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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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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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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
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.
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 ±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-III-R AD predicted by lifetime DSM-III-R 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-III-R 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

$$r_a = 0.31$$

Before Adjustment

$$r_a = 0.68$$
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.