

Polygenic Influences on Alcohol Misuse are Moderated by Romantic Relationships, but Only in Men

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Overview

Alcohol misuse is moderately heritable, with ~50% of the variance attributable to additive genetic influences (Verhulst et al. 2015). However, genetic influences on alcohol misuse are weaker among those in a committed relationship (Barr et al. 2017; Heath et al. 1989), likely due to increased social control (Umberson et al. 2010). Men to over benefit from romantic partnerships in terms of health (Kiecolt-Glaser and Newton 2001). In the current analyses, we replicate findings from twin models using genome wide polygenic scores (GPS) derived from a GWAS of drinks per week in ~1.3 million individuals (GSCAN, *Nature*, Forthcoming). We answer the following research questions:

1. Do polygenic scores from a large scale GWAS (GSCAN PGS) predict various levels of severity in alcohol misuse (from consumption to problems)?
2. Does relationship status moderate the association between GSCAN PGS and alcohol misuse?
3. Are there sex differences in GxE?

Methods

Sample: FinnTwin12 consists of all twins born from 1983 to 1987 identified through Finland's Population Registry (n ~5600, 87% participation). Baseline collection occurred when twins were ~12 years old. Follow-up surveys occurred at ages 14, 17.5, and during young adulthood (age range 20-26). The Helsinki University Central Hospital District's Ethical Committee and Indiana University's Institutional Review Board approved the FinnTwin12 study. We used data from a subset of 1,347 young adult follow-up participants who received in-depth clinical interviews and participated in DNA collection. Of this subset, 1,312 individuals (including DNA inferred to MZ co-twins) provided DNA information which passed QC.

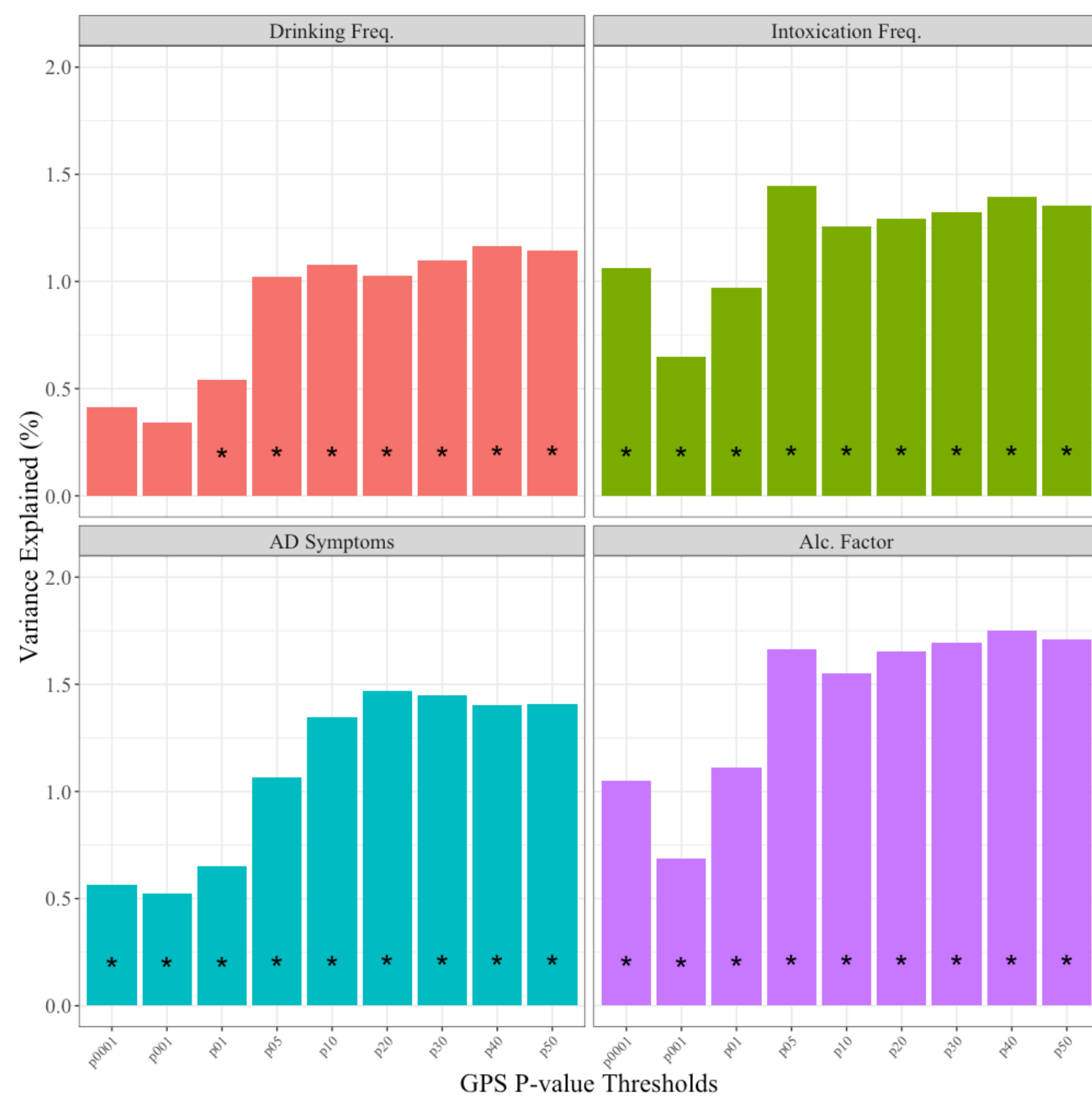
Measures:

- Alcohol Factor Scores generated from 3 measures of alcohol misuse:
 1. Frequency of consumption
 2. Frequency of intoxication
 3. DSM-IV Alcohol dependence symptoms
- Genome-wide Polygenic Scores for Alcohol Consumption (PGS)
 - Using summary statistics from GSCAN GWAS (N ~ 1.3 million)
 - LD clumped (r² = 0.25, 500kb window) scores at multiple p-value thresholds
- Relationship status:
 - Currently in a relationship vs. Not in a relationship
- Additional Covariates
 - Sex: Male/Female
 - Educational attainment (Basic, Primary, Secondary, and Tertiary)
 - Age
 - Student status (currently enrolled as a student)

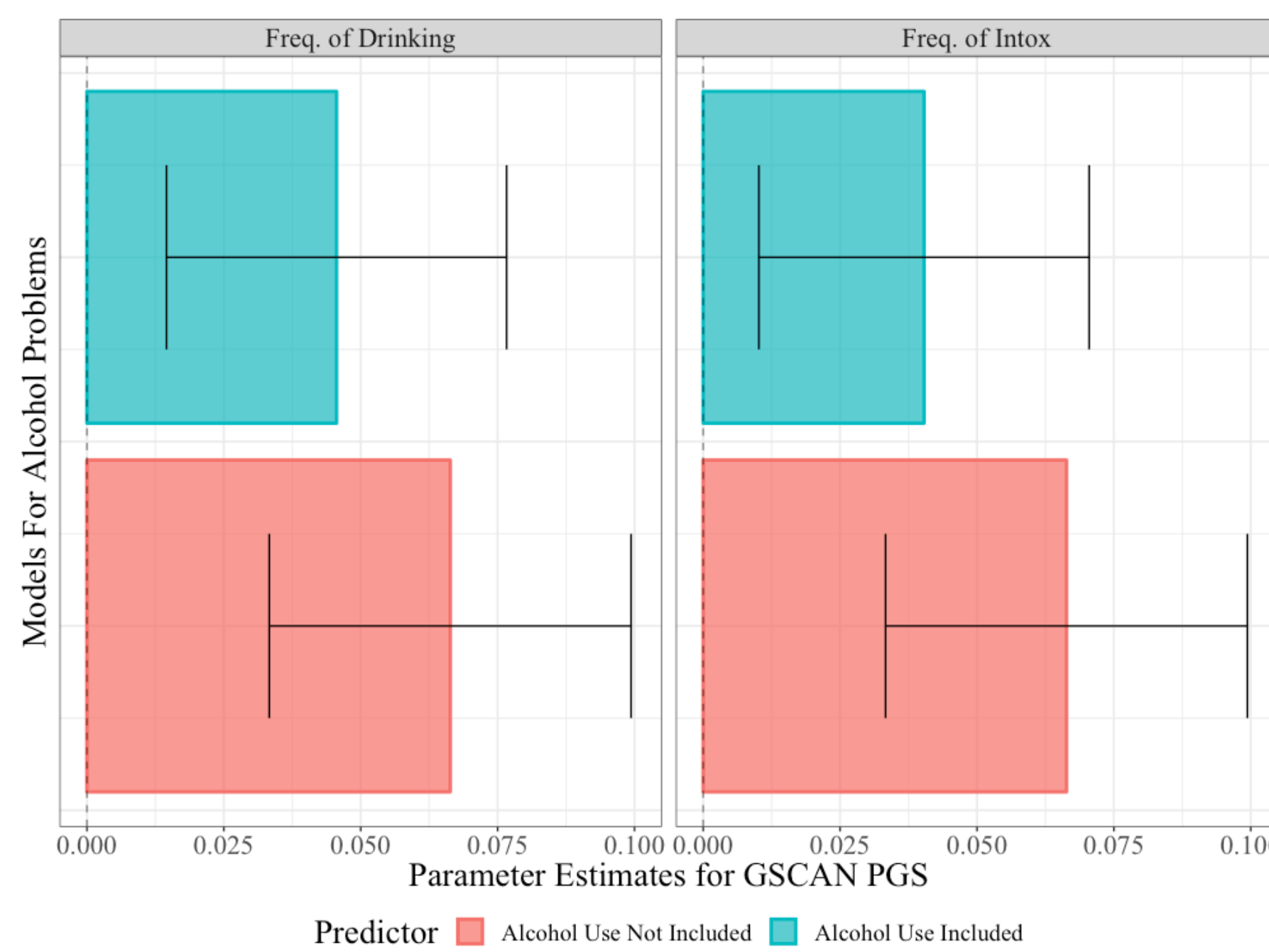
Analytic strategy (using a linear mixed model):

1. Determine the most predictive GPS (based on Δ model R²).
2. Test whether relationship status moderates GPS using a more robust model for determining GxE (Keller 2014).
3. Test for sex-specific GxE by including a three-way interaction term.

Figure 1: Predictive Power of Polygenic Scores

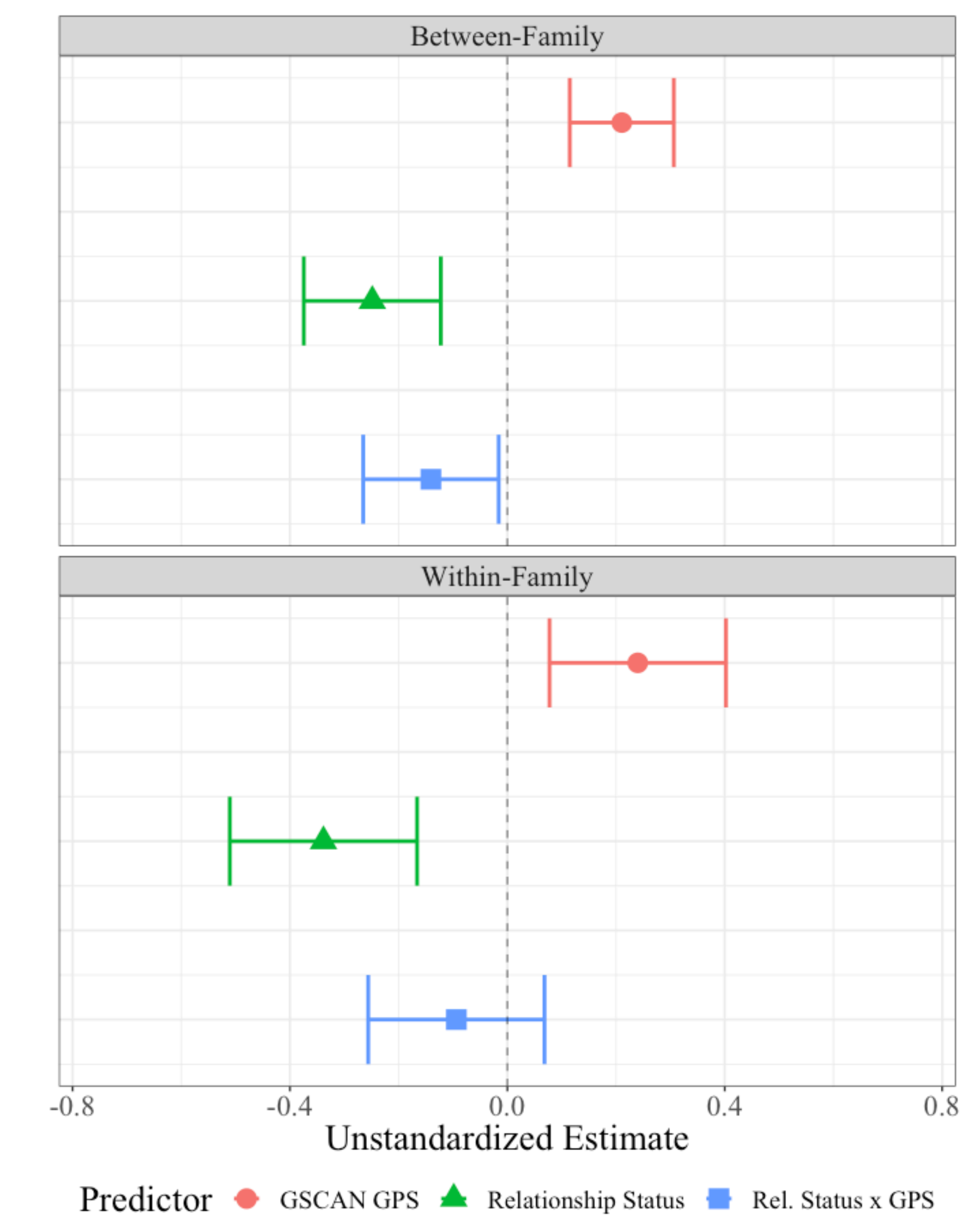


PGS predict all levels of alcohol misuse, from drinking frequency to alcohol dependence symptoms.



PGS show a stronger association in those not in a relationship compared to those in a relationship (top row). A significant 3-way interaction reveals this effect is driven primarily by males (bottom row).

Figure 3: Within and Between Family Estimates in Alcohol Factor Scores



Results from within-family models (bottom, DZ twins only) show that main effects of relationship status and PGS are not confounded by environment, but interaction effect becomes non-significant.

Conclusions

- Polygenic Scores for alcohol consumption from a large scale GWAS predicted all levels of alcohol misuse.
 - Prediction of alcohol problems even after accounting for frequency of drinking or intoxication
- Effect of polygenic scores moderated by relationship status.
 - Polygenic association is stronger for those not in a relationship, similar to previous findings in twins.
- GxE effect driven entirely by males.
 - Men may benefit more from romantic partnerships in terms of reducing their ability to express genetic risk.

References

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