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A Multiple-domain Approach to Determine General and Sex-specific Associated Factors in the Development of Alcohol Dependence in Adulthood

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Introduction

Both theoretical and empirical studies have indicated that alcohol dependence (AD) is a multifaceted disorder and it is associated with factors from multiple domains including but not limited to past alcohol and substance use behaviors, family history, childhood and adulthood environments, and genetics. This study takes advantage of the extensive data available from the Collaborative Study on the Genetics of Alcoholism (COGA) to conduct a secondary, exploratory analysis to examine the likelihood of meeting DSM-IV AD criteria in adulthood given associating factors from eight domains.

Methods

Phenotypic and genetic information from 1723 (48% male) Caucasian COGA participants were used in a sex-specific, multiple-domain, generalized estimating equations (GEE) logistic analysis to examine potential influencing factors for AD at follow-up from eight domains (Table 1). Phenotypic data covered three time periods: childhood (6–13), adulthood at baseline (mean ± se = 30.5 ± 0.2 years old), and adulthood at follow-up (mean ± se = 36.2 ± 0.2 years old) were obtained using two instruments: SSAGA and SRE. In addition, time-invariant information such as background family characteristics and genotype data were considered.

A two-stage analysis was conducted. In Stage one, unadjusted bivariate and within-domain adjusted relationships between outcome and factors were examined. In Stage two, a stepwise procedure was used to determine the most parsimonious sex-specific, multiple-domain model from all the significant domain-specific factors.

Table 1: Outline of the Eight Domains

Domain	Potential Associating Factors
Past alcohol use behaviors	**The number of baseline endorsed DSM-III-R AD criteria** and sex-specific binned maximum number of drinks in any 24-hour period
Demographic characteristics	**Family type**; follow-up **employment status** and years of education; baseline and follow-up age, marital status, and annual household income
Religion	Rules against alcohol use at childhood and at follow-up
Parental disorders	Paternal and maternal DSM-III-R AD and ASPD, and the number of AD parents
Past problematic substance use behaviors	Daily use of tobacco product; DSM-III-R opioid, sedatives, stimulants, cocaine and marijuana disorders; and the number of DSM-III-R substance use disorders
Past psychiatric disorders	DSM-III-R ASPD, MDE and anxiety disorders
Childhood environment	Parent conflict; looked older; **father**'s and **mother**'s parenting style (away from home, strict in setting rules, **consistency in enforcing rules**, and harsh physical punishment) and **relationship with parents**
Biological risk	Initial alcohol sensitivity; and number of high risk alleles in four SNPs, each from a different genes (GABRA2, **GABRG3**, CHRM2 and ADH4)

Results

The outcome and the majority of the factors showed significant sex differences even with the over conservative Bonferroni correction at an overall 5% significance level.

Stage one: [Wald Type 3 GEE $\chi 2$ test statistic (DF) p-value]

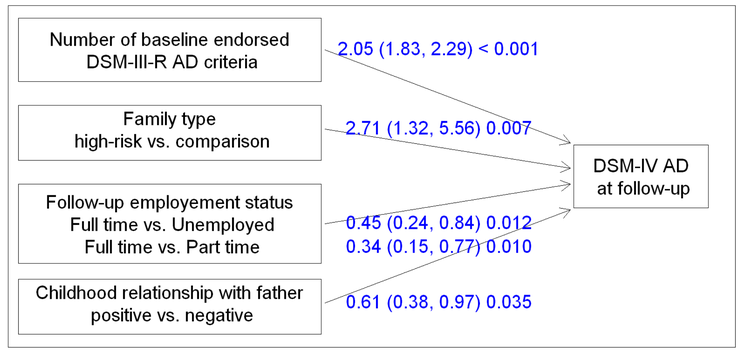
- The strongest associating factor is the number of baseline endorsed DSM-III-R AD criteria [male: 209.58 (1) < 0.001; female: 190.90 (1) < 0.001] in the ***past alcohol use behaviors domain*** for both sexes.
- The next strongest set of domains were ***demographic characteristics*** *and* ***past problematic substance use behaviors*** *domains*. In the **demographic characteristics domain**, family type [male: 47.88 (1) < 0.001; female: 24.16 (1) < 0.001], years of education [male: 19.64 (1) < 0.001; female: 16.60 (1) < 0.001], marital status at follow-up [male: 27.05 (2) < 0.001; female: 19.18 (2) < 0.001], age at follow-up [male: 6.34 (1) 0.012; female: 4.59 (1) 0.032] were significant for both sexes. In addition, employment status at follow-up [male: 18.30 (2) < 0.001] and marital status at baseline [female: 18.00 (2) < 0.001] were significant for males only and females only, respectively. In the **past problematic substance use behaviors domain**, daily use of tobacco product [male: 28.42 (1) < 0.001; female: 21.06 (1) < 0.001] and the number of DSM-III-R substance use disorders [male: 64.19 (1) < 0.001; female: 60.18 (1) < 0.001] were significant for both sexes.
- The next group of associating domains were ***parental disorders***, ***past psychiatric disorders***, ***childhood environment and biological risk*** *domains*. In the **parental disorder domain**, the number of AD parents [male: 13.47 (1) < 0.001; female: 14.62 (1) < 0.001] was significant for both sexes. In the **past psychiatric disorders domain**, ASPD [male: 32.69 (1) < 0.001; female: 32.07 (1) < 0.001] and at least one anxiety disorder [male: 9.85 (1) 0.002; female: 14.56 (1) < 0.001] were significant for both sexes. In the **childhood environment domain**, parent conflict [male: 7.26 (1) 0.001; female: 6.82 (1) 0.009] and looked older as teen [male: 5.90 (1) 0.015; female: 11.62 (1) < 0.001] were significant for both sexes. In addition, childhood relationship with father [9.25 (1) 0.002] and father was strict in setting rules [15.03 (2) < 0.001] were significant for males only; whereas childhood relationship with mother [9.45 (1) 0.002] and mother was inconsistent in enforcing rules [19.40 (1) < 0.001] were significant for females only. In the **biological risk domain**, initial alcohol sensitivity [male: 5.10 (1) 0.024; female: 13.75 (1) < 0.001] was significant for both sexes. For females only, the number of high risk (T) alleles in rs140679 from gene GABRG3 [6.87 (1) 0.009] was also significant.
- The least associating domain is ***religion***. Involvement in religious with rules against alcohol use at follow-up [6.29 (1) 0.012] was only significant among females.

Stage two: See Figures 1 and 2

- The **number of baseline endorsed DSM-III-R AD criteria** [male: 160.42 (1) < 0.001; female: 94.51 (1) < 0.001] was the only common significant factor for both sexes.
- Within the ***demographic characteristics domain***, **family type** [7.38 (1) 0.007] and **follow-up employment status** [11.71 (2) 0.003] were significant for males only.
- Within the ***childhood environment domain***, **relationship with father** [4.44 (1) 0.035] was significant for males only, whereas **relationship with mother** [4.40 (1) 0.036] and **mother's consistency in enforcing rules** [4.25 (1) 0.039] were significant for females only.
- Within the ***biological risk domain***, the **number of high risk (T) alleles of rs140679 from gene GABRG3** [6.64 (1) 0.010] was significant for females only.

Figure 1: Male Multiple-domain GEE logistic regression model

Odds Ratios (95% confidence intervals) p-values

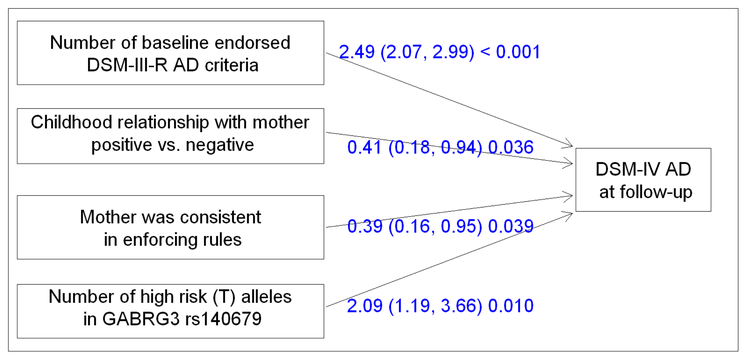


High-risk family type: at least one AD relative in extended family

Comparison family type: community sample regardless of density of AD relatives

Figure 2: Female Multiple-domain GEE logistic regression model

Odds Ratios (95% confidence intervals) p-values



Conclusions

1. ***There are both general and sex-specific associated factors for AD in adulthood.***
2. ***Childhood relationship with parent is a significant factor even after controlling for past alcohol use behaviors five year earlier. In particular, this factor depends on both the sex of the parent and the sex of the offspring.***
3. ***These findings support the important of sex-specific screening and intervention methods for identifying and reducing AD risk in adulthood.***