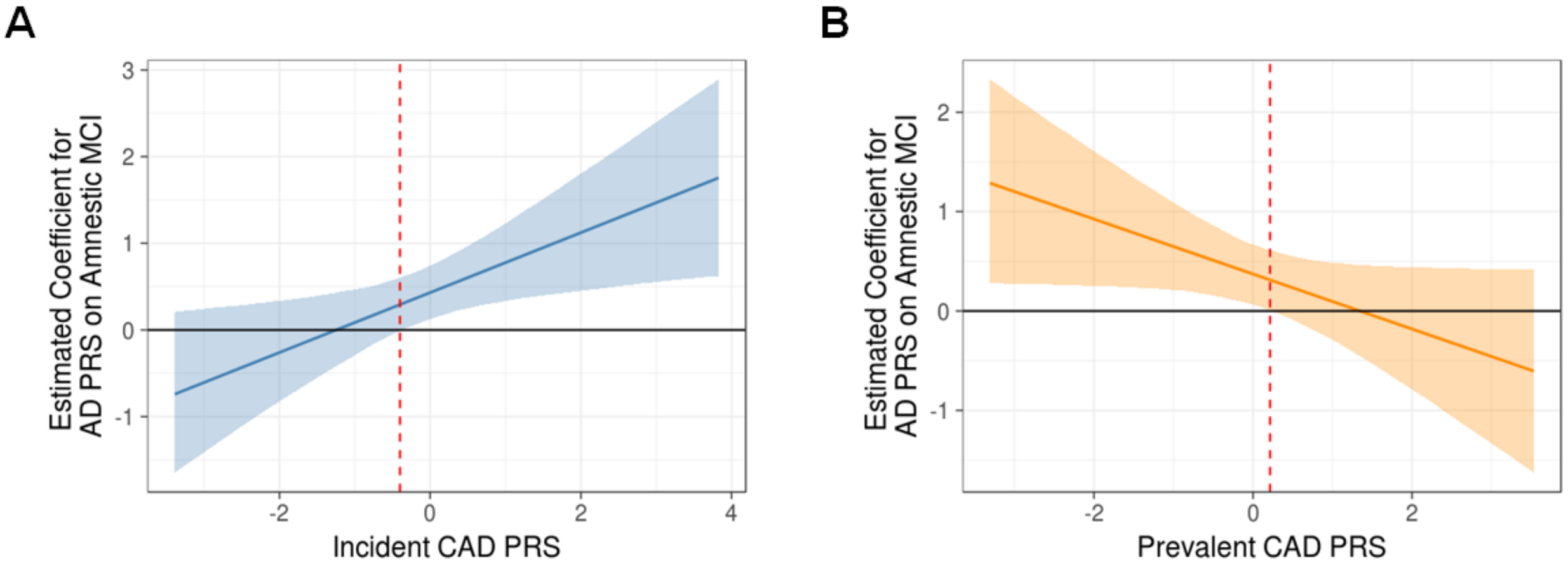
Factor Score Notes

- Factor scores do not all have same error variance
- Factor scores of A, C & E components may correlate highly
- Latent trait may be non-normal (Schmitt et al 2006 Multiv Behav Res)
- Factor loadings (precision) may vary across the distribution and give spurious GxE results
- Variation may be discrete not continuous
- For PRS, consider trait as measured at GWAS

Mild Cognitive Impairment VETSA Data: CHD & AD PRS

Ischemic heart disease: summary measure history of myocardial infarction, cardiac procedure or angina.

Group	Cognitively Normal	Amnestic MCI
N	1119	89
Age, *mean (SD)*	56.7 (3.3)	57.2 (3.5)
APOE-ε4+	29.4%	26.2%
Ischemic Heart Disease*	13.3%	3.5%
Depressive symptoms, *mean (SD)*	7.8 (7.6)	9.0 (8.4)
Diabetes	10.7%	11.5%



Plots of the interaction of an Alzheimer's disease polygenic risk score with A) a prevalent coronary artery disease polygenic risk score (CAD-PRS) and B) an incident CAD-PRS on amnestic mild cognitive impairment (MCI) status. The regression coefficient of the AD-PRS on amnestic MCI status is on the y-axis and is plotted across varying levels of CAD-PRSs on the x-axis. The dashed red line indicates the threshold of statistical significance for the AD-PRS as a predictor of aMCI status. In A the AD-PRS is more predictive of risk for aMCI to the right of the dashed line (i.e., people with higher AD-PRSs are more likely to have aMCI if they also have *higher incident* CAD--RSs). In B the AD-PRS is a significant predictor of increased risk for aMCI to the left of the dashed line but is not significant to the right of the dashed line.

Item Response Probability

Example item response probability shown in white

Possible population distribution in green

AFQT

100 Items

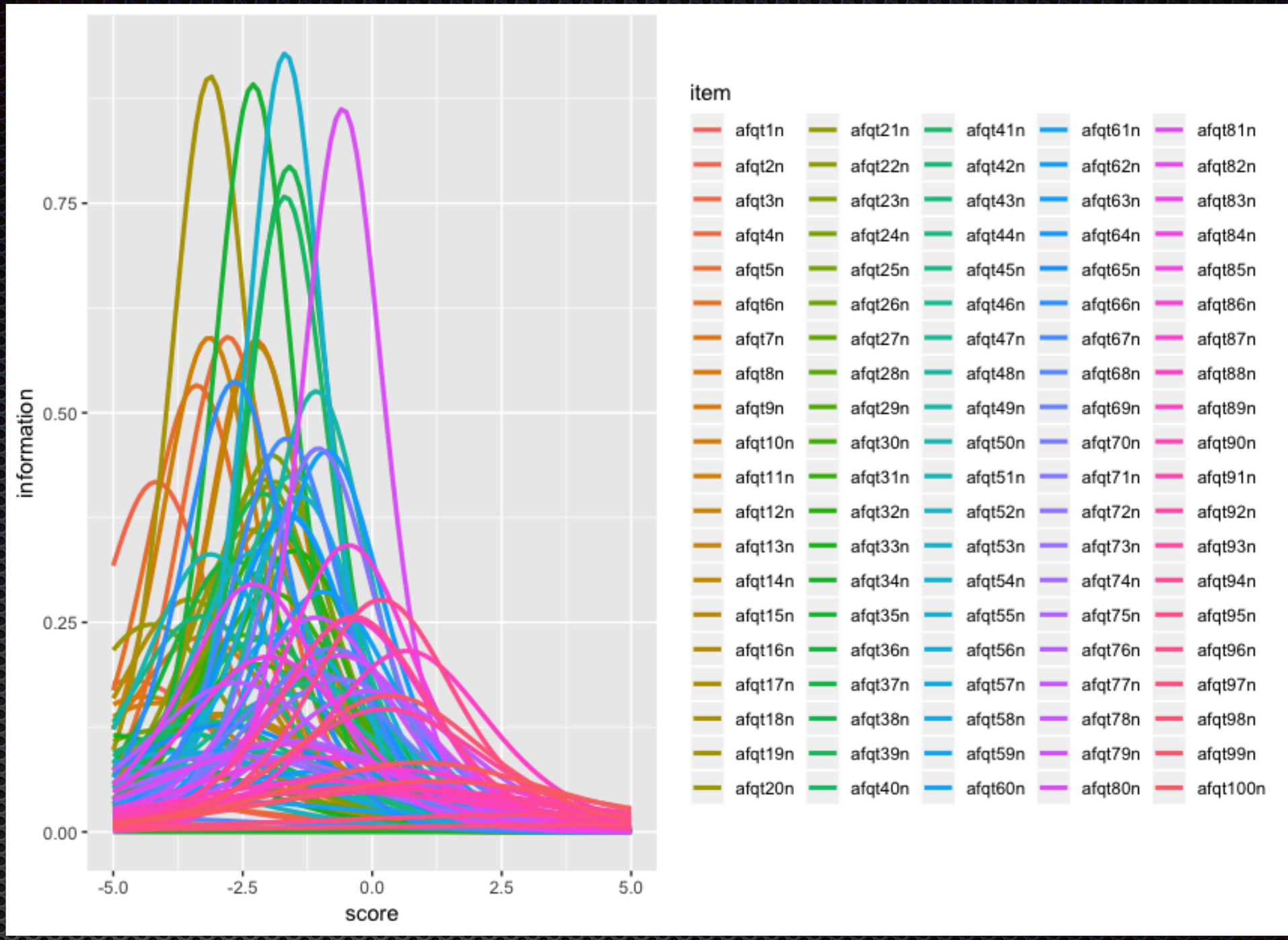
Subscales

1 Arithmetic Reasoning

2 Mathematics Knowledge

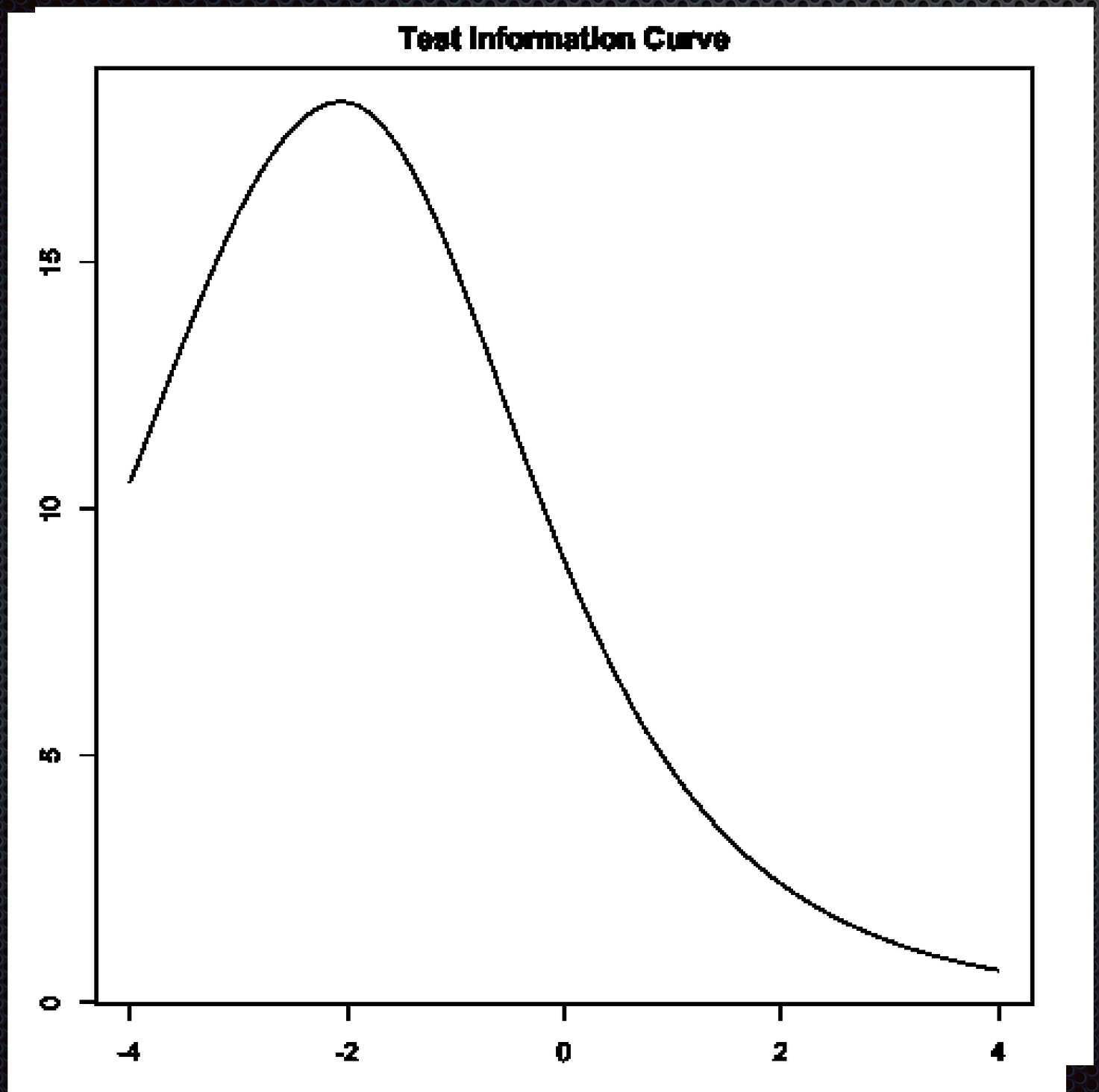
3 Word Knowledge

4 Paragraph Comprehension



Script & Fake Data are in workshop/faculty/mcn/2019

AFQT: Overall Test Information Curve



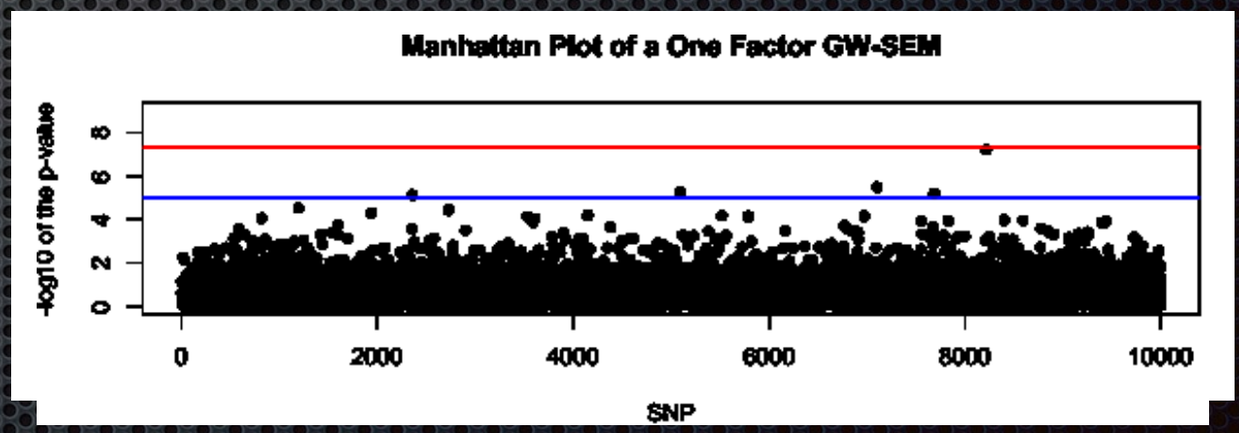
More information at left

By design

Consequences for GxE?

Genome-wide SEM

- Avoid problems with factor scores
- Fit factor or growth curve models to ordinal data
- Include effect of SNP on factor or items
- Repeat for the other 8m-1 SNPs
- Manhattan plot results
- http://goo.gl/f44UmD



Verhulst, B, Maes, H, & Neale, M (2017) GW-SEM: A Statistical Package to Conduct Genome-Wide Structural Equation Modeling. *Behav Genet 47(3):345-359*

Testing Hypotheses about Gene Action: FTND

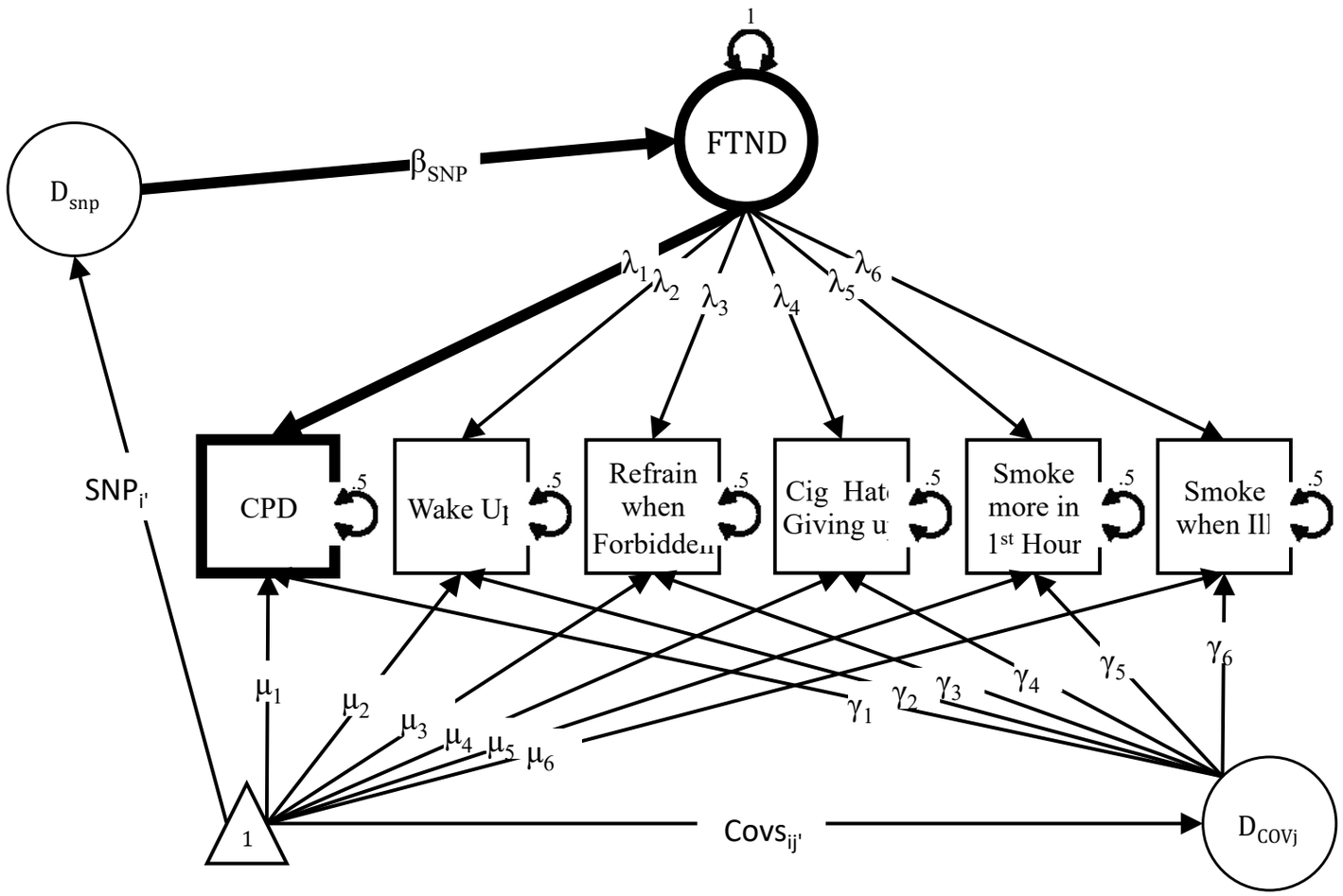
Table 1: Percentage of Variance Accounted for by the SNP rs16969968 in Latent FTND and Measured CPD

Sample	N	FTND	Total CPD	Indirect Effect
Sage	2,461	0.46	1.70	0.08
Smoking Cessation (SC)	574	0.48	1.76	0.08
CIDR	296	0.50	1.85	0.08
COPD	2,042	0.45	1.67	0.08

Note: The Direct Effects of FTND and the Total and Indirect Effects on CPD are taken from the best fitting model (H_{1c}).

- rs16969968 Neuronal acetylcholine receptor subunit α-5 CHRNA5 associated with both ND and CPD
- What is the mechanism of action?
- CPD mere symptom of FTND
- Increases CPD increases addiction?
- Feedback loop between CPD and addiction?

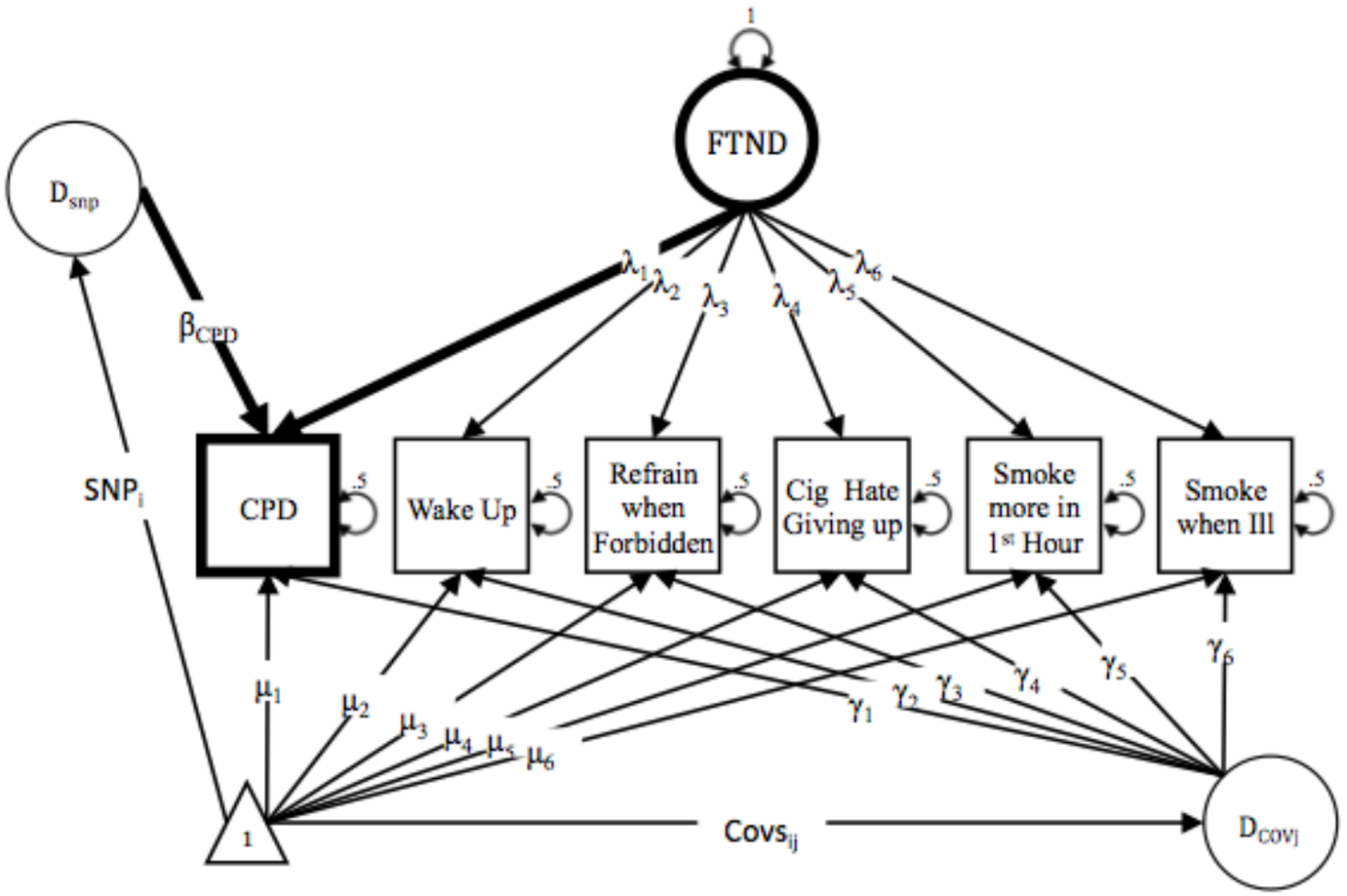
H1a SNP Causes Factor Only



(b) H_{1a}: Path diagram for regression of the latent FTND factor on the SNP.

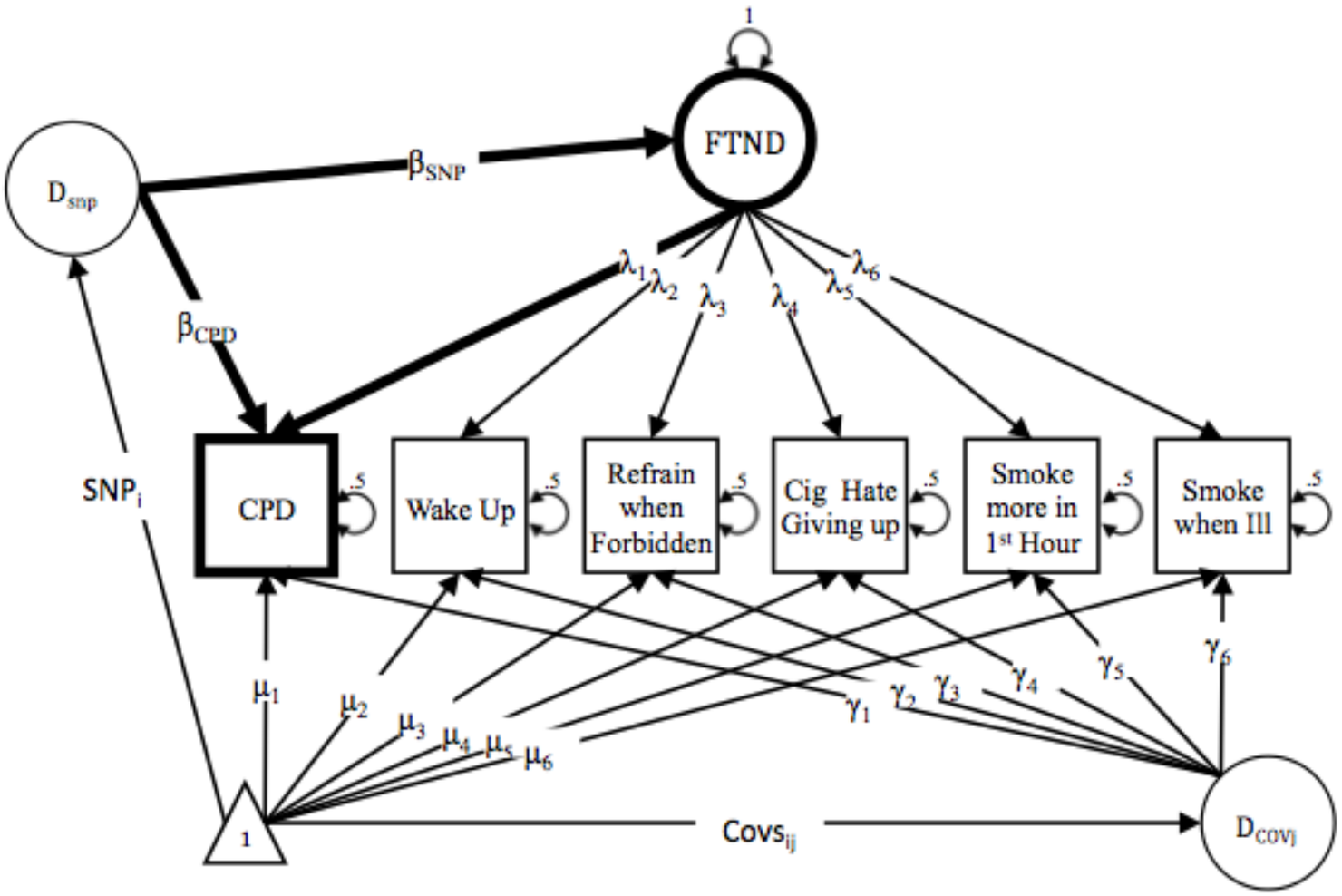
rs16969968 CHRNA5

H1b SNP Causes CPD Only



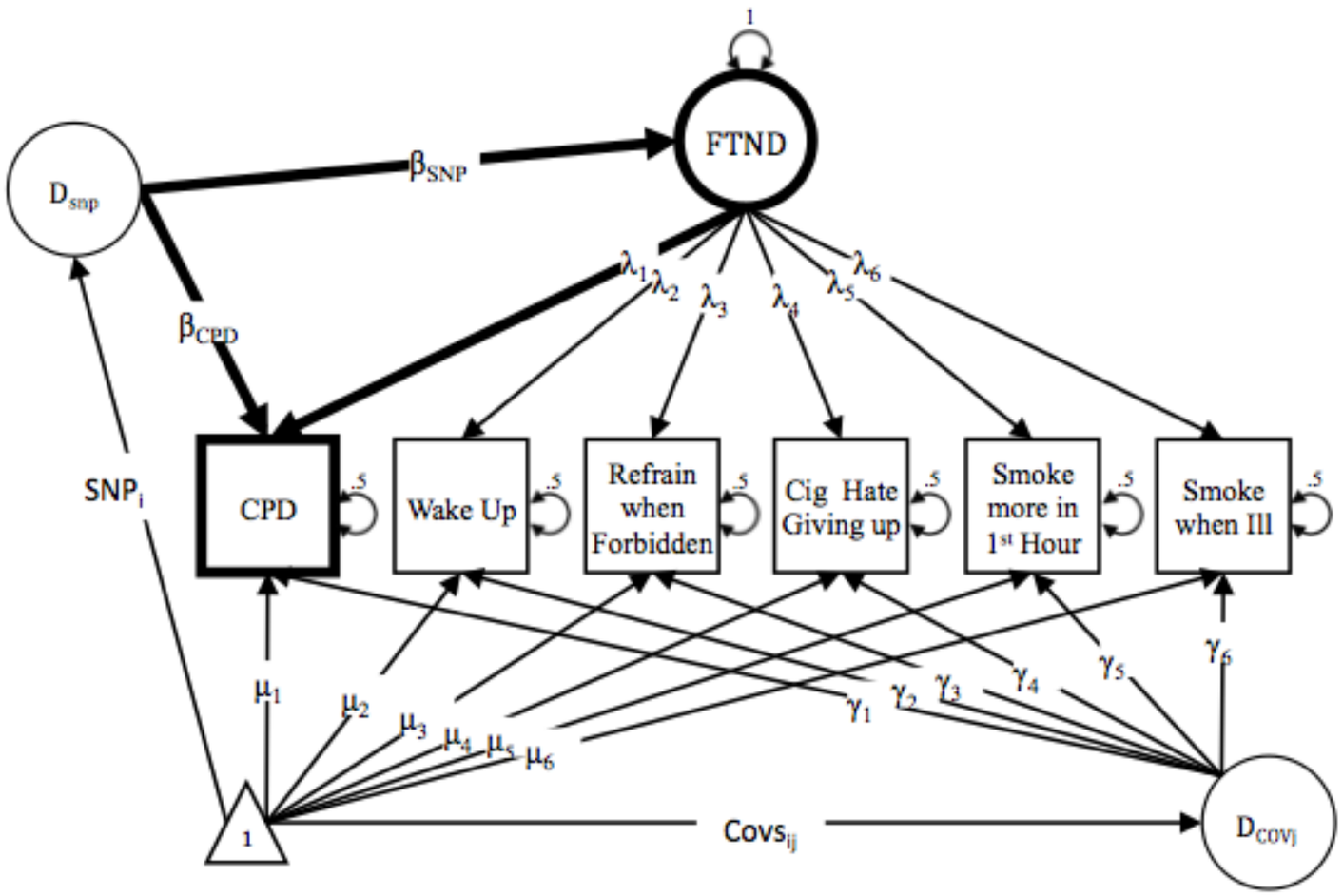
(c) H_{1b}: Path diagram for regression of CPD on the SNP

H1c SNP Causes Factor & CPD



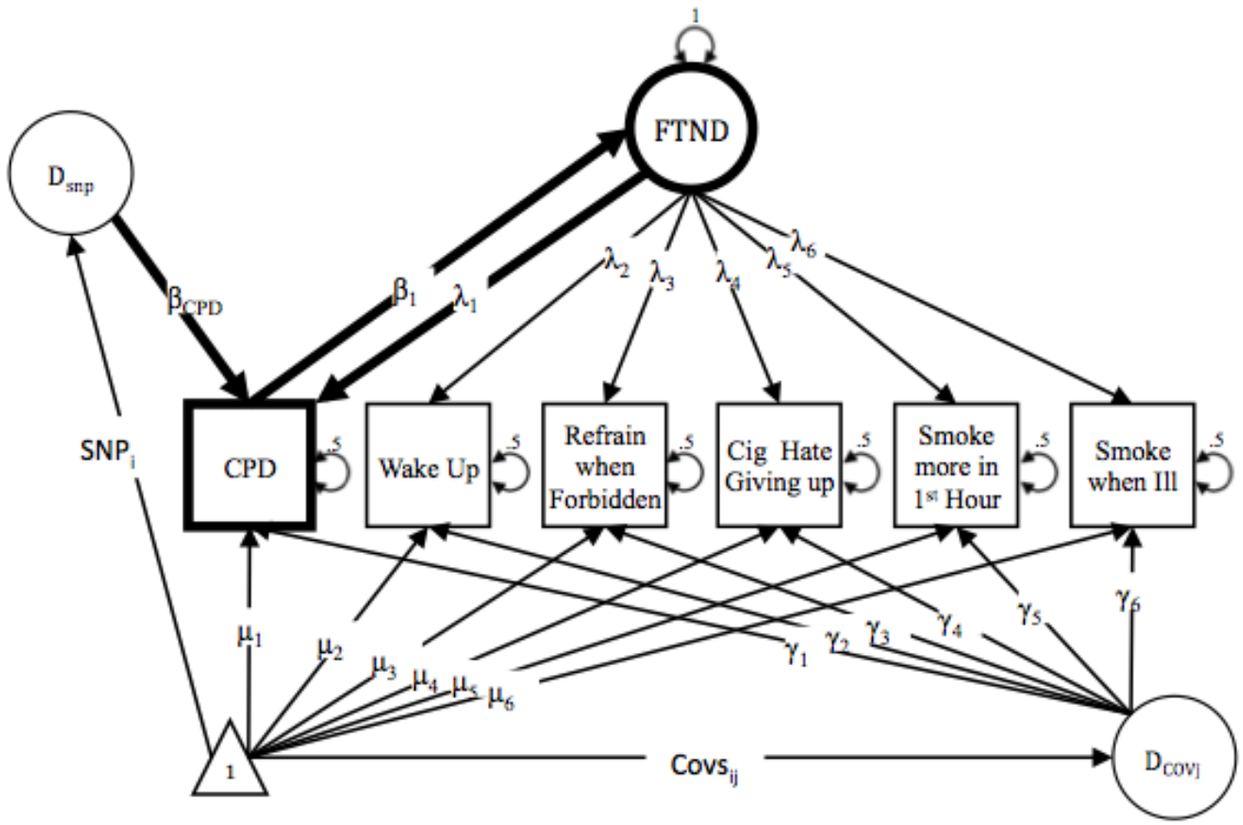
(d) H_{1c}: Path diagram for regression of the latent FTND factor and CPD on the SNP

H2a CPD Only & CPD causes Factor



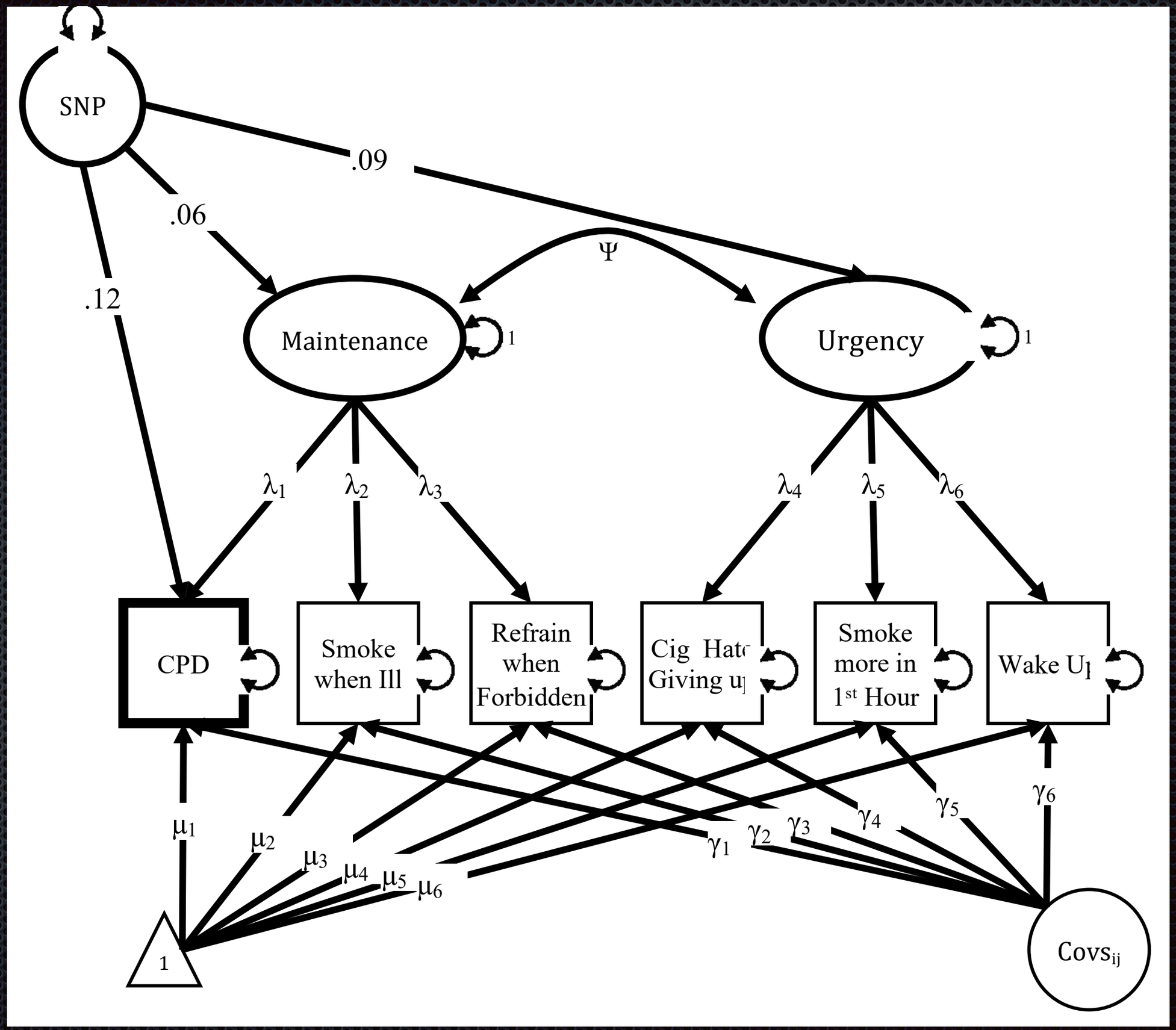
(d) H_{1c}: Path diagram for regression of the latent FTND factor and CPD on the SNP

H2b SNP to CPD & Reciprocal Factor



(f) H_{2b}: Path diagram for the the SNP causing CPD, which reciprocally causes Nicotine Dependence.

Two Factor Model



Model-Fitting Results: Bidirectionality

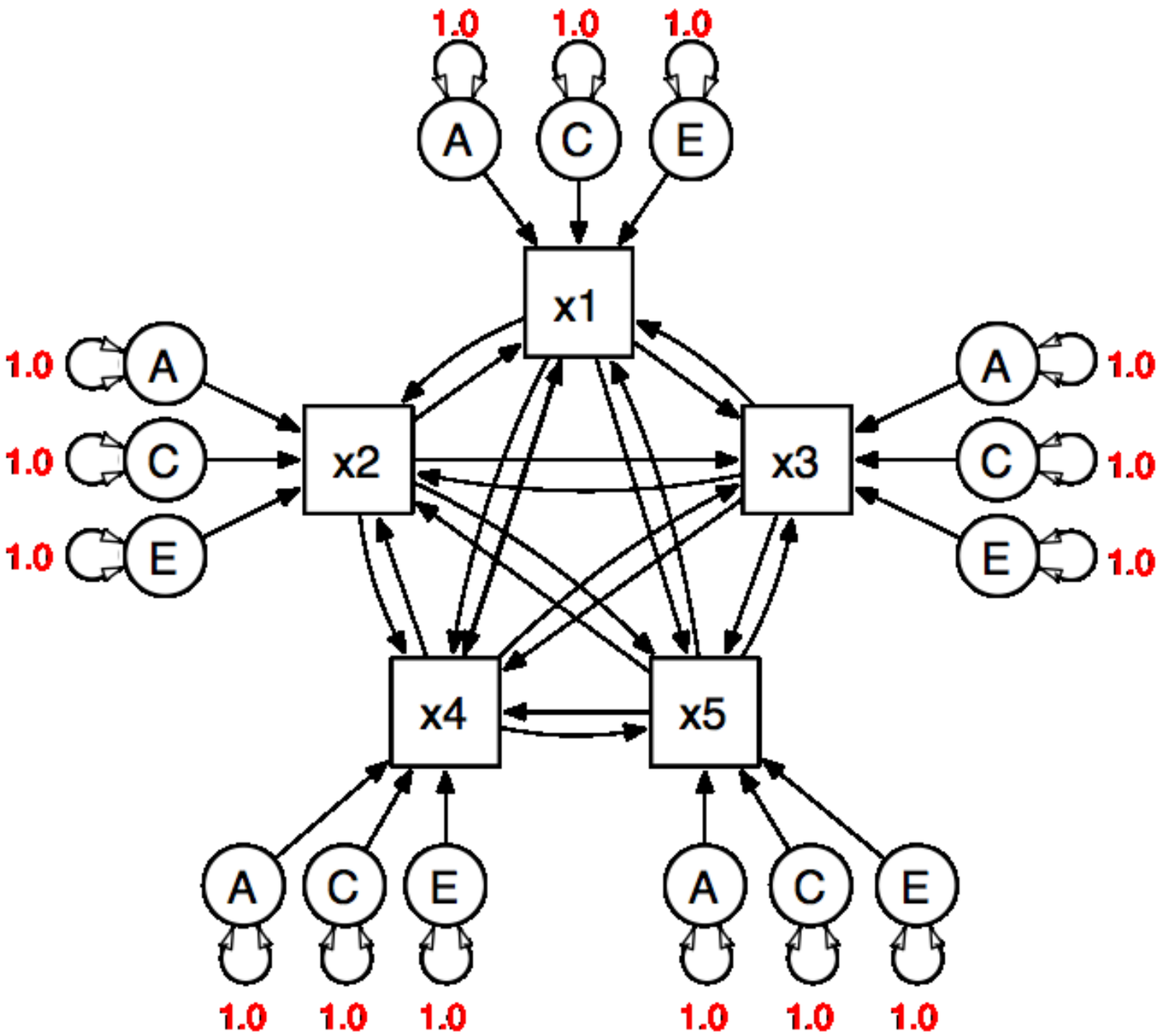
Table 2: Model fit statistics for tests of mediation of SNP rs16969968 effects via FTND latent factor (upper panel), or via CPD item (lower panel).

	-2LL	AIC	ΔRef	Δ2LL	Δdf	p
FTND Mediation Models						
1 Free SNP Paths	41730.04	-22665.96	-			
2 Equated SNP Paths	41740.10	-22673.90	1	10.06	9	0.35
3 Full Mediation	41756.33	-22659.67	2	16.29	1	5.45e-05
4 Direct Effect	41747.72	-22668.28	2	7.62	1	5.73e-03
CPD Mediation Models						
5 All Free Regressions	45141.80	-19254.20	-			
6 Equal Regression for F1	45142.37	-19259.63	5	0.57	3	0.90
7 Equal Regression for F2	45168.74	-19235.26	6	26.94	4	2.04e-05
8 Equal Regression for CPD	45319.72	-19082.28	6	177.92	3	2.48e-38
9 Equal Regression	45145.56	-19256.44	6	3.76	3	0.29

Definitions: FTND, Fagerstrom Test for Nicotine Dependence; CPD, Cigarettes per day; -2LL, twice negative log-likelihood; AIC, Akaike Information Criterion; ΔRef, reference model for likelihood ratio test; ΔLL, difference in -2LL from reference model (likelihood ratio test); Δdf, degrees of freedom of ΔLL; p, p-value of ΔLL. AIC is calculated as -2LL-2*df* where *df* is the number of raw data observations minus the number of free parameters; lower values represent more parsimonious fit.

```
> mxCompare(BidirectionalFit,TwoFit1a)
  base comparison ep minus2LL df      AIC   diffLL diffdf       p
1 FullRev       <NA> 44 41709.37 32194 -22678.63     NA     NA      NA
2 FullRev       Full 40 41730.04 32198 -22665.96 20.67327      4 0.00036275709
```

Factor Model Alternative: Mutualism



Identified with data from relatives

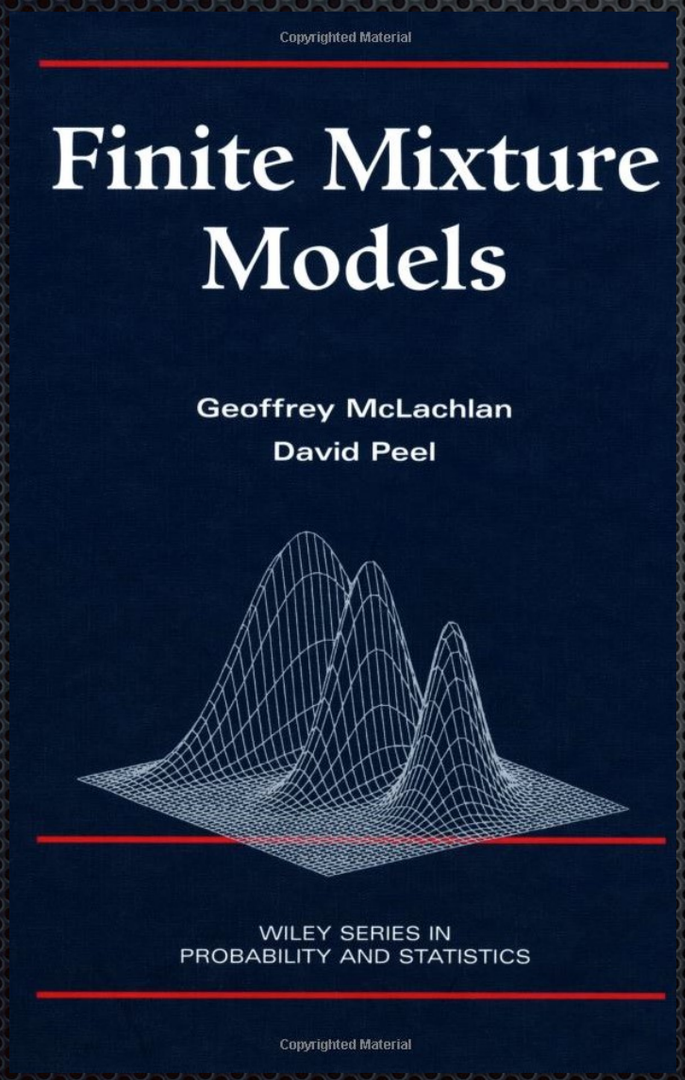
MZ & DZ Twins or adoptees needed for A/C resolution

What if Variation is Discrete?

- Latent Class and Latent Profile Models
- Factor Mixture Models
- Latent Growth Curve Mixture Models
- Regime Switching

Mixture Distributions

Pearson, K. (1894). Contributions to the mathematical theory of evolu

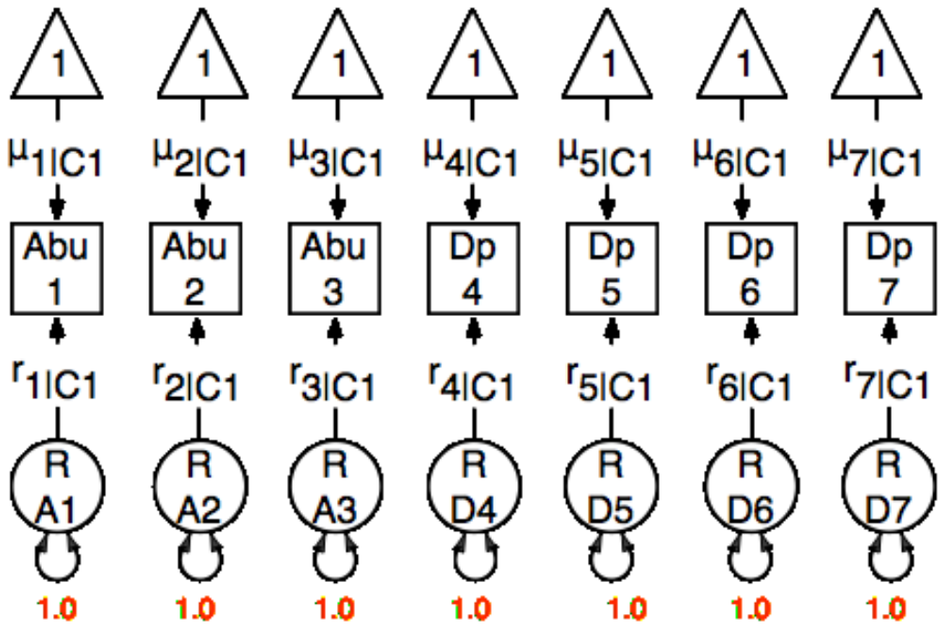


- Skewness in a set of measurements of the ratio of forehead to body length of crabs

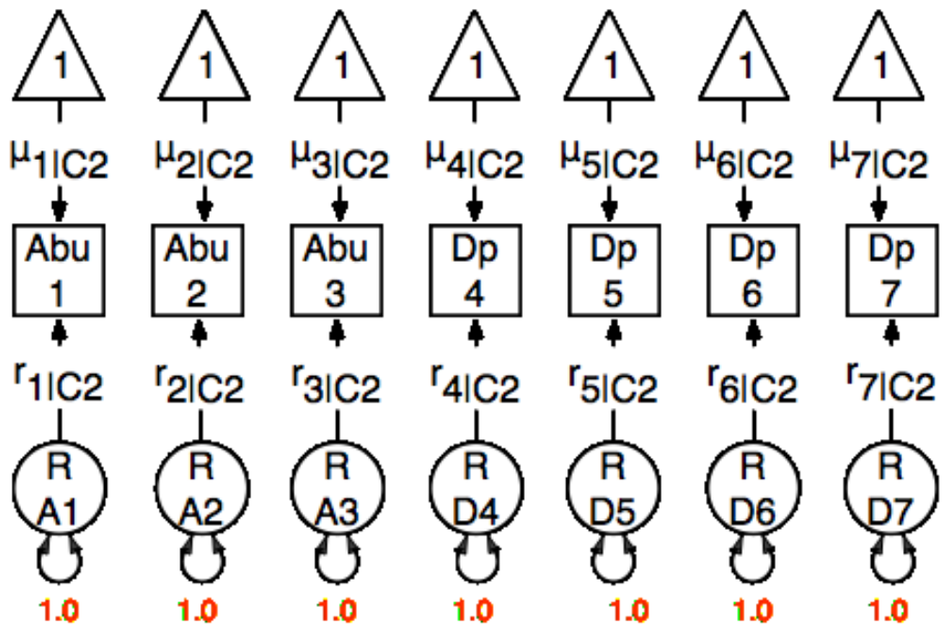
- Two species or one?

Latent Class (Subgroup) Analysis

Class 1 probability *p*



Class 2 probability (1-*p*)



Conditionally Independent ?!

Expensive!

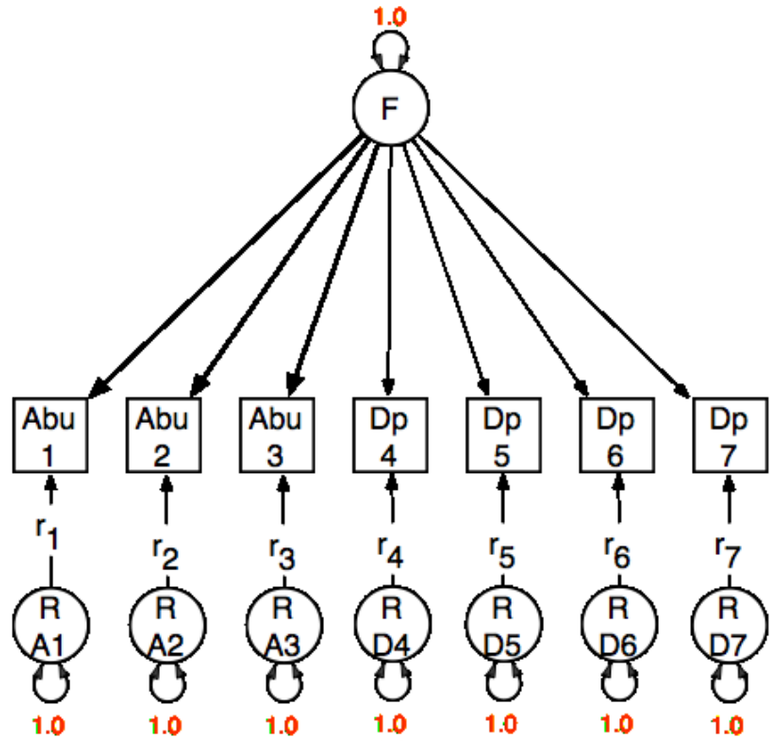
Published in final edited form as:
Int J Methods Psychiatr Res. 2010 June ; 19(2): 63–73. doi:10.1002/mpr.301.

Searching For Valid Psychiatric Phenotypes: Discrete Latent Variable Models

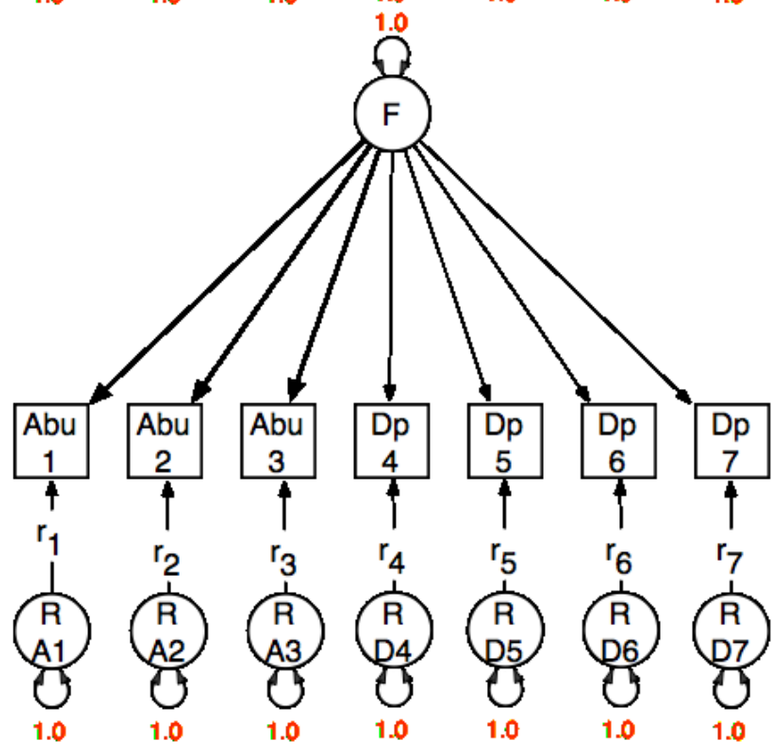
Jeannie-Marie S. Leoutsakos, PhD, MHS[1], Peter P. Zandi, PhD, MHS[2], Karen Bandeen-Roche, PhD[3], and Constantine G. Lyketsos, MD, MHS[1,2]

Factor Mixture Model

Class 1 probability *p*



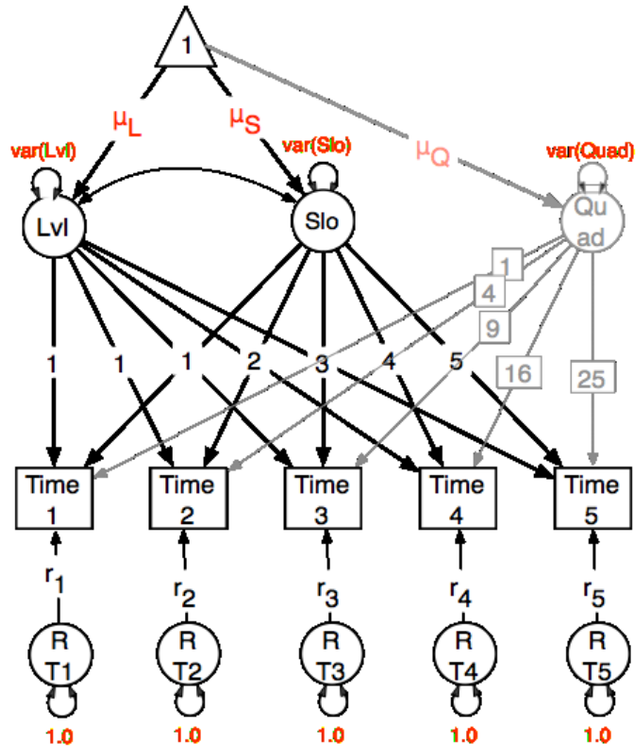
Class 2 probability (1-*p*)



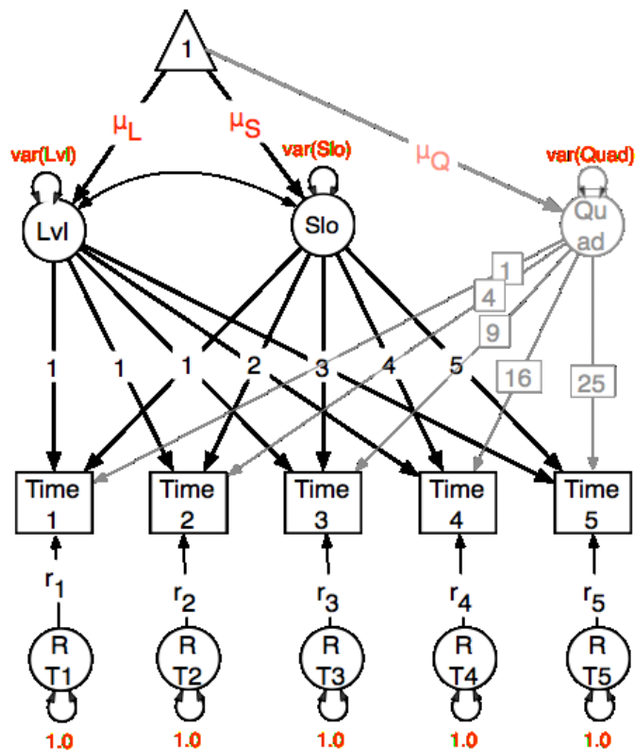
Very Expensive!

Growth Curve Mixture

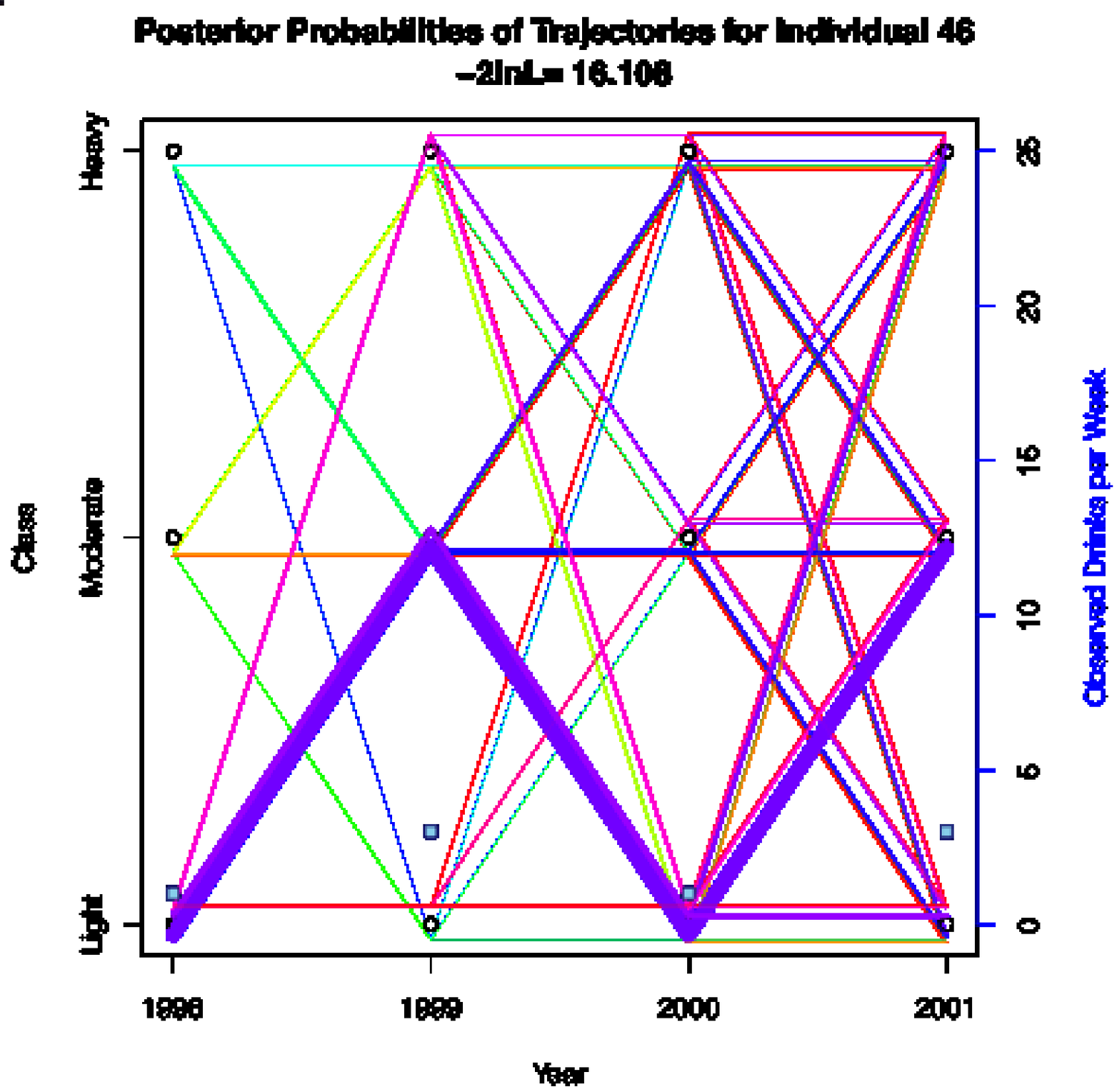
Class 1 probability *p*



Class 2 probability (1-*p*)



Regime Switching Model



Obligate Missingness

- Estimating correlation between Stem and Probe
  - 3+ categories of Stem and at least 2 lead to probe
  - 2 binary Stem items and endorsing either or both = probe
  - Binary Stem but collected from relatives who correlate < 1

- Do not mark missing probes as zero! Usually causes inflated item correlations

Obligate Missingness

- Stem: Have you ever used cocaine? 0/1/2
- Probe: Was it difficult to cut down or quit?
- Probe items are MAR conditional on Stem being 1 or 2
- WLS but not ML drastically attenuate correlation estimate
- Must code probes as missing!

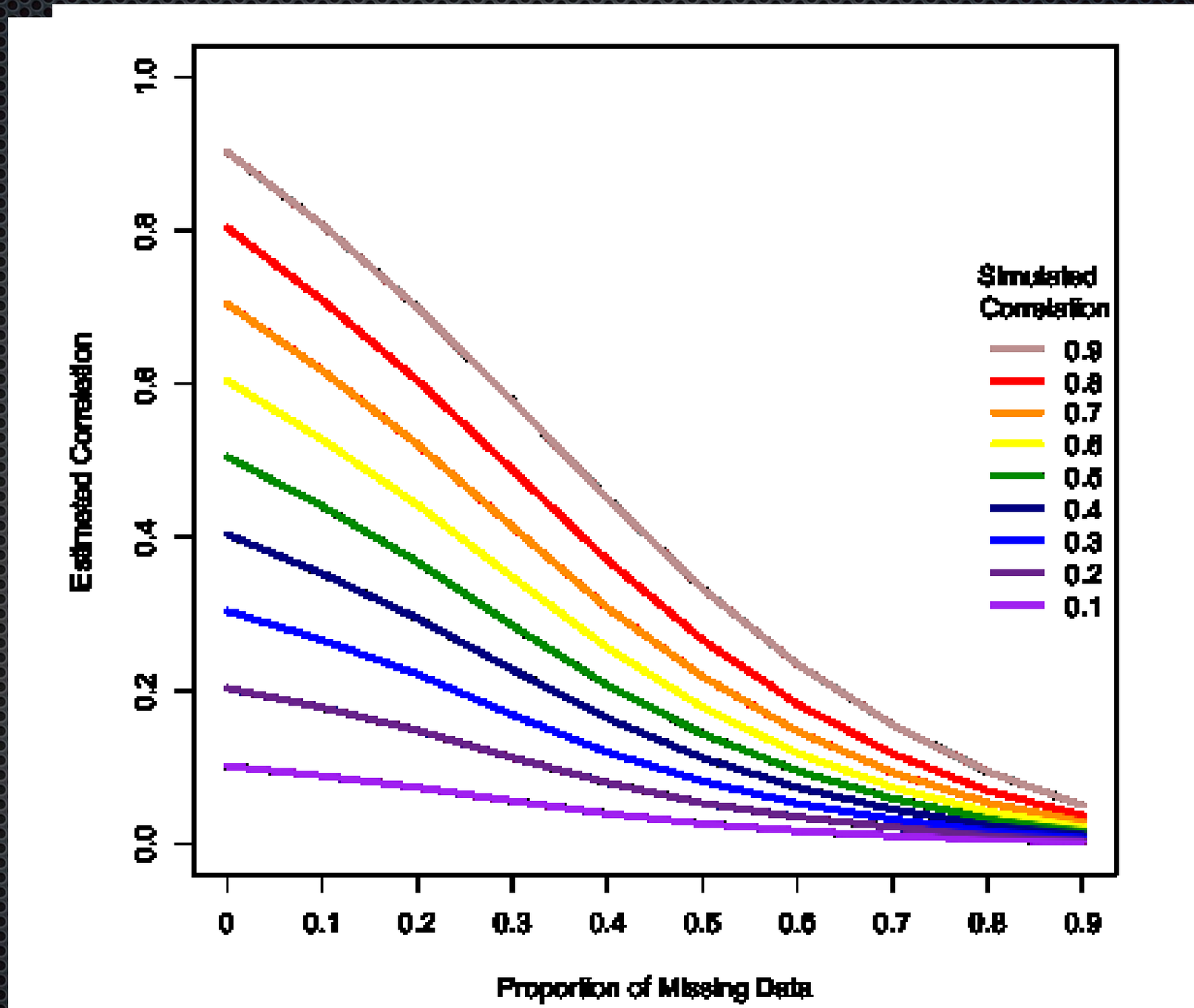
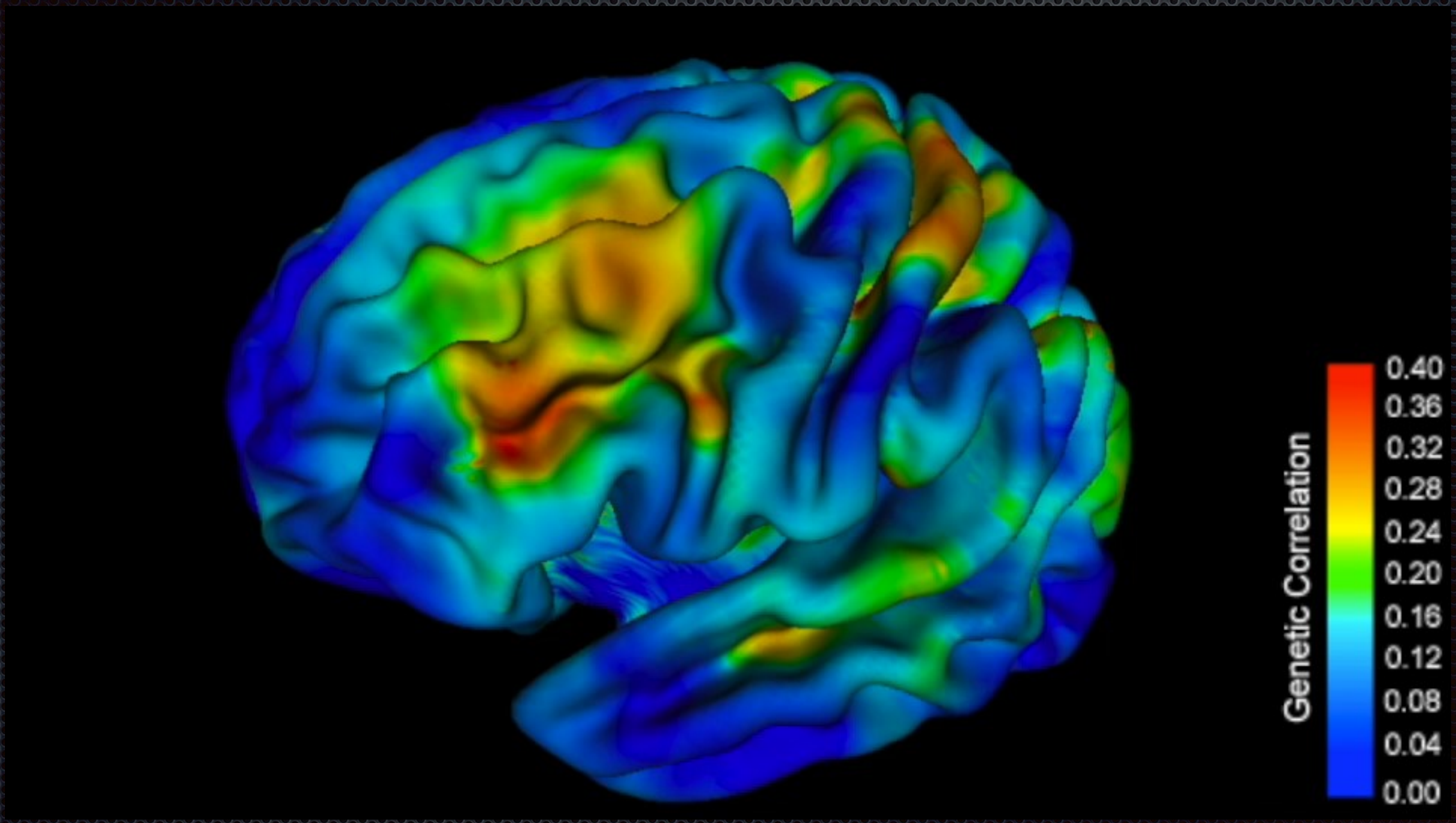


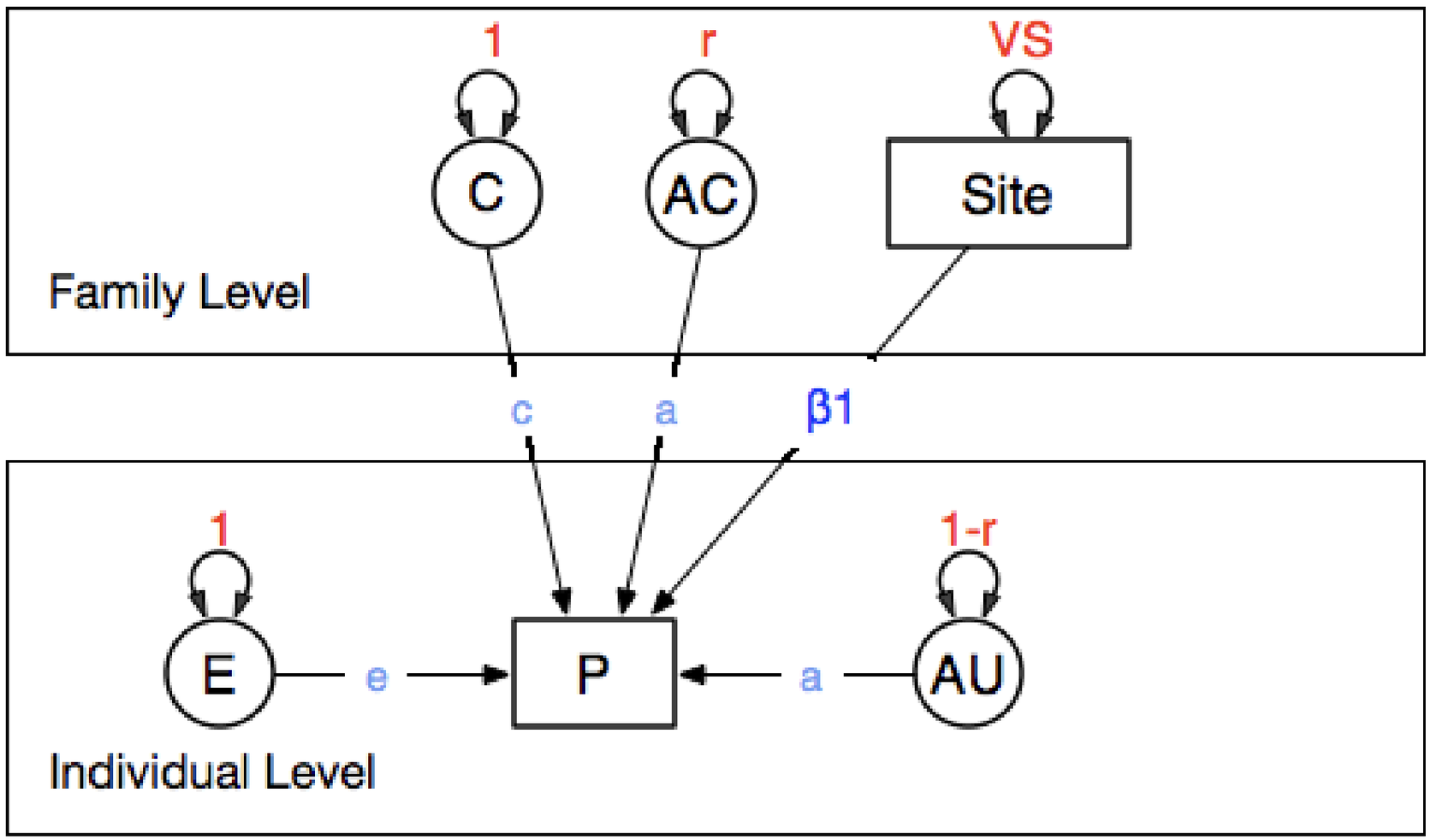
Figure 2: Attenuation of the estimated correlation using WLS based on the level of MAR missingness.

Genetic Correlations Vary with Age 8-18yrs, Giedd Study N~700



Multilevel Model for Twin Data

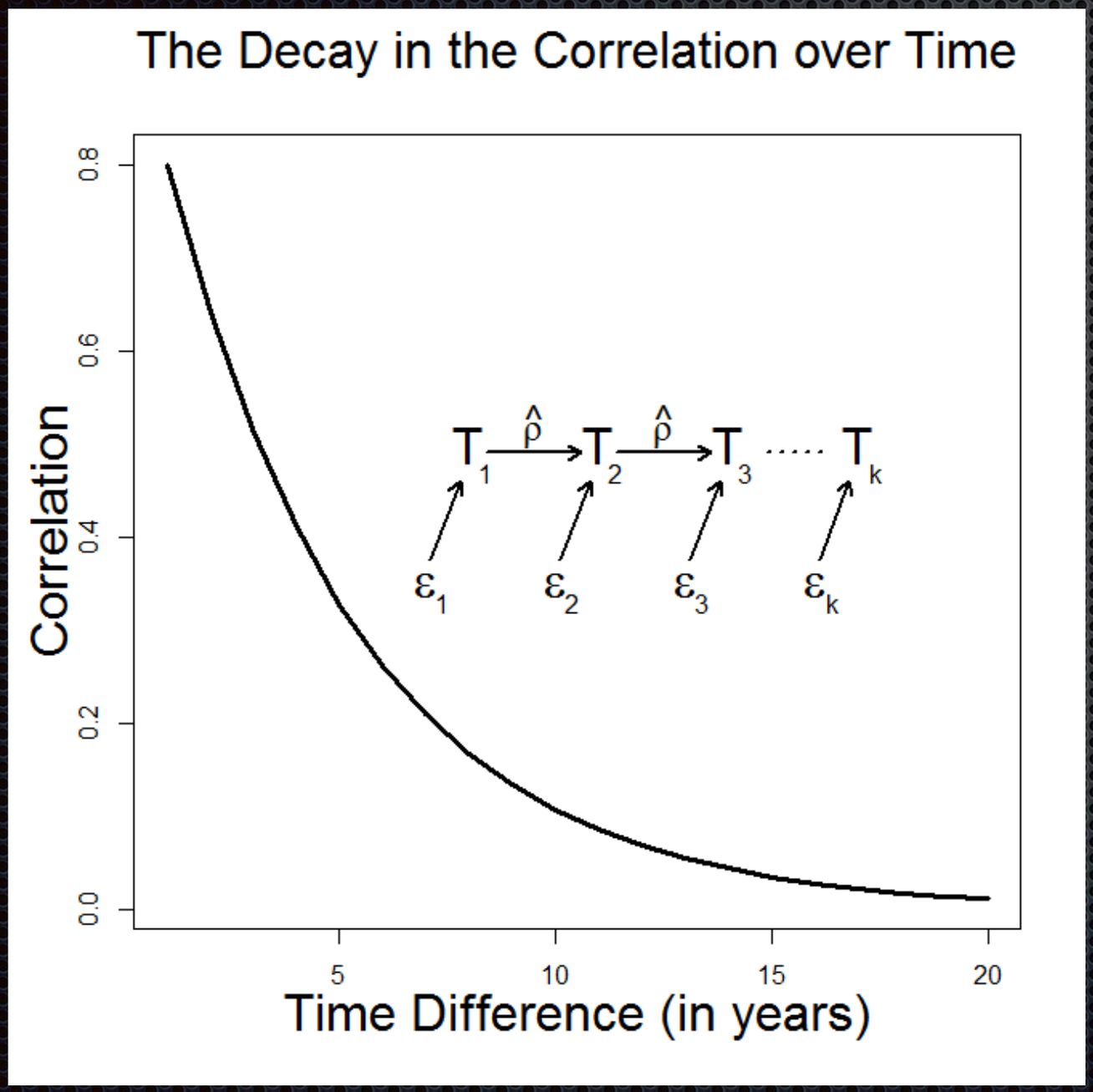
Adding Site Effects



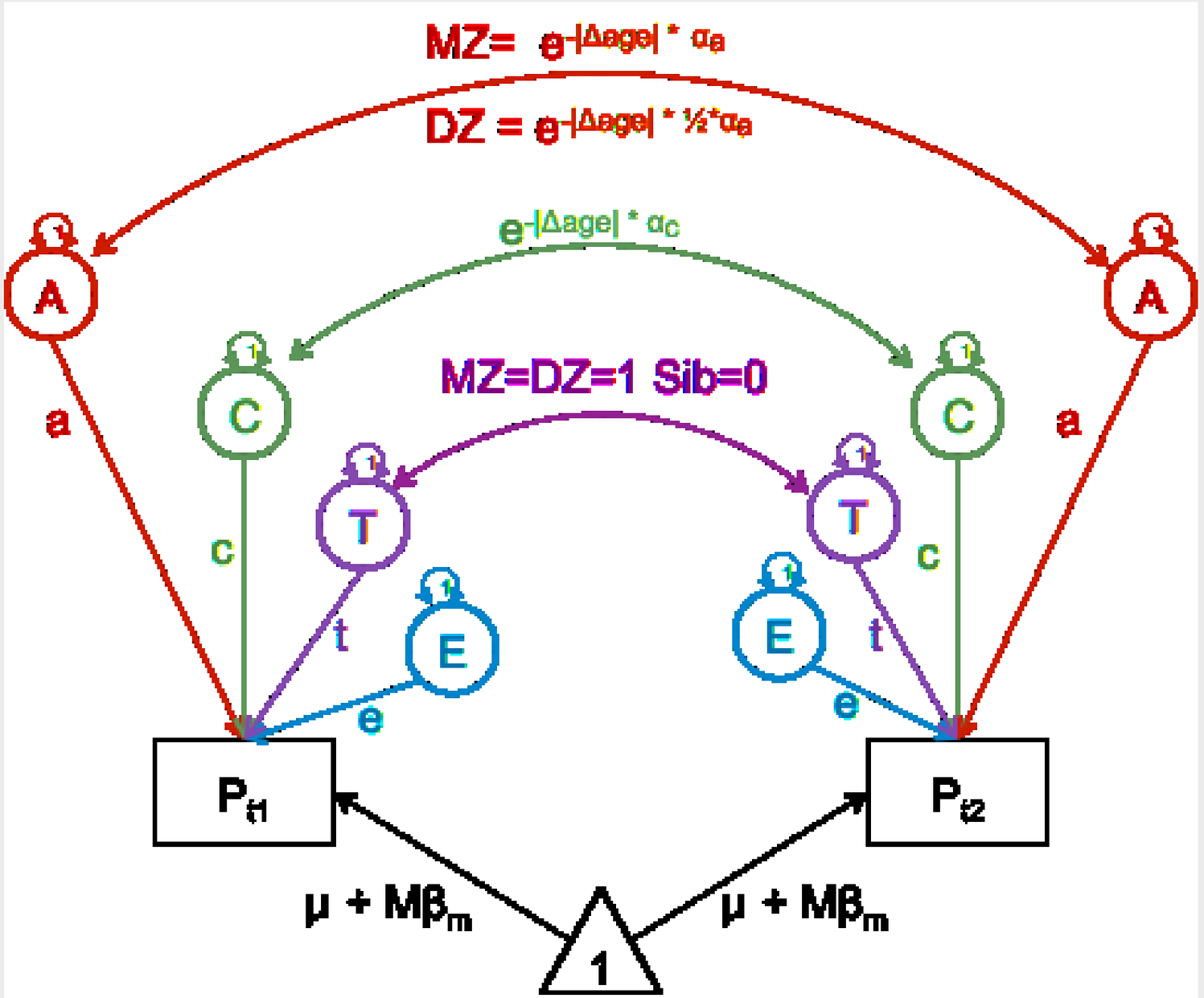
Genetic Heterogeneity with Age/Cohort

- Neuroticism within-person .6 correlation over 10 years
- Twin studies show rG < 1 over time
- Expressed genetic factors change during development
- Substance Use

Different age, different genes?



Age-Related Decay of Correlation



Verhulst, B., Eaves, L. J., and Neale, M. C. (Jul 2014). Moderating the covariance between family member's substance use behavior. Behav Genet, 44(4):337–46.

$$Cov = Acov^{*} e^{-|\Delta age|*\alpha a} + Ccov^{*} e^{-|\Delta age|*\alpha c} + Tcov$$

Application

Virginia 30,000 Data on Smoking

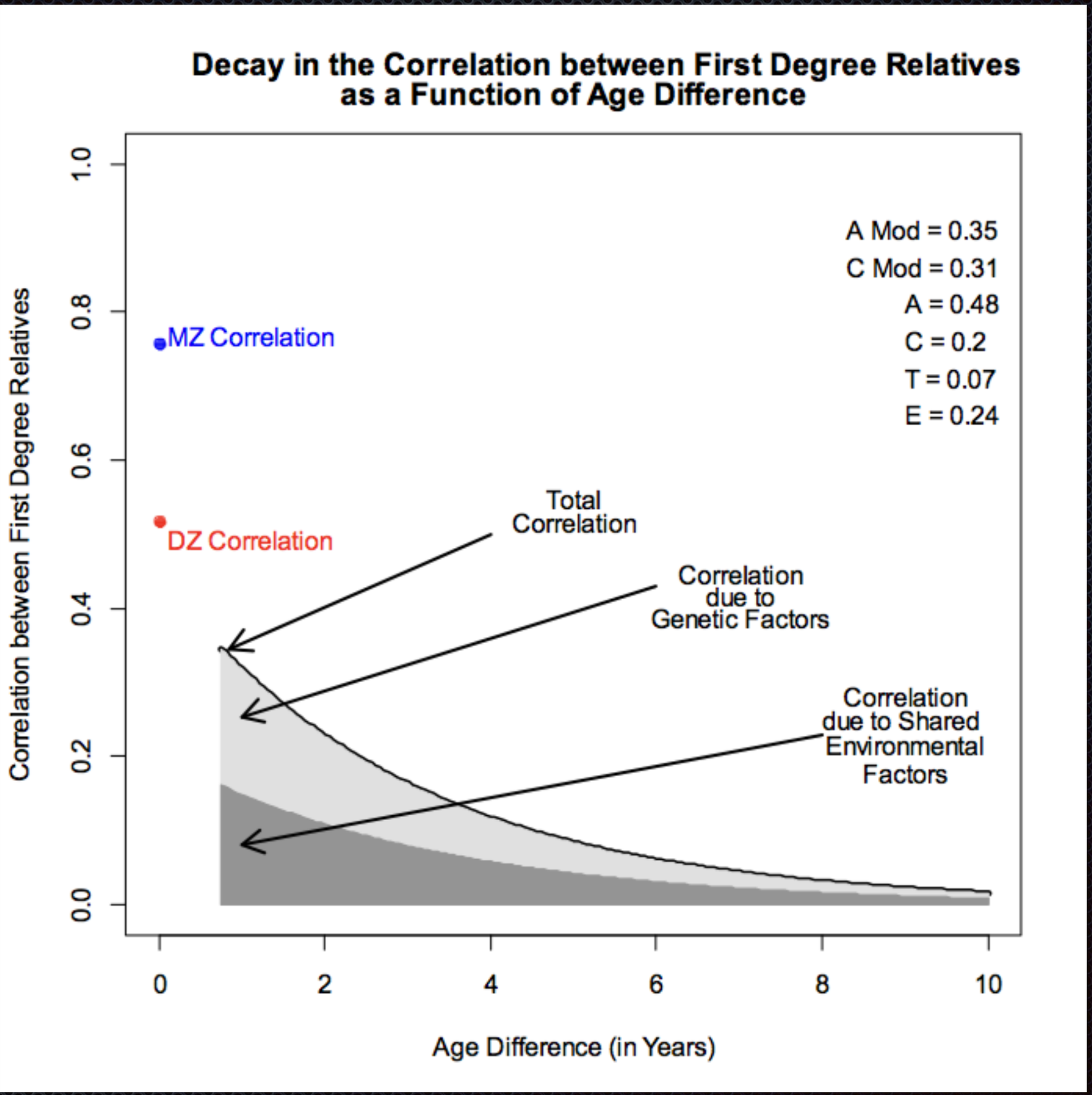
Twins, their parents, spouses, sibs and children

Twins only here, N=14,763

Crude smoking measure (1980s)

(1) never smoked, (2) used to smoke but gave it up, (3) smoked on and off, (4) smoked most of his/her life.

Strong evidence of decay with age difference



Future Directions

- Use Genetic relatedness matrices GRMs in place of close family relatives
  - Technical challenges, invert 20k x 20k matrices or larger
- Extend GW-SEM
- Extend tests for direction of causation with combined twin family, multivariate and repeated measures data
- Dynamical models for high density repeated measures

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Study participants

Workshop participants

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