Polygenic Risk Scores Predict the Development of Alcohol and Nicotine Use Problems from Adolescence through Young Adulthood

Joseph D. Deak, Ph.D.[1, 4], D. Angus Clark, Ph.D.[1], Mengzhen Liu. Ph.D.[2], C. Emily Durbin, Ph.D.[3], William G. Iacono, Ph.D.[2], Matt McGue, Ph.D.[2], Scott I. Vrieze, Ph.D.[2], & Brian M. Hicks, Ph.D.[1]

[1] University of Michigan

[2] University of Minnesota

[3]Michigan State University

[4] VA Ann Arbor Healthcare System

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Correspondence: Address correspondence to Joseph D. Deak, VA Ann Arbor Healthcare System, 2215 Fuller Rd (116C), Ann Arbor, MI 48105. Electronic mail may be sent to jdeak@med.umich.edu.

Key Points

Question: Do polygenic risk scores (PRS) for drinking and smoking predict problematic alcohol and nicotine use from late childhood to early adulthood?

Findings: In the current study, drinks per week and regular smoking PRS generated from the GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN) were associated with higher levels of problematic alcohol and nicotine use assessed longitudinally from ages 14 to 34 in a sample of 3225 individuals.

Meaning: Polygenic risk scores validated within longitudinal study designs may help inform future substance use intervention and prevention efforts.

Abstract

Importance: Molecular genetic studies of alcohol and nicotine use have identified hundreds of genome-wide risk loci. Few studies have examined the influence of aggregate genetic risk on substance use trajectories over time.

Objective: We examined the predictive utility of drinking and smoking polygenic risk scores (PRS) for alcohol and nicotine use from late childhood to early adulthood, substance-specific versus broader-liability effects of the respective PRS, and if PRS performance varied between regular consumption versus pathological use.

Design: Latent growth curve models with structured residuals were used to assess the predictive utility of drinks per week and regular smoking PRS for measures of alcohol and nicotine consumption and problematic use from age 14 to 34.

Setting: PRS were generated from the largest discovery sample for alcohol and nicotine use to date (i.e., GSCAN), and examined for associations with alcohol and nicotine use outcomes in the Minnesota Twin Family Study (MTFS).

Participants: Participants were members of the MTFS (*N*=3225), a longitudinal study investigating the development of substance use disorders and related conditions.

Main Outcomes and Measures: Outcomes included alcohol and nicotine use disorder symptoms as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, measures of alcohol and nicotine consumption (i.e., drinks per occasion, cigarettes per day), and composite variables for alcohol and nicotine use problems.

Results: The drinks per week PRS was a significant predictor of problematic alcohol use at age 14 and increases in problematic use during young adulthood. The regular smoking PRS was a significant predictor for all nicotine use outcomes. After adjusting for the effects of both PRSs,

the regular smoking PRS demonstrated incremental predictive utility for most alcohol use outcomes and remained a significant predictor of nicotine use trajectories.

Conclusions and Relevance: Higher PRS for drinks per week and regular smoking were each associated with more problematic levels of substance use over time. Additionally, the regular smoking PRS seems to capture both nicotine-specific and non-specific genetic liability for substance use problems, and may index genetic risk for externalizing behavior in general. Longitudinal PRS prediction approaches may inform personalized substance use intervention approaches.

Introduction

Alcohol and nicotine use, respectively, contribute to 3 million (5.3%) and 7 million (12.3%) deaths worldwide each year, making both leading causes of global mortality [1,2]. While public health interventions have reduced the negative consequences of alcohol and nicotine use, a significant portion of the population continue to meet criteria for nicotine use disorder (NUD) and alcohol use disorder (AUD), suggesting genetic influences contribute to problem use for important subgroups. Twin studies report heritability estimates of 50% for AUD [3] and NUD [4-6], and large consortia of genome-wide association studies (GWAS) have identified hundreds of loci that exhibit genome-wide significant associations with alcohol and nicotine use phenotypes [7-10], providing new avenues for research on the genetic influences on substance use.

Polygenic risk scores (PRS) are one method for modeling aggregate genetic risk across the genome, and have provided valuable information about the unique and shared genetic influences on alcohol and nicotine use. PRS are generated from a GWAS discovery sample by weighting SNPs relative to the strength of their association with a given phenotype to calculate a measure of individual genetic risk in a target sample. For example, PRS calculated from GWAS-identified associations for alcohol use have predicted alcohol-related outcomes in independent samples [11-12]. PRS for alcohol and nicotine use have also predicted use of a variety of other substances (e.g., cannabis, cocaine, amphetamines, ecstasy, hallucinogens [7,13,14]), suggesting these PRS index non-specific genetic influences on substance use.

While studies using PRS are beginning to trace the contours of the genetic architecture of substance use, they have yet to examine the influence of aggregate genetic risk on patterns of

substance use over time. This is an important next step, because alcohol and nicotine use exhibit strong age-related mean-level trends, with typical initiation in adolescence followed by peak use in young adulthood and normative declines in heavy use and substance use disorders by age 30 [15]. Understanding the etiology of substance use then requires accounting for these normative patterns of emergence, escalation, and decline, and there is some evidence that genetic influences for substance use varies across development [16,17].

Initial efforts using PRSs to predict alcohol and nicotine use trajectories over time have had some success. A PRS for cigarettes smoked per day predicted later cigarette smoking and NUD in early adulthood [18,19], but not alcohol use [18], suggesting the PRS measured substance-specific genetic influences on nicotine use. Evidence for the predictive utility of alcohol-related PRS has been mixed. One study found that a PRS for AUD was associated with levels of alcohol use in males at age 15.5 and greater increases of alcohol use at age 21.5 [20], while other studies predicting alcohol use in college student drinkers over time have returned both positive [21] and null results [22]. Most prior studies were limited by smaller GWAS discovery samples relative to the much larger recent GWAS consortia of alcohol and nicotine use. Additionally, the longitudinal studies of alcohol use-related PRS primarily examined college student populations assessed across a four-year timespan during which environmental influences are enriched for substance use, potentially limiting the influence of polygenic contributions in this context.

We address these limitations using PRS prediction measures derived from the GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN), the largest GWAS discovery sample for alcohol and nicotine use to date [7], and examine their utility to predict trajectories of

alcohol and nicotine use and problem use from late childhood through young adulthood. Strengths of this approach include the ability to make stronger inferences about when in the developmental progression of substance use (e.g., initiation of use, escalation of use) these genetic influences have their effects, and the long follow-up period ensures that polygenic influences for alcohol and nicotine use are likely to have been expressed for most people. Given prior evidence suggesting differences in the genetic architecture of alcohol use versus AUD [23,24], we also tested whether the predictive utility of the PRSs varied across measures of use and symptoms of AUD and NUD. A final aim was to examine whether the predictive utility of respective alcohol and nicotine-related PRS were limited to their specific substance or generalized to predict trajectories of both alcohol and nicotine use.

Methods

Participants

Participants were members of the Minnesota Twin Family Study (MTFS), a longitudinal study of 3762 (52% female) twins (1881 pairs) investigating the development of substance use disorders and related conditions [25-27]. All twin pairs were the same sex and living with at least one biological parent within driving distance to the University of Minnesota laboratories at the time of recruitment. Exclusion criteria included any cognitive or physical disability that would interfere with study participation. Twins were recruited the year they turned either 11-years old (*n*=2510; the younger cohort) or 17-years old (*n*=1252; the older cohort). Twins in the younger cohort were born from 1977 to 1984 and 1988 to 1994, while twins in the older cohort were born between 1972 and 1979. Families were representative of the area they were drawn from in terms of socioeconomic status, mental health treatment history, and urban vs rural residence [25].

Consistent with the demographics of Minnesota for the target birth years, 96% of participants reported European American ancestry.

The younger cohort was assessed at ages 11 (M_{age}=11.78 years; SD=0.43 years) and 14 (M_{age}=14.90 years; SD=0.31 years), and all twins were assessed at target ages 17 (M_{age}=17.85 years; SD=0.64 years), 21 (M_{age}=21.08 years; SD=0.79 years), 24 (M_{age}=24.87 years; SD=0.94 years), and 29 (M_{age}=29.43 years; SD=0.67 years). A subgroup of twins from the younger cohort were also assessed at age 34 (M_{age}=34.62 years; SD=1.30 years). Supplemental Table 1 provides the number of participants for each assessment and descriptive statistics for the study measures. Participation rates ranged from 80% to 93% among those recruited for a given assessment. The total sample included 1205 monozygotic (51.5% female) and 676 dizygotic (52.8% female) twin pairs [25,28].

Alcohol Use and AUD. All alcohol and nicotine variables were assessed during structured clinical interviews, while the use variables were also assessed using a computerized self-report questionnaire at ages 11, 14, and 17 that was completed in private. Alcohol variables included the average number of drinks per occasion in the past 12 months (i.e., alcohol quantity), *DSM-III-R* symptoms of alcohol abuse and dependence (the diagnostic system when the study began, hereafter referred to as AUD symptoms), and an alcohol problems composite variable calculated at each age consisting of the average of mean alcohol quantity, AUD symptoms, and maximum number of drinks consumed in 24 hours (i.e., max drinks). Free responses to alcohol quantity and max drinks, as well as the number of alcohol abuse and dependence symptoms were converted to scales that ranged from 0 to 8. In terms of problem use, the lifetime prevalence of *DSM-III-R* AUD (3 or more symptoms of abuse or dependence) was 26%.

Nicotine Use and NUD. Nicotine variables included average quantity per day (e.g., cigarettes smoked per day), *DSM-III-R* symptoms of nicotine dependence (hereafter referred to as NUD symptoms), and an age-specific nicotine use problems composite variable calculated from the averages of mean nicotine quantity, NUD symptoms, and typical frequency of nicotine use (i.e., number of days per month) in the past 12 months. Free responses were converted to a 0 to 4 scale for nicotine frequency and a 0 to 6 scale for nicotine quantity and NUD symptoms. The lifetime prevalence of *DSM-III-R* NUD was 33%.

PRS Methods. PRS were generated from the GSCAN discovery sample using GWAS summary statistics for drinks per week and ever being a regular smoker, following removal of the MTFS sample to avoid overlap with the target sample [7]. PRS were created for participants of European ancestry in the MTFS target sample following imputation to the most recent Haplotype Reference Consortium reference panel [29] and restricted to autosomal HapMap3 variants with a minor allele frequency (MAF) ≥ 0.01 and an imputation quality > 0.7. The resulting filtered variants (i.e., ~1 million variants) were then submitted to LDpred [30] to generate beta weights in the MTFS sample, including variants of all significance levels (i.e., *p*-value threshold ≤ 1). Individual PRS were then calculated in PLINK 1.9 [31] for all individuals meeting inclusion criteria for the present study (N=3225).

Data Analytic Strategy

Latent growth models with structured residuals (LGM-SR; see Figure 1) were used to model developmental trends in the alcohol and nicotine use outcomes [32,33]. These models include intercept factors that reflect status at the first time point (age 14 as there was almost no substance use at age 11), and slope factors that reflect the rate of change over the course of the

study. Slope factors were specified using a latent basis approach. That is, the first and last basis coefficient were fixed to 0 and 1, respectively, and the intervening coefficients were estimated, which provides a parsimonious way of capturing non-linear trajectories [34][1]. Intercept and slope factors were allowed to vary to capture individual differences in growth. The residual structure included occasion-specific latent factors that account for deviations from the intercept and slope implied trajectories. The autoregressive paths linking adjacent residual factors capture associations between variables over time after accounting for general growth trend (Figure 1) and were included because not accounting for residual autoregressive effects can lead to biased variance estimates in the growth factors [35,36].

Unconditional LGM-SR models were first fit to each outcome (Figure 1-Panel a). Conditional models were then fit in which the growth factors were regressed on a single PRS and the control variables (Single PRS Predictor Model; Figure 1-Panel b). The control variables included participant sex and the first five genetic principal components [37] to adjust for underlying ancestral substructure. Finally, conditional models were estimated in which the growth factors were regressed on both PRS' simultaneously along with the control variables (Two PRS Predictor Model; Figure 1-Panel c). All major analyses were conducted using Mplus v8.4 [38] with full information maximum likelihood estimation [39]. Confidence intervals were derived using clustered percentile bootstrapping (with 1000 draws), which is effective when estimating confidence intervals with skewed variables such as substance use [40].

[1] Alternative specifications of the growth model (e.g., piecewise models) were considered, and lead to the same conclusions as reported here

Results

Descriptive information for the study variables is reported in the supplemental material (https://osf.io/zep8q/). Mean-levels of the alcohol and nicotine use outcomes increased from age 11 to age 20, and then decreased from age 20 to age 34. The rank-order stability of the alcohol and nicotine use outcomes between adjacent time points ranged from r=.33 to .83 (mean r=.57). Models were fit both with and without participants that consistently abstained from substance use across time. Conclusions were similar across these models, and so we report the results for models fit using the full sample.

The univariate models for alcohol and nicotine use related outcomes all fit the data well by conventional standards [41]. Parameter estimates were consistent with the observed trajectories, suggesting a rise in alcohol and nicotine use throughout adolescence, and then a gradual decline in values after age 20. There was a statistically significant degree of variability in all of the growth factors (see https://osf.io/zep8q/).

Alcohol Use Outcomes

Standardized path coefficients from the single PRS conditional models can be found in Table 1. The drinks per week PRS was a statistically significant predictor of small magnitude (mean β=.09) for all alcohol use-related growth factors except for the alcohol quantity intercept, though the effect size was similar (β=.10). The regular smoking PRS was a statistically significant predictor of small to medium magnitude (mean β=.17) for all alcohol use-related growth factors except for the alcohol quantity slope (β=.05).

Standardized path coefficients from the two PRS conditional models can be found in Table 1. Most of the effects for the drinks per week PRS were not significant and negligible in magnitude (mean β=.05), except for the statistically significant but small effects on the AUD

intercept factor (β=.10) and alcohol composite slope factor (β=.06). The regular smoking PRS remained a statistically significant predictor of small to medium effect for all the alcohol use-related growth factors (mean β=.15) except for the alcohol quantity slope (β=.03).

Nicotine Use Outcomes

The regular smoking PRS was a statistically significant predictor of small to medium magnitude (mean β=.21) for all nicotine use-related growth factors. The drinks per week PRS was a modest, statistically significant predictor (mean β=.11) of all of the intercept factors, but none of the slope factors (mean β=.03). In the two PRS conditional models, the regular smoking PRS remained a statistically significant predictor of small to medium effect for all nicotine use-related growth factors (mean β=.18). None of the drinks per week PRS effects remained significant (mean β=.03). Substance use growth trajectories for individuals with high (i.e., 1.5 standard deviation above the mean), low (i.e., 1.5 standard below the mean), and average scores for the respective PRSs can be found in Figure 2.

Supplemental Analyses

We also fit models that regressed scores for each growth factor (e.g., AUD slope) on the same predictors of the two PRS conditional models, but also added scores for the comparable growth factor of the other substance (e.g., NUD slope). Results were consistent with those of the two PRS conditional models (see https://osf.io/zep8q/) indicating the PRS retained predictive utility even after adjusting for the phenotypic overlap between alcohol and nicotine use.

Discussion

We extended prior studies investigating genetic influences for alcohol and nicotine use by examining the utility of PRS to predict the developmental progression of alcohol and nicotine use. Using a longitudinal design, we found that higher drinks per week PRS and regular smoking

PRS were each associated with more problematic levels of use of the respective substances in middle adolescence, and a greater rate of increase in alcohol and nicotine use problems through early adulthood. These findings demonstrate that alcohol and nicotine use-related PRS are robust predictors of trajectories for problematic alcohol and nicotine use, and suggest the potential for clinical applications utilizing polygenic risk profiles to help inform intervention strategies.

We also examined differences in prediction for regular use versus symptoms of substance use disorder. Though most effects were consistent across regular use and substance use disorder symptoms, we found that the drinks per week PRS and regular smoking PRS were more predictive of AUD symptoms relative to average quantity of alcohol consumed per drinking occasion. Notably, previous studies have suggested only partial genetic overlap between alcohol consumption and AUD, and the potential for unique genetic etiologies between normative alcohol consumption and pathological alcohol use [23,24]. Conversely, a recent study reported a genetic correlation of ~0.7 between PRS for drinks per week and problematic alcohol use [42], suggesting the presence of genetic similarities across varying levels of alcohol use, further reinforcing the need for future studies to decipher common and unique genetic influences on regular versus pathological alcohol use.

We also examined the substance-specific versus generalized effects of the PRS, as well as their incremental predictive utility. We found that the regular smoking PRS was a stronger predictor of both nicotine and alcohol use-related phenotypes, even after adjusting for its overlap with the drinks per week PRS. In contrast, the predictive utility of the drinks per week PRS was mostly specific to alcohol use, and even most of these associations were non-significant after adjusting for its overlap with the regular smoking PRS. Thus, the regular smoking PRS seems to

measure both nicotine-specific and non-specific genetic liability for substance use problems, potentially serving as an index of externalizing behavior more broadly (i.e., poor impulse control and norm violating behavior), while the drinks per week PRS seems to measure genetic risk that is relatively specific to alcohol.

The notion that smoking polygenic risk is broadly predictive of externalizing behaviors is supported by results from the initial wave of GSCAN showing that the regular smoking PRS was associated with a variety of substances (e.g., alcohol use, cannabis use, cocaine use [7]). The evidence for common genetic influences across substances is also consistent with prior multivariate twin studies that posited a common genetic etiology for engaging in externalizing behaviors [43-45]. Given these prior findings, the regular smoking PRS may index non-specific genetic risk for externalizing behaviors, which would account for its robust prediction of nicotine and alcohol use outcomes and its incremental predictive utility relative to the drinks per week PRS.

Polygenic risk prediction approaches, particularly those validated within longitudinal designs, may inform personalized substance use intervention and prevention approaches and have demonstrated the ability to predict negative health outcomes later in life [46]. For substance use, specific polygenic risk profiles may be associated with certain substance use trajectories or negative outcomes that might be curtailed with the benefit of PRS-informed interventions and lifestyle changes [47]. These PRS-informed approaches have the potential to be particularly useful if interventions were able to incorporate this information (e.g., via genetic feedback) during developmental periods prior to increased rates of problematic use.

Limitations of the study include that the PRS were generated from large GWAS that were conducted in countries in which the population is primarily of European descent, and due to varying allele frequencies across ancestral groups, the degree to which the current results generalize to other ancestral groups is uncertain [48,49]. Notably, this limitation has the potential to proliferate health disparities with precision medicine efforts if these findings are only applicable to individuals of European ancestry, further prioritizing the importance of extending these efforts to diverse ancestry groups [50]. Additionally, genetic influences on substance use behaviors are influenced by a variety of environmental factors (e.g., peer influences), and genetic and environmental influences vary across development stages [18,51]. Thus, future studies examining how these PRS interact with environmental influences longitudinally are needed.

Despite these limitations, the current study represents a successful extension of prior work by validating the predictive utility of the PRS approach in longitudinal models of alcohol and nicotine use phenotypes across late childhood and early adulthood. The results also provide initial evidence that the regular smoking PRS may index non-specific genetic risk for substance use and externalizing behaviors in general. This validation serves as a key step in demonstrating polygenic prediction of alcohol and nicotine use outcomes across important developmental periods, and has the potential to have meaningful implications for the future of personalized substance use prevention and intervention efforts.

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Table 1
Standardized Coefficients to Intercept and Slope Factors From Single and Double PRS Predictor Models

	Drinks Per Week PRS				Regular Smoking PRS			
	Intercept (1 PRS)	Intercept (2 PRS)	Slope (1 PRS)	Slope (2 PRS)	Intercept (1 PRS)	Intercept (2 PRS)	Slope (1 PRS)	Slope (2 PRS)
Alcohol Use Disorder	**.12**	**.10**	**.06**	.04	**.12**	**.10**	**.12**	**.11**
	[.06, .22]	**[.04, .18]**	**[.01, .11]**	[-.02, .09]	**[.06, .25]**	**[.04, .22]**	**[.07, .17]**	**[.06, .16]**
Alcohol Quantity	.10	.01	**.07**	.07	**.36**	**.35**	.05	.03
	[-.04, .48]	[-.17, .27]	**[.01, .15]**	[.00, .14]	**[.19, 1.32]**	**[.19, 1.33]**	[-.02, .12]	[-.04, .10]
Alcohol Composite	**.10**	.04	**.08**	**.06**	**.25**	**.24**	**.11**	**.09**
	[.01, .26]	[-.05, .17]	**[.03, .13]**	**[.01, .11]**	**[.16, .53]**	**[.15, .53]**	**[.05, .16]**	**[.04, .15]**
Nicotine Use Disorder	**.10**	.06	.04	.00	**.19**	**.17**	**.18**	**.18**
	[.03, .18]	[-.02, .13]	[-.02, .10]	[-.06, .06]	**[.12, .28]**	**[.11, .27]**	**[.12, .23]**	**[.12, .24]**
Nicotine Quantity	**.12**	.05	.02	.00	**.30**	**.29**	**.09**	**.09**
	[.03, .27]	[-.05, .18]	[-.04, .08]	[-.07, .07]	**[.19, .57]**	**[.18, .55]**	**[.02, .16]**	**[.02, .16]**
Nicotine Composite	**.11**	.06	.03	.00	**.23**	**.22**	**.18**	**.18**
	[.03, .22]	[-.03, .15]	[-.02, .09]	[-.06, .05]	**[.15, .38]**	**[.14, .35]**	**[.12, .24]**	**[.12, .24]**

1 PRS=coefficients from single PRS predictor model; 2 PRS=coefficients from double PRS predictor model; Bold=95% confidence interval does not include 0. Only one PRS was entered as a predictor in each single PRS predictor model; both PRSs were entered as predictors simultaneously in the double PRS predictor model. Eigenvalues 1 through 5 and sex were entered into each model along with the PRS as control variables; coefficients for control variables not presented. Confidence intervals derived via clustered non-parametric percentile bootstrap with 1,000 draws.

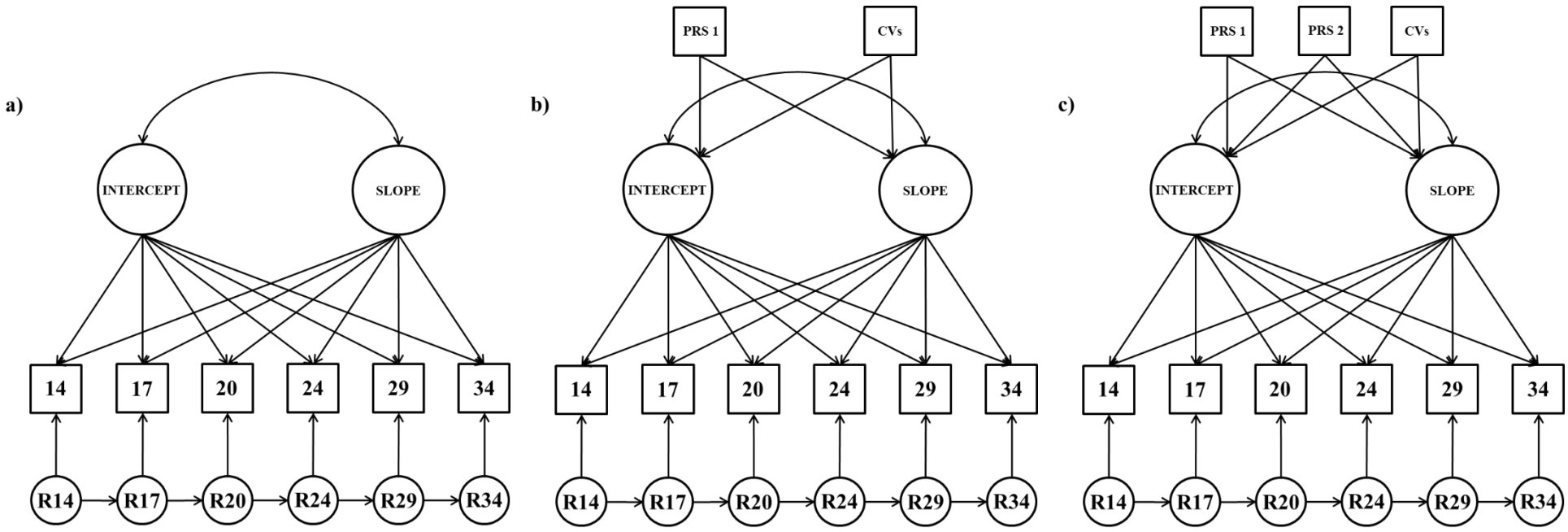

Figure 1. Unconditional and Conditional Latent Growth Models with Structured Residuals. Panel a depicts the unconditional latent growth model; Panel b depicts the single PRS conditional latent growth model; Panel c depicts the two PRS conditional latent growth model. R=residual factor; PRS=polygenetic risk score; CVs=covariates (first 5 eigenvalues and sex). Variances and mean structure omitted from figure for clarity of presentation.

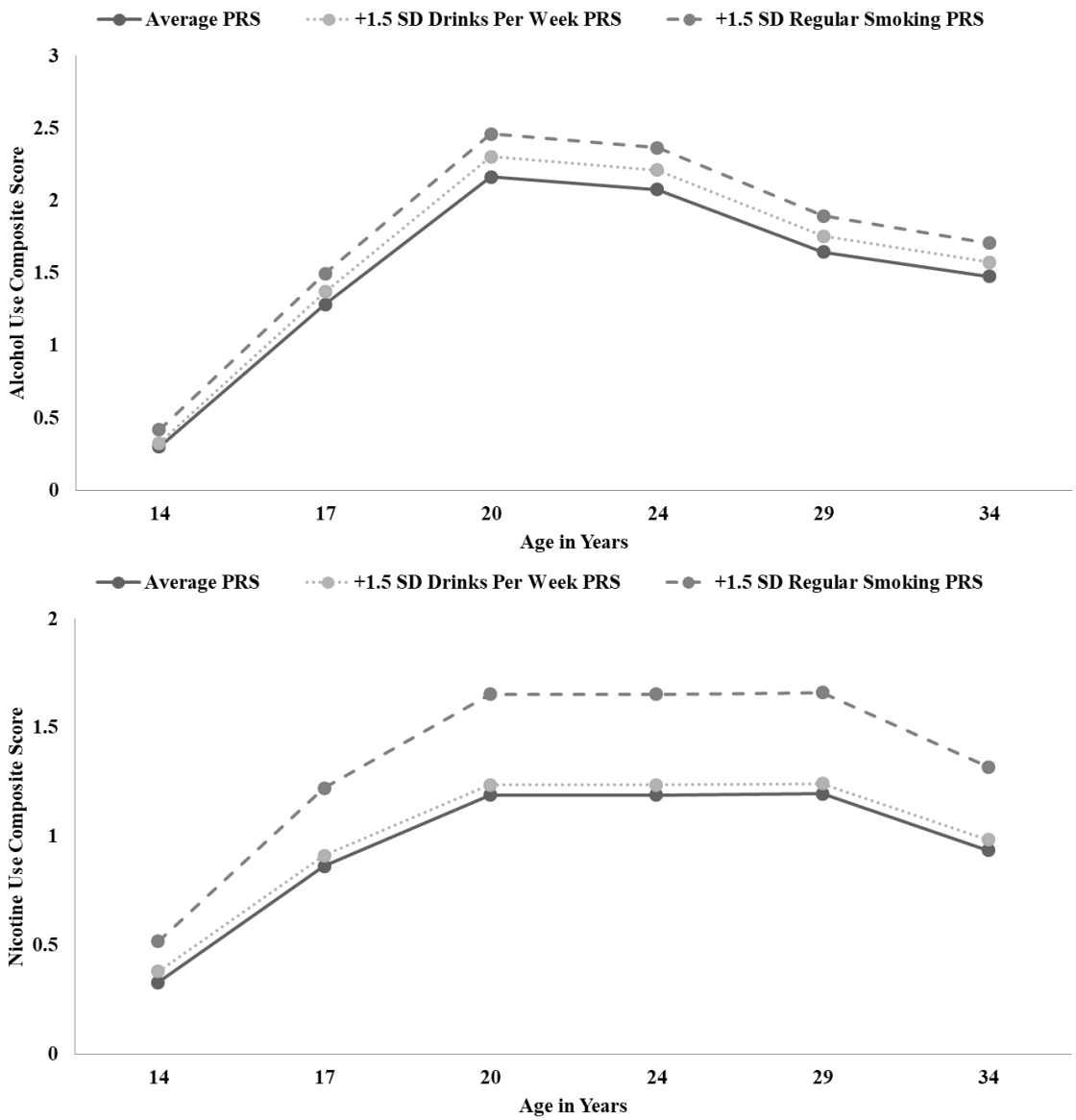

Figure 2. Growth Trajectories from the Two PRS Predictor Models for Alcohol and Nicotine Use Composites. Growth trajectories for the alcohol composite presented in the top panel, growth trajectories for the nicotine composite presented in the lower panel. Age in years presented on X axis, composite scores presented on Y axis. Trajectories are based on the parameter estimates from the full two PRS predictor models. The three lines depict trajectories for those with average scores on both PRSs (solid line), high scores (1.5 standard deviation above the mean) on the drinks per week PRS and average scores on the regular smoking PRS (dotted line), and average scores on the drinks per week PRS and high scores on the regular smoking PRS (dashed line).