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Comorbidity between Alcohol Dependence (AD) and Nicotine Dependence (ND): The Genetic Contributions from Antisocial Personality Disorder (ASPD) and Major Depression (MD)

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Introduction

- Tobacco use and heavy alcohol consumption represent a public health concern. A synergistic interaction between alcohol and tobacco increases the risk for (Groppelli et al. 1992; Wynder et al. 1977)
  - hypertension
  - certain types of cancers
    - Oral cavity, esophagus, and larynx

Introduction

- The strong relationship between alcohol and tobacco use and dependence

    - In general population, twofold risk for smoking cigarettes after drinking alcohol (Shiffman et al. 1994)

    - Smoking prevalence among alcoholics from 75 to 90 percent (Burling and Ziff 1988; Istvan and Matarazzo 1984; Toneatto et al. 1995)

    - Whereas the rates of smoking have declined in the general populations, rates among heavy drinkers have not.

    - Heavy drinkers smoke more cigarettes per day and have higher levels of nicotine dependence and shorter latency to first cigarette smoked on waking (Abrams et al. 1992; DiFranza and Guerrera 1990; Joseph et al. 1990; Kozlowski et al. 1989; Orleans and Hutchinson 1993).

Introduction

- Genetic contribution to the close relationship between tobacco and heavy drinking and dependence

  - A genetic correlation between smoking and alcohol consumption of 0.47 in male World War II US veteran twins (Swan et al.1996)

  - A genetic correlation between AD and ND of 0.68 in male US veteran twins who served on military duty from 1965-1975 (True et al. 1999).

  - Prescott and Kendler (1995) reported family environmental experiences modestly contributed to AD and ND, with only very small genetic influences common to both substances in female US twins.

Introduction

- The purpose of the present study
    - To examine how genetic and environmental risk factors for ASPD explain the covariance of AD and ND in a genetically-informative sample of U.S. adult men.

Sample

- The Vietnam Era Twin Registry (VETR), N=7,369 male-male twin pairs, assembled from computerized Department of Defense databases in the 1980s.

    - Monozygotic twins: 53.5%; dizygotic twins: 43.8%; indeterminate zygosity: 2.7%.

- A total of 3,360 *complete* twin pairs from the Harvard Twin Study of Substance Abuse and Dependence surveyed by telephone in 1992.

    - the overall pairwise response rate: 66.1%
    - individual response rate: 79.7%.

Sample Characteristics

- The mean age at interview:
    - 42.0 years (SD $\pm$2.7, range 33-52 years)
- Ethnicity:
    - 93.8% non-Hispanic white
    - 5.8% African American
    - <1% Hispanic
    - 0.3% other
- Education:
    - 33.3% high school graduates
    - 38.7% college graduates
- Employment:
    - 98.2% full-time
    - 1.8% part-time

Psychiatric Assessment

- Lifetime DSM3R diagnoses of ASPD, MD, AD, and ND were obtained using a computerized telephone version of the Diagnostic Interview Schedule, Version 3, Revised (DIS3R).

Analyses

- Logistic regression used to examine the association between AD and ND before and after controlling for ASPD and MD.
  - The method of generalized estimating equations (GEE) as operationalized in PROC GENMOD (SAS) was used to adjust for non-independence of twin observations.
- Biometric Model
  - Liability is assumed to be continuous and normally distributed in the population, with individuals who exceed a theoretical threshold expressing the disorder.
  - A standard normal liability-threshold model was used to estimate genetic and environmental contributions to twin resemblance.

Analyses

- Biometric model
  - Tetrachoric correlation and asymptotic covariance matrices computed using PRELIS 2.
  - A Cholesky model was fitted to the data by the weighted least square (WLS) method using Mx (Neale, 1999).
  - The goodness-of-fit chi-squared test and Akaike's Information Criteria (AIC) was used to evaluate overall fit of models.
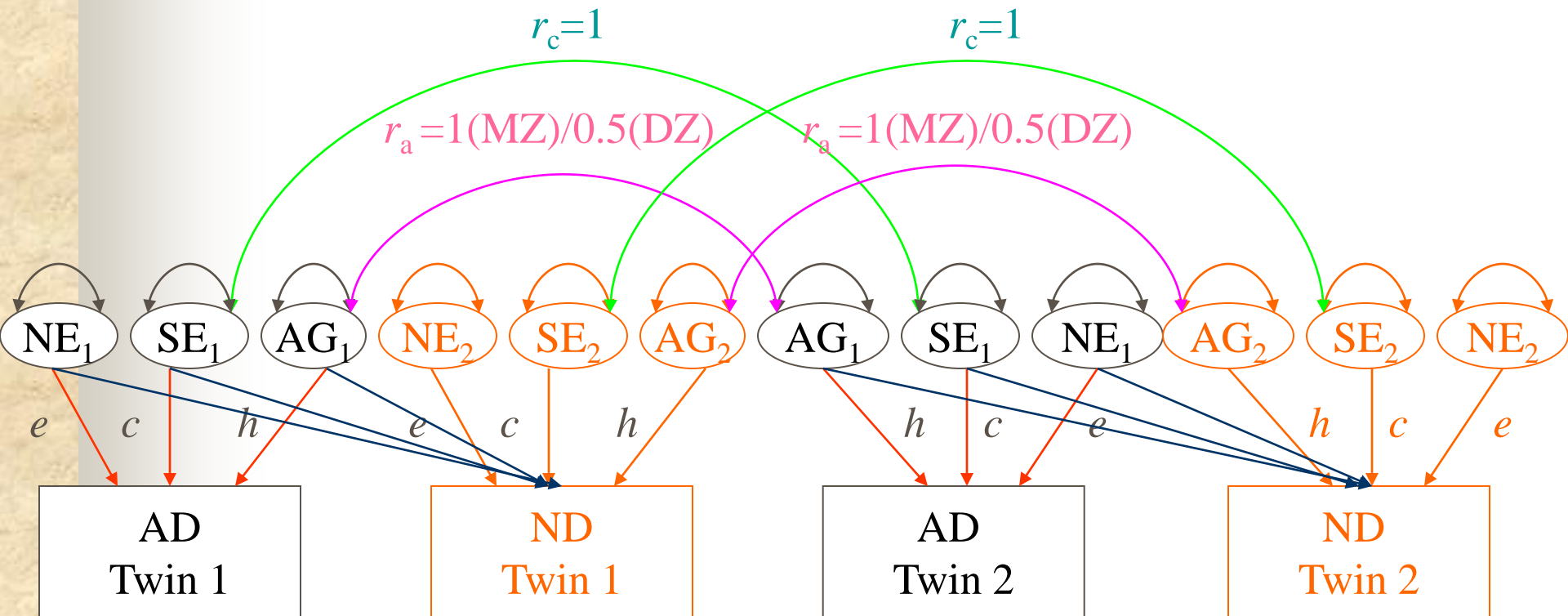
Results

Figure 1. Increased risk of lifetime DSM-IIIR AD predicted by lifetime DSM-IIIR ND, MD, and ASPD in phenotypic univariate (unadjusted) and multivariate (adjusted) analyses
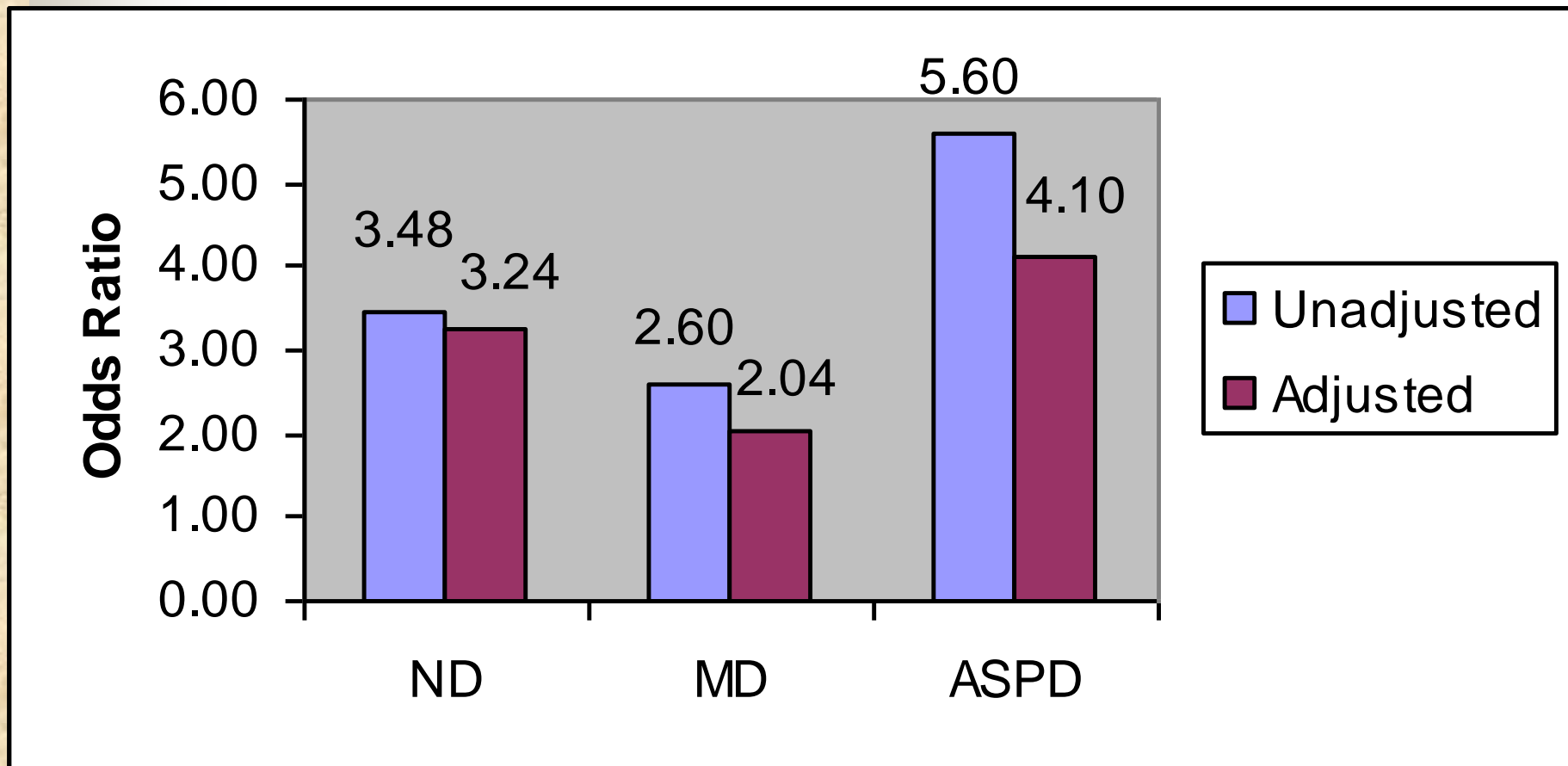
Results

Figure 2. A schematic bivariate biometric model: additive genetic (AG), shared environmental (SE), and non-shared environmental (NE) latent factors

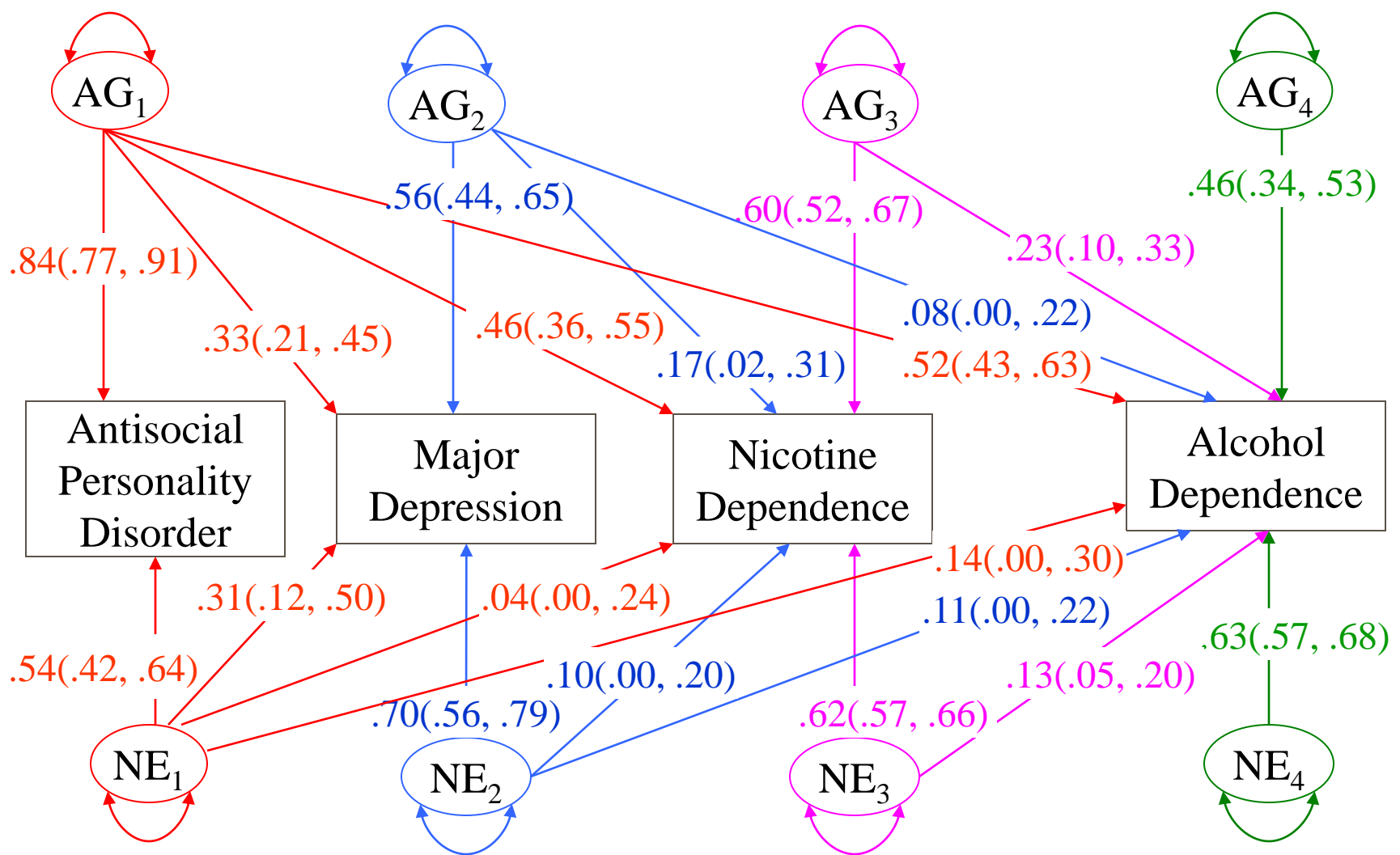h, c, and e: path loadings; r_i: correlation coefficient

Figure 3. Path coefficients and 95% confidence intervals of the Cholesky model for lifetime DSM-IIIR ASPD, MD, ND, and AD. Chi-squared fit of model=44.9, df=36, p=0.15, AIC=-27.1
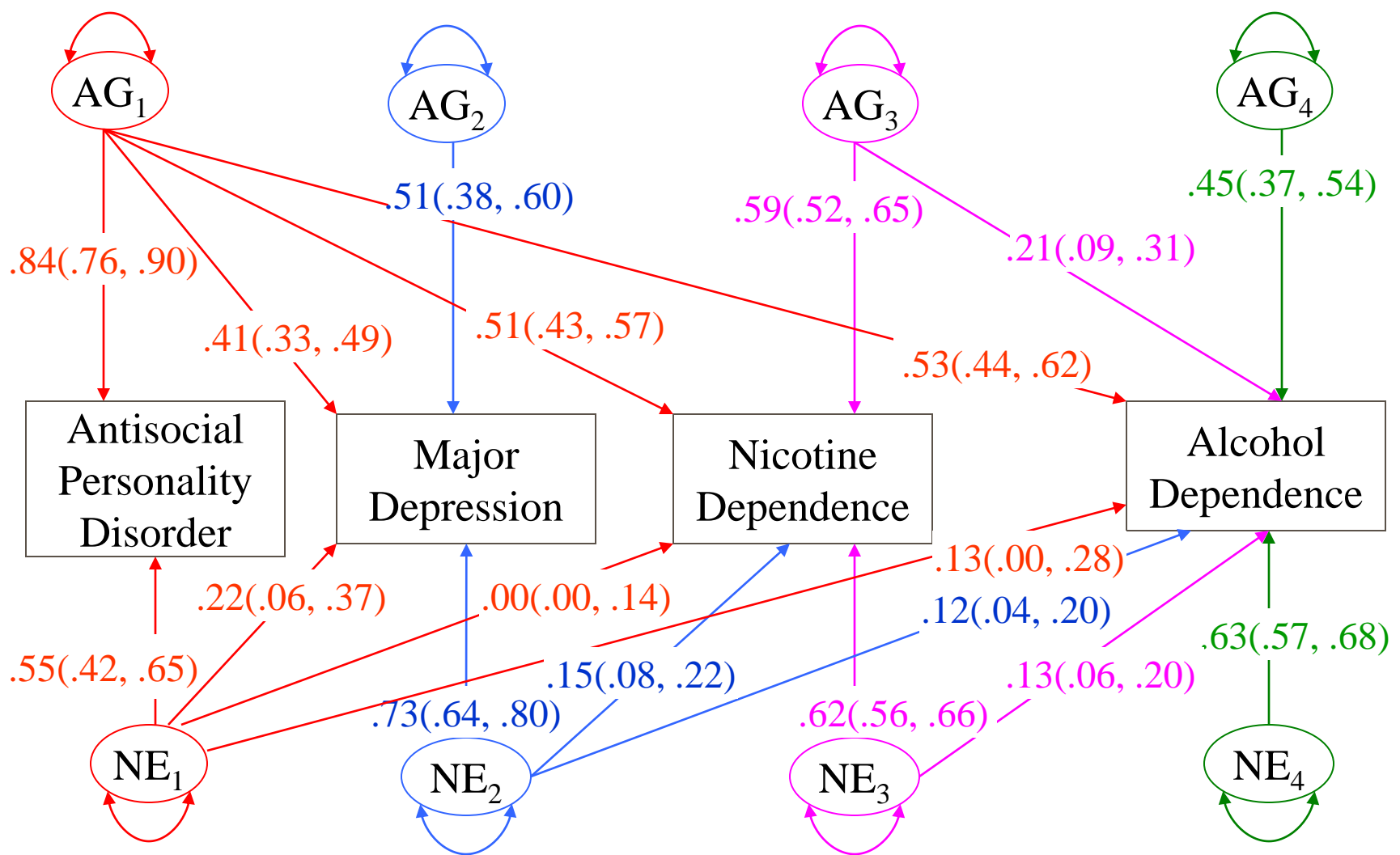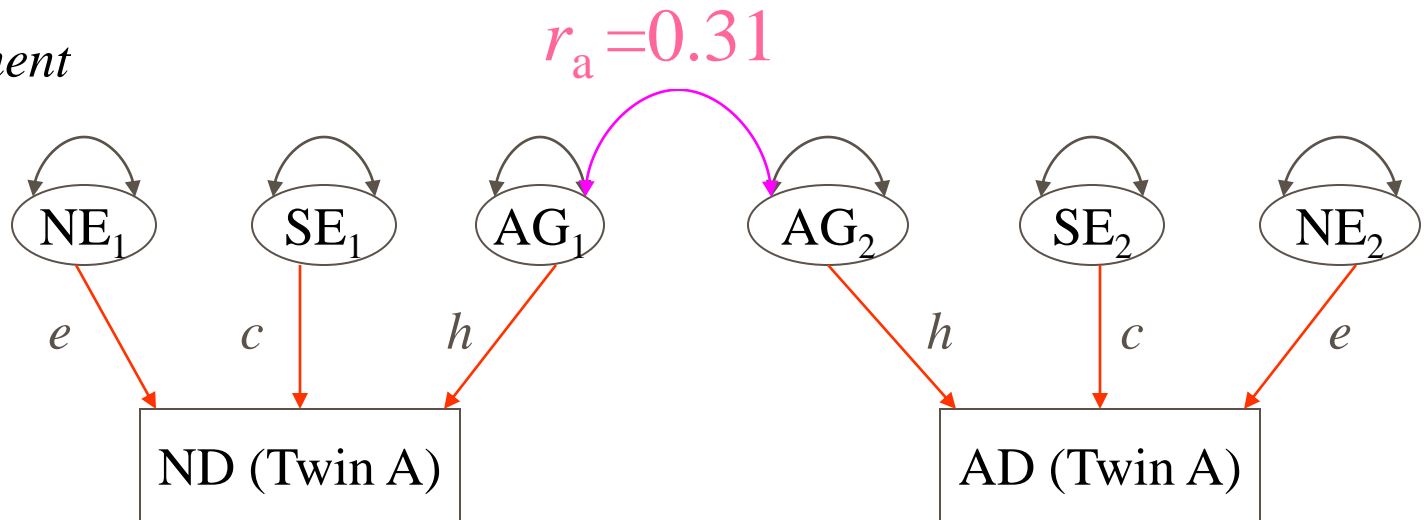
Figure 4. Path coefficients and 95% confidence intervals of the Cholesky model for lifetime DSM-IIIR ASPD, MD, ND, and AD. Chi-squared fit of model=49.9, df=38, p=0.1, AIC=-26.2
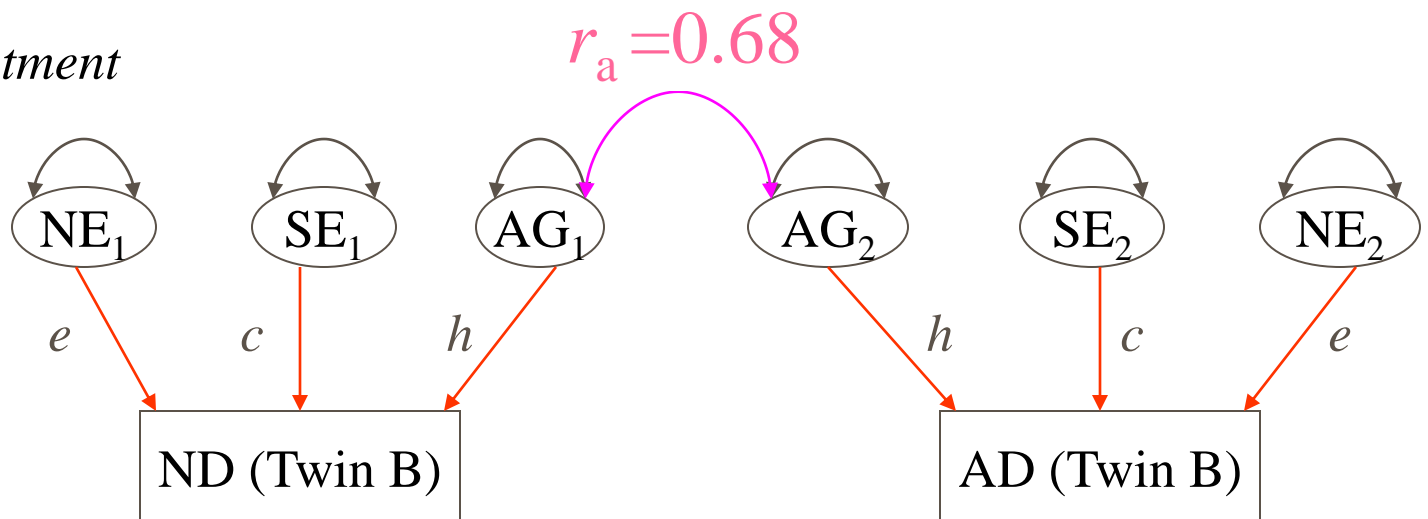
Results

Figure 5. Summary of Findings

After Adjustment

$r_a = 0.31$

NE$_1$ SE$_1$ AG$_1$ AG$_2$ SE$_2$ NE$_2$

e c h h c e

ND (Twin A) AD (Twin A)

Before Adjustment

$r_a = 0.68$

NE$_1$ SE$_1$ AG$_1$ AG$_2$ SE$_2$ NE$_2$

e c h h c e

ND (Twin B) AD (Twin B)

Conclusions

- The inter-relationships among DSM-III-R ASPD, MD, ND and AD almost entirely reflected common genetic (rather than common environmental) vulnerability.

- Adjustment for genetic risk factors associated with ASPD reduced the genetic correlation between ND and AD substantially.

  - Approximate 69% [0.31 / (0.31 + 0.68)] of the genetic correlation between ND and AD was accounted for by genes associated with ASPD.

- In contrast, the association between ND and AD did not change significantly after adjusting for ASPD and MD in phenotypic analyses.

Limitations

- Results limited middle aged and white male military veterans

- The selection bias

    - Selection process for entry into military service probably excluded individuals with severe, early onset antisocial behaviors .

    - This may result in only individuals with mild to moderate antisocial behaviors being included.

    - Thus, the association between ASPD and comorbidity of ND and AD may be underestimated.