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Genetic and Environmental Influences on Alcohol Consumption in Middle to Late Life

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Abstract

Objective: Alcohol use is common in older adults and linked to poor health and aging outcomes. Studies have demonstrated genetic and environmental contributions to the quantity of alcohol consumption in mid- to late life, but less is known about whether these influences are moderated by sociodemographic factors such as age, sex, and educational attainment. This study sought to better understand socio-demographic trends in alcohol consumption across the second half of the life course and their underlying genetic and environmental influences.

Method: Primary analyses were based on 64,140 middle-aged or older-adult twins (40 to 102 years) from 14 studies in the Interplay of Genes and Environment across Multiple Studies (IGEMS) consortium. We harmonized a measure of weekly alcohol consumption (in grams of ethanol per week) across all studies.

Results: Older age was associated with lower alcohol consumption, primarily for adults over age 75, for individuals with higher education, and for males. Trends were similar across birth cohorts and after excluding current abstainers. At mean age 56, alcohol use was moderately heritable in females (.34, 95% CI [.26, .41]) and more heritable in males (.42, 95% CI [.38, .45]]). Heritability was lower in older-aged adults and in females with higher education.

Conclusions: This study represents the largest twin study of alcohol consumption in middle-aged and older adults. Results highlight that genetic and environmental factors influence alcohol consumption differently across age, sex, and educational attainment and that intervention efforts may need to be tailored based on individuals' backgrounds.

Keywords

heritability; twin study; alcohol; gene-by-environment interaction; aging

Introduction

Alcohol is one of the most used drugs in the world, but its use varies widely globally (Calvo et al., 2021). Genetic factors have a substantial influence on alcohol use and misuse (Verhulst et al., 2015), with correlated but distinct genetic influences on measures of alcohol initiation, quantity and frequency of use, and dependence/misuse (Agrawal et al., 2011; Brazel et al., 2019; Dick et al., 2011; Mallard et al., 2022; Saunders et al., 2022).

Greater and more frequent alcohol use is also associated with sociodemographic factors, including age (Geels et al., 2013) and greater educational attainment (Rosoff et al., 2021), particularly among females (Huerta & Borgonovi, 2010). Importantly, alcohol consumption is considerable in some elderly populations (Geels et al., 2013) and may be associated with cognitive decline (Järvenpää et al., 2005; Yen et al., 2022) and brain damage (Wiegmann et al., 2020). Individuals at high genetic risk for Alzheimer's Disease may also use alcohol more frequently (Kapoor et al., 2021; Slayday et al., 2021).

Alcohol consumption has been widely studied in adolescence and earlier adulthood, but studies focusing on older adults are less frequent (Zellers et al., 2021). Thus, understanding the etiology of alcohol consumption in older adults is important, including whether sociodemographic characteristics such as educational attainment and sex magnify or reduce the impact of genetic and environmental influences on alcohol consumption. The current study leveraged data from 14 large twin studies from Europe, North America, and Australia in the Interplay of Genes and Environment Across Multiple Studies (IGEMS) consortium (Pedersen et al., 2019) to quantify the genetic and environmental influences on alcohol consumption in mid to late-life and examine whether age, sex, and educational attainment moderate these relationships.

Alcohol Use: Trends and Relevance to Aging

Alcohol use can be assessed in many ways, including the average frequency or quantity of alcohol use, frequency or quantity of heavy alcohol use (e.g., binging), and alcohol use disorder. Such measures demonstrate strong correlations across the lifespan, especially at the level of genetic influences (Agrawal et al., 2011), but also carry unique genetic and environmental influences (Dick et al., 2011; Mallard et al., 2022). Here, we focus on typical quantity of alcohol consumption (i.e., grams of ethanol consumed per week).

Cross-sectional trends across many countries find that alcohol consumption generally increases throughout adolescence, adulthood, and mid-life, but may begin to decline among older adults (Calvo et al., 2021). Some individuals stop drinking for health and/or other reasons, but many older adults continue to drink frequently, and these alcohol use trends may relate to cognitive and physical outcomes in older age. Further, while ample studies have found lower educational attainment to be associated with more risky alcohol use behaviors (Crum et al., 1993), even causally so (Rosoff et al., 2021), lower education is associated with greater genetic variance in some (Hamdi et al., 2015) but not all studies (Barr et al., 2016). Finally, while risky alcohol use is more prevalent among men, the gender gap has been narrowing over the past two decades (White, 2020). In addition, the source and magnitude of genetic influences on risky alcohol use appear to be consistent across the sexes (Prescott et al., 1999), although it is unclear as to whether there are sex-specific gene-by-environment effects (Salvatore et al., 2017). Thus, it will be important to better understand alcohol use trends in older adults, their genetic and environmental underpinnings, and whether these trends differ across sexes, ages, and cohorts.

Moderation of Genetic and Environmental Influences on Alcohol Consumption

Existing studies suggest that the heritability of alcohol use in middle aged and older adults is considerable. For example, genetic influences explain about 39%−65% of the variance in quantity of alcohol consumption in samples of adults mean aged 30s and 40s (Dick et al., 2011; Hettema et al., 1999) with similar estimates for adults in their 50–60s or older (Reynolds et al., 2006; Swan et al., 1990). Prior work has primarily focused on adolescent and adult samples rather than older adult samples (Zellers et al., 2021), but there is some evidence that heritability estimates for quantity of alcohol use are similar or slightly lower in samples that spanned the full range of adulthood (e.g., 18 to 88+) (Virtanen et al., 2019; Whitfield et al., 2004). Some of the variability across these studies may be attributed to age differences between samples, especially if alcohol use trends depend on age (Zellers et al., 2021), or cohort effects (Virtanen et al., 2019). Specifically, alcohol consumption may not simply stabilize throughout adulthood and decrease in older adults, but the relative proportion of genetic and environmental variance may also depend on age. Indeed, prior analysis of data from the IGEMS consortium demonstrated that genetic variance on cognitive and health traits can vary considerably across mid- to late life (Franz et al., 2017; Gustavson et al., 2021; Luczak et al., 2023).

In addition to age, it is important to evaluate whether sociodemographic correlates of alcohol use also impact the magnitude of genetic and/or environmental variance on alcohol consumption. In contrast to problematic drinking which is often associated with lower educational attainment (Murakami & Hashimoto, 2019), individuals with higher educational attainment may consume more alcohol on average (Huerta & Borgonovi, 2010; Murakami & Hashimoto, 2019; Virtanen et al., 2019). This trend has been observed in multiple countries, may be even stronger in females (Huerta & Borgonovi, 2010) and may reflect increased availability of alcohol for those with higher income and/or environmental niches where alcohol consumption is normalized. However, studies have not yet examined whether levels of educational attainment also alter the contribution of genetic and/or environmental influences on alcohol consumption (i.e., gene by environment interactions), including whether such associations differ across sex. This is important because many older adults continue to drink frequently.

Moreover, consideration of how educational attainment moderates genetic or environmental influences on alcohol use is relevant to models of gene-by-environment interplay (for review, see Boardman et al., 2013). In summary, these frameworks suggest that genetic variance on a given outcome may vary as a function of environmental risk (i.e., socioeconomic status, indexed here by educational attainment). For example, genetic variance may decrease at lower levels of environmental risk (i.e., the diathesis stress model), increase at lower levels of environmental risk (i.e., the social distinction model), or increase at both ends of environmental exposures (i.e., the differential susceptibility model) (Boardman et al., 2013). Recent work in IGEMS indeed suggests that genetic variance on self-rated health was largest in the unfavorable environments (i.e., high financial strain), supporting the diathesis-stress model (Finkel et al., 2022). Examining how genetic

influences on alcohol consumption vary based on educational attainment (as well as other factors such as age and sex) will support further development of theoretical models of gene-environment interplay on health.

The Current Study

The current study examined cross-sectional age-related trends in alcohol use in relation to socio-demographic variables including age, sex, and educational attainment. We also examined whether genetic and environmental influences on alcohol consumption are moderated by these factors. We accomplished these goals by harmonizing data across 14 large twin samples. Weekly alcohol consumption was harmonized and pooled across N=72,371 individuals (n=64,140 with complete data), spanning 4 countries (Australia, Denmark, Sweden, USA), with a complementary meta-analysis including an additional sample of over 10,000 Finnish twins. We hypothesized that alcohol consumption would be greater in males and in individuals with higher educational attainment, and that quantity of alcohol consumption would be relatively consistent across mid-life but lower in the oldest adults (e.g., after about age 70; Calvo et al., 2021). We also conducted a series of sensitivity analyses to examine how different factors affect our estimates, including cohort effects, year of data collection, and analyses excluding individuals who report currently abstained from alcohol use or individuals who drink more heavily. Furthermore, we did not make *a priori* hypotheses regarding the direction in which genetic and/or environmental influences on alcohol consumption would be moderated by age and educational attainment. We therefore evaluated three competing alternatives for the moderation of genetic or environmental variance by age and educational attainment: increasing genetic or environmental variance, decreasing genetic or environmental variance, or no moderation.

Method

Participants

Primary analyses were based on 72,371 individual twins (30,158 females, 42,213 males), including 9,445 complete monozygotic (MZ) twin pairs and 14,211 dizygotic (DZ) twin pairs (including 6,723 opposite sex pairs) where both twins were represented and had data for all covariates. This sample was drawn from 14 studies from the IGEMS consortium (Pedersen et al., 2013; Pedersen et al., 2019), which spanned Australia (2 studies), Denmark (3 studies), Sweden (6 studies), and the USA (3 studies). Thus, the vast majority of the sample was from white, non-Hispanic individuals of (northern) European genetic ancestry. We analyzed data from these 14 samples in a pooled analysis, but also conducted a complementary meta-analysis within 9 of the largest studies (i.e., running models separately within each study and meta-analyzing estimates; n=67,125), which included an additional large twin study of middle-aged Finnish twins (n=10,037) that could not be analyzed in the pooled sample due to lack of consent to share data.

Detailed information on each study is summarized elsewhere (Pedersen et al., 2019), and studies are briefly described in the Supplemental Method. Histograms of study characteristics by sample and country are presented in Supplemental Figures S1–S4. Because this study focused on alcohol trends in mid-life and old age, the analytic sample

included only those aged 40 years and older. For longitudinal studies, we typically used data from the first assessment of alcohol only (see Supplemental Method). We focused on sex differences (i.e., female vs. male) rather than gender differences (i.e., women vs. men) given the availability of data.

Measures

Alcohol use. We created a harmonized score for quantity of recent/typical weekly alcohol intake based on questions from each study. Briefly, our harmonization procedure typically involved first computing the total number of drinks per week reported by each subject, collapsing across multiple categories of alcohol (e.g., beer, wine, liquor). Grams of ethanol per week were computed based on country standards for a 'standard drink' (i.e., 10g per drink in Australia, 12g per drink in Europe, 14g per drink in the USA). Some studies directly specified the size of beverages during interviews. In those instances, we used the following formula: g of ethanol = (beverage volume in ml * percent of alcohol by volume) / 1.25. In these computations, we assumed 5% alcohol by volume for beer, 12% for wine, and 40% for liquor. The frame of reference differed from each study, but studies generally asked about alcohol consumption within the past 1–2 weeks, weekly alcohol consumption over the past few months, or general/typical alcohol consumption. See the Supplementary Method for more information about the assessment of alcohol within each sample, including treatment of data which used multiple choice questions with a range of options (e.g., "1–4 beers per week", etc.). We also display means for alcohol consumption by sex, educational attainment, and age (Table S2).

After harmonization, square root and log transformations both appeared to normalize the data well, and we elected to use the square root transformation. Finally, to prevent the influence of outliers, all observations >4 SD above the mean (of the transformed data) were replaced (i.e., winsorized) with the value corresponding to 4 SD above the mean. Even in an extremely large sample of ~70,000 individuals, we would only expect about 2.2 observations >4 SD above the mean (assuming a normal distribution), so this threshold was appropriate given our sample size. The final harmonized measure had a skew of 0.60 and kurtosis of −0.05.

Educational attainment. Harmonization of educational attainment was initially based on the nine-category International standard classification of education (UNESCO Institute for Statistics, 2012), but some categories were combined due to data sparseness and lack of detail in some datasets. Our final measure included 6 levels (see Supplementary Figure S3 and S4 for distributions by sample and country). A score of 1 indicated completion of primary school or less (n=8,645), a score of 2 indicated completion of a lower secondary school (e.g., middle school, n=16,007), a score of 3 indicated completion of upper secondary school (e.g., high school or GED; n=17,374), a score of 4 indicated completion of some post-secondary education (e.g., technical certification, short-cycle tertiary education, or some college; n=7,853), a score of 5 indicated completion of a 4-year degree (e.g., bachelor's degree; n=11,701), and a score of 6 indicated completion of a graduate degree (e.g., masters, PhD, MD, or other doctorate; n=2,560). The final six-item measure had good

distributional characteristics (skew=.29, kurtosis= −.91) and was analyzed as a continuous variable.

Data Analysis

All analyses were performed using R version 4.2.2 (R Core Team, 2022).

Phenotypic analyses. Phenotypic hierarchical regression analyses were conducted using the lme4 package (Bates et al., 2015), which used list-wise deletion and random intercepts to control for the nesting of data at the level of country, sample, and family. Model fit was determined using −2 log-likelihood values (−2LL), the Akaike information criterion (AIC), and the Bayesian information criterion (BIC). Good fitting models had the lowest −2LL and AIC or BIC values (Markon & Krueger, 2004). Given the extremely large sample size, we anticipated that most phenotypic associations (including interaction terms) would be statistically significant. Therefore, we report significant phenotypic results based on an α=.01, but focus on effect sizes rather than statistical significance.

We first examined associations between age, educational attainment (centered), and sex, on weekly quantity of alcohol consumption, including two-way interactions between all variables. Additionally, we evaluated non-linear effects of age using a spline regression with a single cut-point. Potential cut-points were evaluated at 5-year intervals, with an additional model including a cut-point at the sample mean, a model with no cut-point, and a model with linear and quadratic terms for age instead of a regression spline (see Supplemental Method and Table S3 for model comparisons). Sensitivity analyses also considered the role of birth cohort in these analyses, splitting the sample by individuals born before 1931 (n=23,929) and born in 1931 or later (n=48,442), roughly the center of the bi-modal distribution of birth year in the full sample (see Supplemental Results). Sensitivity analyses also compared whether trends were similar after excluding individuals who reported abstaining from alcohol (i.e., 0 grams of ethanol per week; remaining sample n=60,649; n=53,858 with complete data) and after excluding individuals who used consumed alcohol most heavily (>1.5 *SD* or ~20 drinks per week; remaining sample n=66,579; n=59,737 with complete data).

Genetic analyses. Genetic analyses were conducted using the OpenMx package in R (Neale et al., 2016), which uses likelihood-based 95% confidence intervals (95% CIs). OpenMx accounts for missing observations using a full-information maximum likelihood approach, but genetic moderation models required subjects to have data for all moderators. Significant results are reported based on α=.05 because the power to observe moderation of genetic and environmental influences (e.g., by age) is modest even in very large samples.

Models were based on the standard assumptions in twin designs as follows: Additive genetic influences (A) correlate at 1.0 in MZ twin pairs and 0.5 in DZ twin pairs because MZ twins share 100% and DZ twins share, like full-siblings, on average 50% of their alleles identical-by-descent (assuming random mating). Common/shared environmental influences (C) are correlated at 1.0 in both MZ and DZ twin pairs because they are environmental factors that make siblings in a family more similar to one another. Non-shared environmental influences (E), which include measurement error, are set to not correlate in either MZ or

DZ twin pairs by definition. We also assumed equal means and variances within pairs and across zygosity. The latter assumptions were supported with regard to twin pair (i.e., means and variances in alcohol consumption could be collapsed across twin 1 and twin 2 without a decrement in fit, $\chi^2(8)=14.52$, $p=.069$), but not for zygosity, $\chi^2(8)=16.02$, $p=.042$, though the difference for zygosity was statistically significant at the $p=.05$ (but not $p=.01$) threshold; hence, we do not interpret our data as strongly violating the equal means and variances assumptions.

The full genetic model is displayed in the supplement (Figure S7). To test moderation by age and educational attainment, standardized measures of twins' age and education were allowed to moderate the paths on their A, C, and E variances, as well as the mean (i.e., the phenotypic effect). Age was included as a family-level moderator (i.e., the mean age for each twin pair at which they provided data) because twins were essentially the same age at assessment ($r=.998$). Only a single linear effect of age was estimated in the genetic model because phenotypic analysis revealed similar effect sizes across two slopes estimated in that model, and to aid in model convergence. Additionally, because educational attainment differed within pair, we used the bivariate approach in which each twins' education was formally included in the model (Purcell, 2002; van der Sluis et al., 2012). This approach simultaneously models the genetic and environmental associations between education and alcohol while testing whether education (and age) moderate the genetic and environmental influences on alcohol. Moderation of sex was tested by estimating all parameters separately in male and female twins, and examining whether parameters in females could be equated with parameters in males (using χ^2 difference tests). For opposite-sex twin pars, twin 1 was always coded as the male twin and twin 2 was the female twin. Finally, the genetic model included fixed effects of country on the mean using a set of orthogonal codes based on the number of individuals per country available. Codes were assigned so that the intercepts reflect the mean of the group means (rather than the grand mean). Parameters were significant if they could not be removed from the model without a significantly worse fit (using χ^2 difference tests).

Results from this pooled analysis were also compared with a meta-analysis in which the model was fit separately in 9 of the individual samples that were large enough to fit the model ($n>1000$; excluding 1 study of $n>1000$ that did not converge). This included data from an additional twin sample from Finland that could not be included in the pooled analysis due to data sharing restrictions (see Supplemental Results). Thus, this approach provides a robustness check of our primary findings (with slightly different datasets) and also sheds light on the sample-level and country-level variability in heritability and moderation effects of age, sex, and education.

Transparency and Openness

We report how we determined our sample size, all data exclusions (if any), all manipulations, and all measures in the study. No hypotheses or analysis plans were preregistered. The sample size was determined by including all subjects with available data from the first wave of alcohol assessment (with one exception; see Supplemental Method) for all studies from the IGEMS consortia. There were no manipulations or data exclusions

(except when subjects participated in multiple studies; see Supplemental Method). All analyses, code, and research materials are available upon request to the corresponding author. IGEMS data are not publicly available given the variety of data agreements and regulations governing the different studies and countries. However, many of the individual studies participating in IGEMS do have ways to access their data, and many of the datasets may be accessed through National Archive of Computerized Data on Aging (NACDA).

Results

Descriptive Statistics and Preliminary Analyses

Demographic characteristics of the full sample, including country-level and sample-level demographic information, are displayed in Table 1. The average level of educational attainment (M=3.09) corresponded closely to completion of upper secondary school. Phenotypic correlations between alcohol use and age, sex, and educational attainment (see Table 2) show a modest negative correlation with age, and a strong negative correlation with lesser consumption in women; the associations with educational attainment are more varied. Table 2 also displays the intraclass correlations for MZ and DZ pairs, together and by sex, for the countries and studies in the analysis. In general, the within-twin pair MZ correlations were higher than the DZ correlations (i.e., indicating heritability), but with considerable heterogeneity by study. Supplemental Table S2 also displays means for alcohol consumption by sex, educational attainment, and age (including comparisons within each country).

Phenotypic Analyses

The best fitting model of the association of age, educational attainment, and sex on weekly alcohol consumption included a spline at age 75. Standardized regression coefficients from this model are displayed in Table 3, and main effects should be interpreted at the zero-point for all other variables (i.e., at the age spline of 75 years, the mean level of education, and for males). Results indicated that older age was associated with less alcohol consumption, but this effect was smaller for adults younger than age 75 (β= −.05) compared with adults aged 75 or older (β= −.09). Males reported drinking more alcohol than females (β= −.57) and a two-way interaction (sex * age below 75) suggested that the associations between age and alcohol use were slightly less pronounced for middle-aged females than middle-aged males (see Figure 1a). The main effects of age can be interpreted as roughly 0.3 fewer drinks per week per 1 SD increase in age (i.e., ~11 years) prior to age 75 and 0.6 fewer drinks per week per 1 SD increase in age above 75 (based on European metrics, for males at the mean for educational attainment). The main effect of sex can be interpreted as about 2.9 fewer drinks per week for females than males (at age 75 and mean educational attainment).

Additionally, higher education was associated with increased alcohol use (β= .08), corresponding to roughly 0.5 greater drinks per week per 1 SD increase in education (for males at age 75). Education also interacted with both linear effects of age (see Figure 1b for a visual depiction after dichotomizing subjects into low vs middle/high education). In this case, for individuals younger than 75, the weak negative association between age and alcohol consumption was most pronounced for individuals with lower educational attainment, with those at higher levels of education displaying null (or weakly positive)

associations with age. In contrast, for individuals older than 75, the negative association between age and alcohol consumption was more pronounced in those with middle-to-high levels of education compared to those with low education. Moreover, there was a weak but significant two-way interaction between sex and education (β= .03), suggesting the small association between higher education and increased alcohol consumption was more pronounced for females than males.

Finally, there was a weak significant three-way interaction between sex * education * age (below 75) (β= −.03). This suggests the sex * age (below 75) interaction above was only observed for those with lower to moderate educational attainment, or conversely, that the education * age (below 75) interaction was slightly weaker for females. However, sensitivity analyses (below) indicate that this interaction may be driven by effects of cohort and/or year of assessment, and was nonsignificant after excluding heavier drinkers, so we do not discuss it further.

Sensitivity analyses. First, we modified the regression model from Table 3 to include a main effect of birth cohort (i.e., whether individuals were born before or after 1931) and interaction terms between birth cohort and all other model terms except those for the age spline above 75 (because few individuals older than 75 were in the later born birth cohort; see Supplemental Results). Model results displayed in Supplemental Table S4 reveal that some of the interaction terms from the primary model (Table 3) were no longer significant after controlling for birth cohort, including sex * age (below 75), sex * education, and sex * education * age (below 75) (all of which were estimated to be very weak in magnitude in the primary analysis). Importantly, there were no significant differences in the total amount of alcohol consumed across the pre-1931 and post-1931 cohorts (β= .03). Moreover, the only significant interaction with cohort (cohort * education * age below 75) suggested that the shallower association between age and alcohol consumption in more educated adults (i.e., education * age below 75) was slightly stronger for those in the more recently born cohort (β= .03).

Similar sensitivity analyses also evaluated the role of year of data collection in these associations. Results are displayed in Supplemental Table S5. In this case, all parameters from the original model (Table 3) remained significant except for the two-way interactions between sex and age. Additional results suggested that alcohol use was considerably higher in more contemporary studies (β=.50) and this trend was slightly stronger for individuals with lower education (β= −.04) or those in late middle age (compared to early middle age; β= .11). Furthermore, a model with only main effects of age, sex, education, cohort, and year of data collection is displayed in Supplemental Table S6.

We also repeated the final regression model after excluding individuals who report abstaining from alcohol (i.e., 0 grams per week; remaining sample n=53,858 with complete data) or excluding heavier drinkers (>1.5 SD above the mean; remaining sample n=59,737 with complete data). Results are displayed in Supplemental Tables S7 and S8. Importantly, compared with our primary analysis (Table 3), all the parameters remained statistically significant and were estimated in the same direction. The only exception was the weak 3-way interaction between sex * education * age (below 75) was no longer significant in the

model excluding heavier drinkers (β= −.03 vs .00), which also did not survive correction for cohort (described above).

Genetic Analyses

Next, we examined whether the genetic and/or environmental variance on alcohol consumption varied as a function of age (Figure 2), as well as by sex or educational attainment (Figure 3). Parameter estimates and standard errors of this full model are displayed in supplemental Table S9 and model comparisons are displayed in Table 4. At the mean level of age and education, alcohol consumption was less heritable in females, a^2=.34, 95% CI [.26, .41], than males, a^2=.42, 95% CI [.38, .45], and the total genetic variance was significantly larger in males, $\chi^2(1)=9.07$, p=.003. Shared environmental influences explained a relatively larger proportion of variance in females, c^2=.12, 95% CI [.04, .18], than males, c^2=.04, 95% CI [.02, .07], but the total shared environmental variance did not differ across sex, $\chi^2(1)=1.61$, p=.204. Nonshared environmental influences explained a similar proportion of variance in females, e^2=.54, 95% CI [.52, .57], and males, e^2=.54, 95% CI [.52, .56], but the total nonshared environmental influences were larger in males, $\chi^2(1)=105.53$, p<.001. These estimates should be interpreted in the context of the moderation effects described next.

Moderation by age. Figure 2 displays moderation effects of age on quantity of alcohol consumption in female and males based on both the total variance (Figure 2a and 2b) and percent variance (i.e., heritability; Figure 2c and 2d). Supplemental Table S10 also displays model estimates for proportion of genetic and environmental influences at various ages. Moderation of genetic, shared environmental, and nonshared environmental influences by age significantly differed across sex, all $\chi^2(2)$ >11.49, p<.003. In females, higher age was associated with greater shared environmental influences, $\chi^2(2)=14.45$, p=.001, and smaller nonshared environmental influences, $\chi^2(2)=23.77$, p<.001. Heritability in females was estimated as 38% at −1 SD (~age 45), 34% at the mean (~age 56), and 25% at +2 SD (~age 77). By contrast, in males, age moderated only the genetic influences on alcohol consumption, such that genetic influences were smaller in older adults, $\chi^2(2)=39.11$, p<.001. Heritability in males was estimated as 47% at −1 SD, 42% at the mean, and 34% at +2 SD. Thus, heritability was lower in both groups with increasing age, but this was due to an increase in shared environmental variance in females and a decrease in genetic variance in males.

Moderation by educational attainment. Figure 3 displays similar curves representing moderation of genetic and environmental influences on quantity of alcohol consumption by educational attainment. Supplemental Table S11 also displays model estimates for proportion of genetic and environmental influences at various levels of education. Again, moderation of genetic, shared environmental, and nonshared environmental influences by education significantly differed across sex, $\chi^2(2)$>8.36, p<.015. For females, genetic variance was smaller in those with higher education, $\chi^2(2)=10.22$, p=.006, whereas shared environmental influences, $\chi^2(2)=10.93$, p=.004, and nonshared environmental influences were larger in those with higher education, $\chi^2(2)=6.64$, p=.036. Heritability was estimated at 41% at −1.5 SD (~ primary school or less), 35% at −0.1 SD (~high school or GED

completion), and 30% at +1.3 SD (~4-year degree). For males, nonshared environmental influences were lower in those with higher education, $\chi^2(2)=11.73$, $p=.003$. Heritability was estimated at 41% at −1.5 SD, 42% at −0.1 SD, and 43% at +1.3 SD. Thus, heritability estimates were very similar in individuals with lower education and were generally consistent for males by level of education but was lowest for females with higher educational attainment (driven by larger environmental variance).

Covariance with educational attainment. Results from this model also enable us to quantify the genetic and environmental associations between alcohol consumption and educational attainment. In females, quantity of alcohol consumption was positively correlated with educational attainment at the level of genetic influences, $r_g=.25$, $p=.002$, 95% CI [.12, .37], and shared environmental influences, $r_c=.35$, $p=.002$, 95% CI [.12, .53]. Again, these associations should be interpreted considering the moderation effects for education described above. Specifically, the genetic correlation decreased with higher levels of education and the shared environmental correlation increased with higher levels of education (see Supplemental Table S9; moderation of a12 and c12 paths).

In males, alcohol consumption was correlated with educational attainment primarily at the level of shared environmental influences, $r_c=.99$, $p<.001$, 95% CI [.93, 1.0]. Shared environmental influences explained a modest portion of variance in both educational attainment (11%) and alcohol consumption (4%), but they were estimated to be nearly identical across both measures. This shared environmental covariance between education and alcohol consumption appeared to weaken with higher levels of education (see Supplemental Table S9; negative moderation of c12 path but positive moderation of c22 path). Additionally, although nonshared environmental influences were essentially uncorrelated at the mean for age and educational attainment, $r_e=.03$, there was a trend for a more positive nonshared environmental association at low levels of education and a more negative nonshared environmental association at higher levels of education (see Supplemental Table S9, moderation of e12 path). However, this effect was small, with the estimated $r_e = -.09$ for those with the highest level of educational attainment.

Comparison with meta-analysis. Results from the meta-analysis of 9 studies were like those from the primary pooled analysis (see Supplemental Table S12 and Figures S12–S16, which include estimates for each sample including the Finnish sample that was only included in the meta-analysis). Estimates of the proportion of genetic/environmental influences explained at the mean age of 55.6 were within a few percentage points of those in the pooled analysis (Females: $a^2=.34$, 95% CI [.27, .41], $c^2=.13$, 95% CI [.07, .18], $e^2=.53$ 95% CI [.50, .56]; Males: $a^2=.40$, 95% CI [.34, .45], $c^2=.07$, 95% CI [.02, .11], $e^2=.54$, 95% CI [.50, .57]). For ACE moderation by educational attainment (Supplemental Figures S13 and S14), like the pooled analysis, genetic variance decreased with higher education while shared environmental variance increased in females. In males, there was only a weak association between higher education and less nonshared environmental influences.

For ACE moderation by age (Figures S15 and S16), genetic variance decreased with higher age while shared environmental variance was larger in females. This differed slightly from the pooled analyses in which the genetic association was nonsignificant, but

nonshared environmental influences decreased with age. In males, there was no evidence for moderation of genetic/environmental influences by age. This also differed from the pooled analysis in which genetic influences slightly decreased with age. Finally, the meta-analysis sheds light on sample-level and country-level variability in these estimates (Figure S12). Estimates were generally consistent in males, though they were near 50% in US samples (range: 48 to 50%) and about 40% in most European samples (range: 29 to 42%). In females, heritability estimates were more varied across country (e.g., 26% in Sweden, 37–40% in Denmark, 51% in Finnish, 67% in US).

Discussion

The current study sought to understand how age, educational attainment, and sex relate to alcohol consumption in middle-aged and older adults. Consistent with other large phenotypic studies (Calvo et al., 2021), cross-sectional phenotypic results indicated that quantity of alcohol consumption is largely consistent across adults in their 40s through 60s, with a slightly stronger negative association between age and alcohol use in adults over age 75. Men, and more highly educated individuals of either sex, reported more alcohol consumption, with both groups showing stronger negative associations between alcohol consumption and age after 75. Findings of lower alcohol consumption with older age are likely driven by a number of factors and may include health (e.g., change in liver function or ability to metabolize alcohol, advice from health professionals), socio-cultural and lifestyle characteristics, as well as selection and mortality (i.e., which individuals are available to participate in research studies in old age) (Geels et al., 2013; Turvey et al., 2006). Survivorship bias may play a particularly important role, as those with higher alcohol consumption are at increased risk for mortality than those with low or moderate alcohol consumption (Zhao et al., 2023), suggesting the stability of alcohol use in older adulthood may be even greater than estimated here.

We also observed that higher education was associated with greater alcohol consumption, but only modestly (e.g., β=.08). These results add to a growing body of evidence from multiple countries in which more highly educated individuals consume more alcohol (Murakami & Hashimoto, 2019; Virtanen et al., 2019), including evidence that these associations are stronger in females (Huerta & Borgonovi, 2010). Although this interaction was also observed in the current study, it was very small in magnitude (β=.03) and was nonsignificant in sensitivity analyses controlling for cohort. Our findings extend this early work by suggesting that individuals with low education may have a steadier decline in alcohol consumption across mid- to late life while those with higher education appear to drink more frequently and more steadily across mid-life before more sharply declining their alcohol consumption in older ages (see Figure 1b). It will be important to use longitudinal data to investigate this relationship further, and to compare these results with those for other measures of alcohol consumption. Unlike average alcohol consumption, binge drinking and alcohol problems are typically higher in those with less education (e.g., Crum et al., 1993), and may show different associations with age. Thus, while policy changes geared towards increasing educational attainment may not lower alcohol consumption in older adults, they still may have important impacts on other aspects of problematic alcohol use and cognitive aging outcomes (Kremen et al., 2019).

These phenotypic results were similar after excluding individuals who report currently abstaining from alcohol or who report heavier alcohol use (about 3 or more drinks per day), and after controlling for potential cohort effects. All parameters from the phenotypic model remained in the same direction even when excluding current abstainers or heavier users (with one exception for an interaction term with weak effect size in the latter model). This robustness of findings is good news for gene identification efforts as it suggests their inclusion/exclusion does not affect associations with sociodemographic factors, though it may be important to further investigate the impact of these individuals in the findings from the genetic model (Dick et al., 2011; Heath et al., 2002; Neale et al., 2006; Saunders et al., 2022) and the robustness of these results with regard to associations with other relevant cognitive or health measures. Moreover, it will be important for future work to explore how genetic influences differ between abstainers who formerly drank regularly and those who never drank regularly as they may differ on socio-demographic, health, and cognitive measures (Slayday et al., 2021). Results also indicated that interaction terms between sex and age (below 75) were nonsignificant after accounting for birth cohort. However, there was no main effect of birth cohort, and cohort only interacted with one term in the model, which suggested that increased alcohol consumption in middle-aged adults is slightly stronger in more recent birth cohorts. Thus, although individuals from the later born cohort did not appear to consume more alcohol than those in earlier born cohort, it will be important to further consider how birth cohort impacts phenotypic trends regarding sex and education, especially in midlife and in more contemporary populations (e.g., individuals born in the late 1950s to 1970s) which were not strongly represented here.

Implications for Genetic and Environmental Influences on Alcohol Use

Genetic analyses revealed that the heritability of alcohol consumption was dependent on the age, educational attainment, and sex of individuals. First, heritability in both females and males was lower in older-aged individuals than middle-aged individuals, but for different reasons. In females, this was driven by larger shared environmental variance in older adults whereas in males this was driven by smaller genetic variance in older adults. These findings highlight the importance of considering total variance rather than focusing on percent variance explained (e.g., heritability), which can alter the interpretation of changes in heritability. Nevertheless, overall heritability estimates were similar to prior analyses of quantity of alcohol consumption that included middle-aged or older adults (Dick et al., 2011; Hettema et al., 1999; Kaprio et al., 1987; Swan et al., 1990; Whitfield et al., 2004), but were generally higher than those from adolescent or young adult samples (Agrawal et al., 2011; Rhee et al., 2003). To the extent that genetic variance does indeed vary by age (as observed in males here), and differs across sex, it will be important for gene discovery efforts to factor these into association study analyses (e.g., sex-stratified association studies). Moreover, as we continue to explore gene-environment interplay for alcohol consumption, it will be important for studies to consider how measures of genetic risk for alcohol consumption derived from association studies (i.e., polygenic scores) may interact with environmental exposures differently at different ages and for different sexes.

Shared environmental influences were estimated as explaining only a small portion of variance in both males and females, consistent with the prior studies of adults described

above, but lower than estimates from adolescents or younger adults (Poelen et al., 2009; Rhee et al., 2003). Specifically, shared environmental influences explained more variance in females than males, particularly in older females (or more educated females), potentially reflecting the different factors that influence alcohol consumption in females (Huerta & Borgonovi, 2010) or other country/cohort differences in females. Additionally, studies of adolescents and young adults suggest that shared environmental influences are much larger when twins' friends were more similar in alcohol use (Poelen et al., 2009), and the correlation between an individuals' alcohol use and their peer's use is primarily explained by shared environmental influences (Dick et al., 2007). We did not measure peer or spouse use here, but it is possible that larger shared environmental influences in older females (or more educated females) may reflect more similar peer use than that for male twins. Future work should evaluate whether these factors, and other variables such as country of origin and cohabitation/social contact among twins (e.g., which may be greater in MZ pairs; Kaprio et al., 1987; Kaprio et al., 1990), also influence the moderation of genetic and environmental influences on alcohol consumption. This may be especially important for the development of interventions which target alcohol consumption in older adults, as it may help identify environmental factors that relate to lasting behavioral changes.

Next, heritability estimates were very similar in those with lower education across female and male groups. However, while heritability was generally consistent across level of education for males, it was smaller for females with higher educational attainment. This was driven by larger shared and nonshared environmental influences in females with higher educational attainment. Moreover, the meta-analysis demonstrated that heritability estimates at mean age 56 were generally consistent across samples in males (i.e., supplemental Figure S12). Greater variability in heritability estimates for females by country may be due to environmental conditions for alcohol consumption varying by country, other legislative and socio-cultural norms related to the acceptability to drink. Educational attainment may be less likely to contribute to country-level differences in heritability (e.g., given that the US had the highest mean education and heritability while Sweden had the lowest education and heritability despite the overall results suggesting heritability is lower with higher education in females).

These findings should be interpreted in light of theoretical models of gene-by-environment interplay (Boardman et al., 2013). Findings for females were most consistent with the diathesis stress model which suggest heritability of negative health outcomes is greatest in most adverse environments (in this case, low educational attainment) and, conversely, that genetic differences are attenuated in low-risk environments. The magnitude of heritability differences in lower versus more highly educated females was not as drastic as the moderation by age (i.e., Figure 2c vs 3c), but results add to a growing body of research suggesting similar trends observed for moderation of financial strain on heritability of self-rated health in many of these same individuals (Finkel et al., 2022). These findings also highlight the importance of educational attainment as a potential modifiable risk factor for later health outcomes, but it will be important for future studies to investigate which facets of educational attainment drive gene-by-environment interactions (e.g., cognitive ability versus non-cognitive facets such as income and financial strain).

Finally, educational attainment also demonstrated different patterns of covariance with alcohol consumption across sex. In females, educational attainment was associated with alcohol consumption due to moderate genetic (r_g=.25) and shared environmental (r_c=.35) correlations, but in males this association was explained primarily by a strong shared environmental correlation (r_c=.99). These patterns of genetic and environmental covariation are consistent with recent findings suggesting at most only a weak genetic association between educational attainment and alcohol use using within-sibship genomic data (Howe et al., 2022). They are also similar to a recent Mendelian randomization study which found no evidence for causal association between educational attainment and weekly drinking habits, though education was associated with less binge drinking, a lower number of total drinks per day, and more frequent alcohol intake (Rosoff et al., 2021). Thus, while associations may be dependent on the measure of alcohol use, alcohol consumption appears to relate to level of education primarily through familial confounds (genetic and shared environmental influences), rather than causal or bi-directional associations.

Strengths and Limitations

First, this study represents the largest twin investigation into the heritability of alcohol consumption, including its association with age and educational attainment. The harmonization procedure enabled us to combine data across 14 studies of middle-aged or older adults representing five countries and three continents. However, these data are still based predominantly on non-Hispanic white individuals, reducing generalizability beyond this population. Indeed, genetic influences on alcohol consumption may differ in other racial and ethnic groups or in other countries and cultures (Saunders et al., 2022). Second, the alcohol measure relied on retrospective self-reports or interviews of recent (or typical) alcohol consumption rather than more detailed methods such as diaries (e.g., over several weeks), and/or specific measures of problematic alcohol use (e.g., based on the AUDIT or DSM criteria) which may show different associations with age, sex, and educational attainment than those observed here. Patterns of drinking were also not assessed.

Third, although a central goal was to examine age-related trends in alcohol consumption and its impact on genetic and environmental variance, it is important to remember that these are cross-sectional data which may show different trends than estimates based on longitudinal data (Stephenson et al., 2024). It will be important to investigate these trends with the longitudinal data available from some of these individual samples and to be able to disentangle cohort effects from effects of age in more detail (e.g., Drouard et al., 2023). Fourth, non-linear associations with age were only examined in the phenotypic model and not the genetic model. Phenotypic trends were similar before and after the regression spline (β= −.05 vs. −.09; and even more so sensitivity analyses) suggesting there may not be strong evidence for nonlinear moderation of age on genetic and environmental influences, but it will be important to consider non-linear approaches in the future as they may shed light on theoretical models not tested here (i.e., differential susceptibility) (Boardman et al., 2013).

Fifth, the square root transformation resulted in a measure of alcohol consumption with acceptable distributional characteristics (skew and kurtosis < 1), but there was some evidence for non-normality of residuals in our final phenotypic model (Supplemental Figure

S9), suggesting it may be important to compare these results with those based on alternate approaches (e.g., bootstrap resampling or Poisson regression) in the future (Neal & Simons, 2007). Finally, results are limited by the basic assumptions of the twin model. For example, the genetic and environmental influences contributing to alcohol consumption likely reflect the contributions of many (hundreds or thousands of) independent genetic polymorphisms or environmental factors. Additionally, we could not estimate both shared environmental and nonadditive genetic influences in the same model. Although twin correlations were consistent with an additive-only model, the additive genetic influences identified here should be interpreted as reflecting all genetic influences (including dominance, epistasis) and potentially include gene-environment interactions.

Concluding Remarks

This study sheds light on the genetic and environmental influences on alcohol consumption in middle-aged and older adults. Heritability of alcohol consumption in middle-aged and older adults was moderate (about 30–45%) and affected by multiple factors such as age, sex, and educational attainment. It will be important to further unpack which specific aspects of age and educational attainment (including unmeasured variables such as health, peer use, and sibling closeness) account for the moderation of genetic and environmental influences, as these have important implications for gene-discovery efforts and intervention development. Moreover, our findings were generally consistent across country and cohort, but it will also be important to evaluate whether historical and social factors explain heterogeneity across the samples and age-groups studied here as we seek to apply these trends to younger generations who experience different socio-political landscapes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Public Health Significance:

Prior genetic studies of alcohol use have focused on adolescent and adult samples despite the fact that it is common in older adults and linked to poor health and aging outcomes. This study demonstrates that genetic and environmental influences on alcohol consumption in middle-aged and older adults vary based on age, sex, and educational attainment.

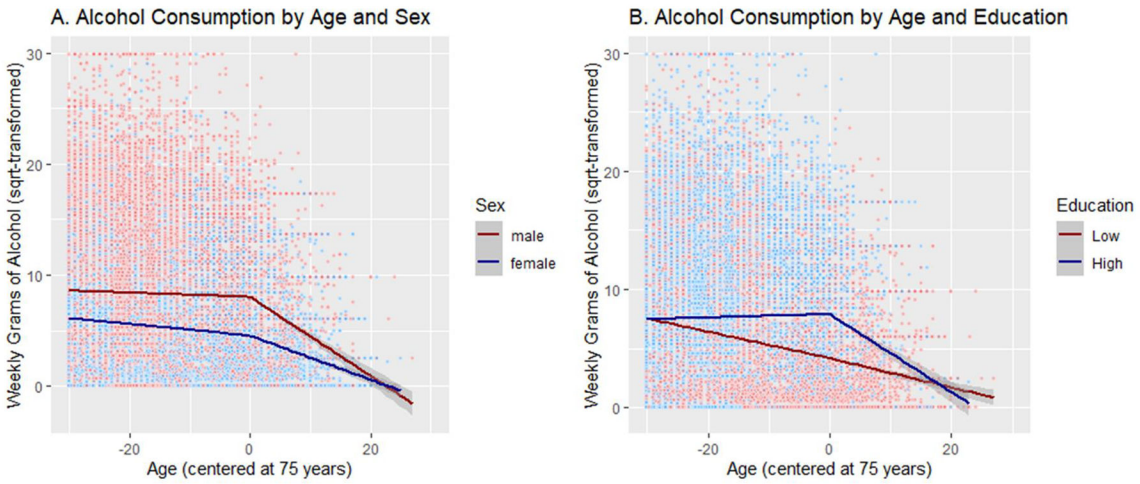

Figure 1:

Scatterplots depicting the interactions between age and sex (A) and age and educational attainment (B) from the phenotypic analysis. Plots are for data visualization purposes, as these estimates do not control for other study variables (e.g., panel A does not control for educational attainment). Moreover, the educational attainment variable used in the actual analyses were based on continuous scores, but were dichotomized here for data visualization (Low=completion of lower secondary school or less [e.g., grades 7–9], n=24,652; High=completion of upper secondary school [e.g., grades 10–12] or more, n=39,488). Grey shading reflects 95% confidence intervals.

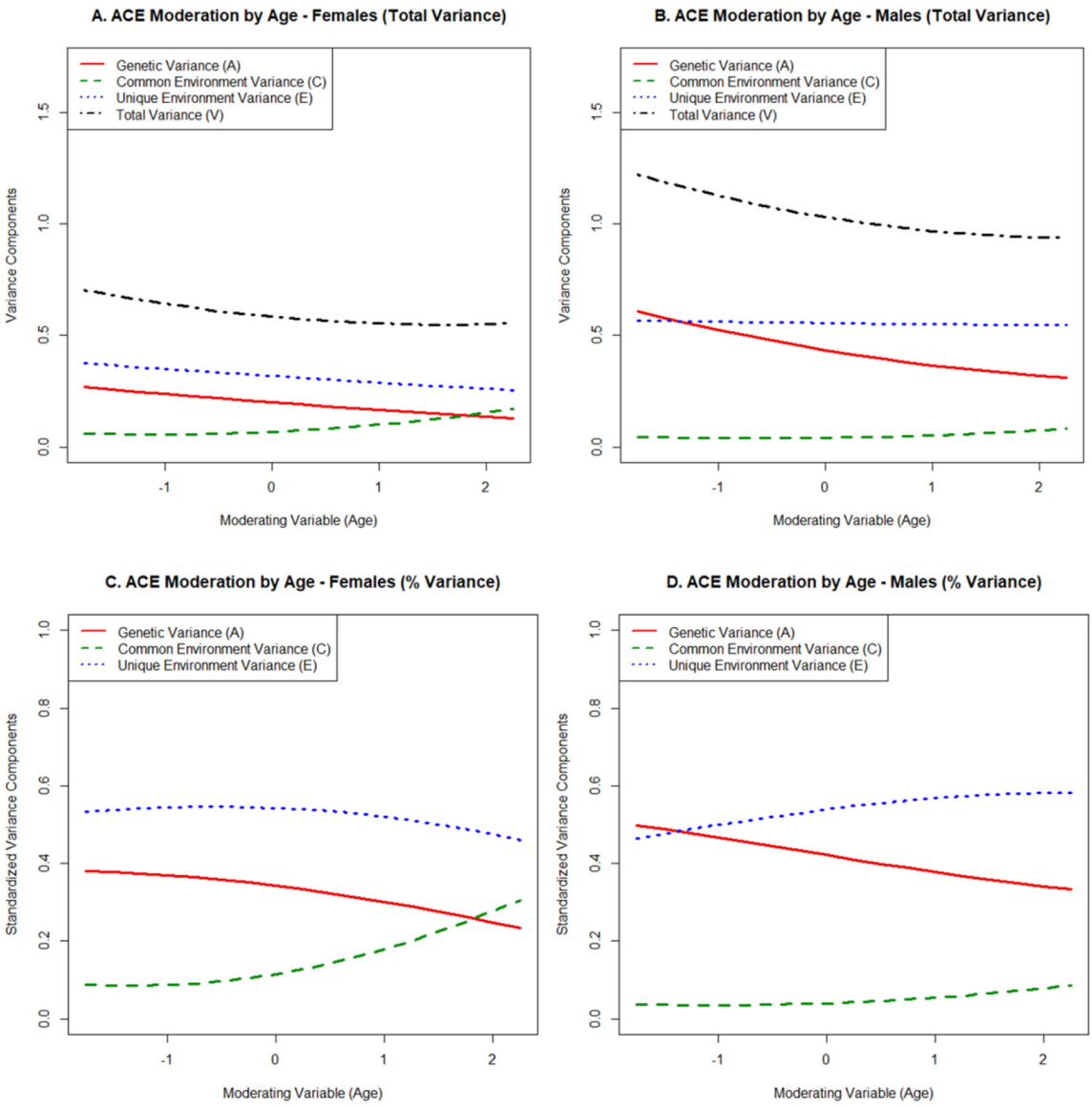

Figure 2:

Moderation of the genetic (A), shared environmental (C), and nonshared environmental (E) influences on weekly alcohol consumption by age. The total variance (V) is also displayed (top 2 panels; standardized prior to analyses). The moderating variable (age) is displayed after being standardized, with the mean representing age 56.1 years. Associations with age are based on cross-sectional rather than longitudinal data. All estimates also assume individuals are at the mean level of education and should be interpreted in light of moderation effects for education (e.g., from Figure 3).

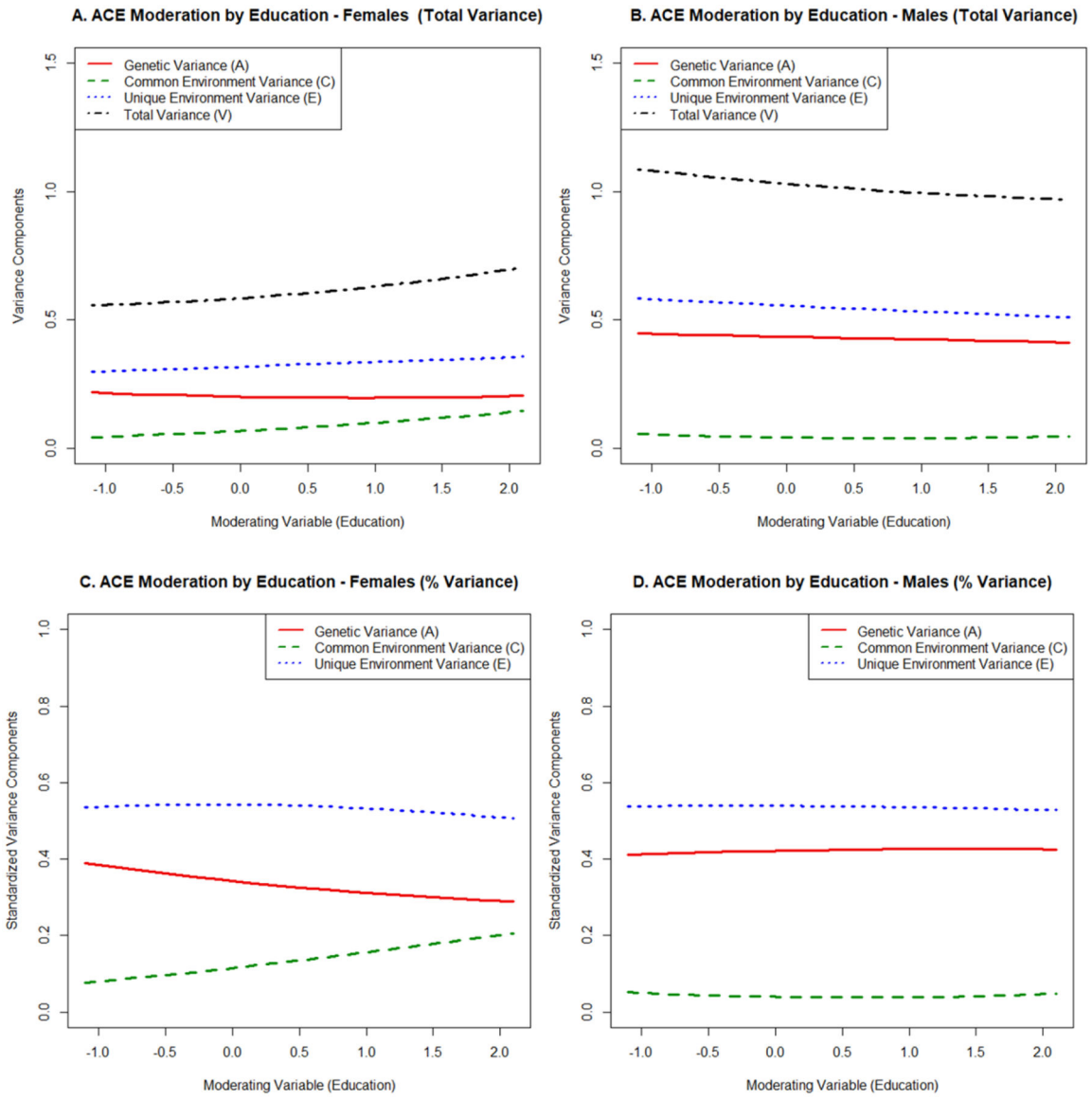

Figure 3:

Moderation of the genetic (A), shared environmental (C), and nonshared environmental (E) influences on weekly alcohol consumption by educational attainment. The total variance (V) is also displayed (top 2 panels; standardized prior to analysis). The moderating variable (educational attainment) is displayed after being standardized, with the mean corresponded closely to completion of upper secondary school (grades 10–12 or equivalent). These estimates assume individuals are at the mean age and should be interpreted in light of moderation effects for age (e.g., from Figure 2).

Table 1:

Demographic Characteristics of the Sample

Variable	Weekly Grams of Ethanol Consumed				Abstain	Sex (Prop.	Age				Educational Attainment			
	N	Mean	SD	Range		Female)	Mean	SD	Range	Cohort	N	Mean	SD	Range
Full Sample	72371	81.62	113.29	[0, 7156]	0.13	0.42	55.57	10.89	[40, 102]	0.67	64140	3.09	1.41	[1, 6]
By Country														
Australia	2528	71.28	109.91	[0, 1400]	0.26	0.68	63.65	8.93	[50, 91]	0.65	2469	3.38	1.08	[1, 6]
Denmark	19008	85.88	101.74	[0, 1464]	0.09	0.54	62.13	11.98	[40, 102]	0.74	17326	3.35	1.36	[1, 6]
Sweden	33659	71.72	104.71	[0, 7156]	0.11	0.51	55.40	9.15	[40, 97.9]	0.89	33481	2.67	1.39	[1, 6]
USA	17176	97.81	137.38	[0, 2870]	0.21	0.06	47.47	6.54	[40, 86.7]	0.15	10864	3.88	1.15	[1, 6]
By Study														
OATS	598	56.79	88.02	[0, 630]	0.20	0.65	71.23	5.44	[65.1, 90.1]	0.83	598	3.51	1.20	[1, 6]
OVER50	1930	75.77	115.51	[0, 1400]	0.28	0.68	61.30	8.49	[50, 91]	0.59	1871	3.33	1.03	[1, 5]
LSADT	4685	59.99	85.28	[0, 788]	0.21	0.59	77.74	5.67	[70, 102]	0.00	4616	2.55	1.18	[1, 6]
MADT	4307	102.53	118.15	[0, 1464]	0.07	0.49	56.89	6.33	[46, 68]	0.96	4297	3.21	1.17	[1, 6]
MIDT	10016	90.82	98.91	[0, 936]	0.04	0.53	57.08	9.41	[40, 80]	1.00	8413	3.87	1.30	[1, 6]
GENDER	1190	19.88	43.29	[0, 556]	0.23	0.50	74.43	4.28	[68.8, 88.7]	0.00	1190	1.60	1.07	[1, 6]
HARMONY	939	30.04	99.32	[0, 2472]	0.32	0.52	78.09	6.71	[65, 95]	0.06	788	1.59	0.96	[1, 5]
OCTOTWIN	659	12.93	59.64	[0, 1305]	0.68	0.66	83.47	3.09	[79.4, 97.9]	0.00	658	1.34	0.78	[1, 5]
SALT	29686	78.20	99.00	[0, 2459]	0.09	0.51	53.11	5.75	[41, 74]	1.00	29660	2.81	1.37	[1, 6]
SATSA	1185	27.27	212.68	[0, 7156]	0.08	0.49	60.16	11.12	[40, 92]	0.29	1185	1.76	1.13	[1, 5]
MIDUS	1190	39.69	88.07	[0, 980]	0.41	0.54	55.27	10.41	[40, 84]	0.92	1188	3.77	1.10	[1, 6]
MTSADA	675	73.44	167.05	[0, 1659]	0.45	0.60	60.21	9.01	[40, 86.7]	0.37	671	3.63	1.03	[1, 6]
NAS-NRC	14020	104.62	133.55	[0, 1330]	0.16	0.00	45.42	3.86	[40, 56]	0.00	7714	3.88	1.19	[1, 6]
VETSA	1291	90.15	178.14	[0, 2870]	0.34	0.00	55.94	2.43	[51.1, 60.7]	1.00	1291	4.09	0.93	[2, 6]
FTC*	10037	100.36	173.97	[0, 2091]	0.13	0.54	59.47	3.75	[53.0, 67.5]	0.95	9505	2.06	1.05	[1, 5]

Note: Weekly alcohol consumption is displayed in grams of ethanol consumed per week, but data were analyzed after a square root transformation and after extreme observations >4 SD above the mean (after transformation) were winsorized to 4 SD. A standard drink contains about 10–14 grams of ethanol, so the overall mean (M=81.62) corresponds to about 6–7 standard drinks per week. See Supplemental Table S1 for additional descriptive statistics, including year of assessment, year of birth, and *n* per education bin. Abstain= the proportion of the sample currently abstaining from alcohol. Cohort= the proportion of the sample born in or after 1931 (i.e., in the later born cohort). Australian Studies: OATS=Older Australian Twins Study, OVER50=Australian Over 50 study; Danish Studies: LSADT=Longitudinal Study of Aging Danish Twins, MIDT/MADT=Middle Age Danish Twin Studies; Swedish Studies: GENDER=Ageing in Women and Men, HARMONY=Study of Dementia in Swedish Twins, OCTO-Twin=Octogenarian Twins, SALT=Screening Across the Lifespan Twin Study, SATSA=Swedish Adoption/Twin Study on Aging; USA Studies: NAS-NRC=National Academy of

Sciences-National Research Council. MIDUS=Midlife in the United States, VETSA=Vietnam Era Twin Study of Aging; Finnish Study: FTC=Finnish Twin Cohort (* this sample was only included in the supplementary meta-analysis).

Table 2:

Phenotypic and Intraclass Correlations for Weekly Alcohol Consumption

		Phenotypic Correlations with:			Intraclass Correlations by Sex and Zygosity						
Sample	**N**	**Age**	**Education**	**Sex**	**MZ All**	**DZ All**	**MZ Male**	**MZ Female**	**DZ Male**	**DZ Female**	**DZ Opp Sex**
Full Sample	72371	**−0.01**	**0.10**	**−0.56**	**0.52**	**0.29**	**0.49**	**0.49**	**0.29**	**0.34**	**0.26**
By Country											
Australia	2528	**−0.01**	**0.13**	**−0.55**	**0.61**	**0.30**	**0.66**	**0.56**	**0.30**	**0.39**	**0.21**
Denmark	19008	**0.01**	**0.14**	**−0.59**	**0.50**	**0.25**	**0.42**	**0.45**	**0.18**	**0.29**	**0.20**
Sweden	33659	**−0.02**	0.10	**−0.55**	**0.53**	**0.29**	**0.48**	**0.49**	**0.28**	**0.35**	**0.26**
USA	17176	**0.00**	0.01	**−0.40**	**0.50**	**0.32**	**0.49**	**0.48**	**0.30**	**0.33**	**0.15**
By Study											
GENDER	1190	−0.01	**0.20**	**−0.41**	NA	**0.21**	NA	NA	NA	NA	**0.21**
HARMONY	939	**−0.02**	0.09	**−0.46**	**0.54**	0.19	0.58	**0.51**	0.16	0.31	0.14
LSADT	4685	**−0.04**	**0.25**	**−0.55**	**0.44**	**0.30**	**0.29**	**0.44**	0.16	**0.27**	**0.55**
MADT	4307	**−0.01**	**0.23**	**−0.69**	**0.51**	**0.20**	**0.45**	**0.44**	0.08	**0.25**	**0.18**
MIDT	10016	**0.02**	**0.06**	**−0.57**	**0.50**	**0.24**	**0.43**	**0.45**	**0.21**	**0.27**	**0.19**
MIDUS	1190	**−0.01**	0.02	**−0.31**	**0.56**	0.12	**0.43**	**0.75**	**−0.01**	**0.26**	0.15
MTSADA	675	−0.01	0.13	**−0.52**	**0.36**	**0.44**	**0.34**	**0.35**	**0.41**	**0.39**	NA
NASNRC	14020	0.00	0.01		**0.49**	**0.31**	**0.49**	NA	**0.31**	NA	NA
OATS	598	−0.02	0.10	**−0.43**	**0.70**	**0.37**	**0.68**	**0.68**	0.02	**0.53**	0.33
OCTOTWIN	659	−0.02	**0.26**	**−0.23**	**0.63**	**0.28**	**0.63**	**0.64**	0.04	**0.45**	NA
OVER50	1930	−0.01	**0.14**	**−0.59**	**0.55**	**0.26**	**0.64**	**0.49**	0.36	**0.32**	0.16
SALT	29686	**−0.02**	**0.10**	**−0.58**	**0.51**	**0.24**	**0.43**	**0.46**	**0.23**	**0.31**	**0.20**
SATSA	1185	**−0.01**	**0.12**	**−0.28**	**0.35**	**0.36**	**0.23**	**0.55**	**0.23**	**0.46**	NA
VETSA	1291	−0.01	−0.10		**0.48**	**0.22**	**0.48**	NA	**0.22**	NA	NA
FTC*	10037	0.01	0.08	−0.66	**0.54**	**0.32**	**0.42**	**0.55**	**0.21**	**0.29**	NA

Note: Columns 6–12 display the intraclass correlations for quantity of alcohol consumed in past week among monozygotic (MZ) and dizygotic (DZ) twin pairs overall and by sex, unadjusted for age, educational attainment, and sex effects. Significant associations are displayed in bold ($p < .01$). Australian Studies: OATS =Older Australian Twins Study, OVER50=Australian Over 50 study; Danish Studies: LSADT=Longitudinal Study of Aging Danish Twins, MIDT/MADT=Middle Age Danish Twin Studies; Swedish Studies: GENDER=Ageing in Women and Men, HARMONY = Study of Dementia in Swedish Twins, OCTO-Twin=Octogenarian Twins, SALT=Screening Across the Lifespan Twin Study, SATSA =Swedish Adoption/Twin Study on Aging; USA Studies: NAS-NRC=National Academy of Sciences-National Research Council, MIDUS=Midlife in the United States, VETSA=Vietnam Era Twin Study of Aging; Finnish Study: FTC=Finnish Twin Cohort (* this sample was only included in the supplementary meta-analysis).

Table 3:

Phenotypic Model of Weekly Alcohol Consumption Predicted by Age, Sex, and Educational Attainment

Independent Variable	*β*	*SE*	*p*	95% CI
(Intercept)	0.12	0.11	3.26E-01	[−.09, .33]
Age (Below 75)	−0.05	0.01	2.99E-11	[−.07, −.04]
Age (Above 75)	−0.09	0.01	4.70E-26	[−.10, −.07]
Sex	−0.57	0.01	0.00E+00 *	[−.58, −.55]
Education	0.08	0.01	1.90E-46	[.07, .09]
Sex * Age (Below 75)	0.02	0.01	8.87E-03	[.01, .04]
Sex * Age (Above 75)	0.02	0.01	7.62E-02	[.00, .04]
Education * Age (Below 75)	0.09	0.01	1.73E-56	[.08, .10]
Education * Age (Above 75)	−0.03	0.01	2.67E-04	[−.04, −.01]
Sex * Education	0.03	0.01	2.26E-04	[.01, .04]
Sex * Education * Age (Below 75)	−0.03	0.01	2.49E-04	[−.05, −.01]
Sex * Education * Age (Above 75)	−0.01	0.01	1.95E-01	[−.03, .01]

Note: This hierarchical linear model included a regression spline at age 75, informed by the best-fitting model with a single spline (see Supplemental Table S3 for competing models). All effect sizes are standardized with respect to all variables, and sex was treated as a factor (with the estimate displaying the effect for females). To account for the nesting of data (e.g., within samples), this model included random intercepts for country, sample, and family.

* indicates that the exact *p* value for the main effect of sex could not be computed.

Table 4:

Model Comparisons for Genetic and Environmental Moderation by Sex, Educational Attainment, and Age

Model	ep	neg 2LL	df	AIC	diff −2LL	diff df	p
Full Model	**68**	**235844.98**	**94556**	**46733**	-	-	-
Equate ACE Variance Across Sex (Sex Limitation)							
Equate A Variances Across Sex	68	235854.05	94557	46740	9.07	1	0.003
Equate C Variances Across Sex	68	235846.59	94557	46733	1.61	1	0.204
Equate E Variances Across Sex	68	235950.51	94557	46837	105.53	1	< .001
Test ACE Moderation for Education							
No A Moderation of Education for Females	66	235855.2	94558	46739	10.22	2	0.006
No C Moderation of Education for Females	66	235855.91	94558	46740	10.93	2	0.004
No E Moderation of Education for Females	66	235851.62	94558	46736	6.64	2	0.036
No A Moderation of Education for Males	66	235845.36	94558	46729	0.38	2	0.827
No C Moderation of Education for Males	66	235850.21	94558	46734	5.23	2	0.073
No E Moderation of Education for Males	66	235856.71	94558	46741	11.73	2	0.003
Equate ACE Moderation of Education Across Sex							
Equate A Moderation of Education Across Sex	66	235853.34	94558	46737	8.36	2	0.015
Equate C Moderation of Education Across Sex	66	235857.53	94558	46742	12.55	2	0.002
Equate E Moderation of Education Across Sex	66	235855.15	94558	46739	10.17	2	0.006
Test ACE Moderation for Age							
No A Moderation by Age for Females	66	235846.57	94558	46731	1.59	2	0.452
No C Moderation by Age for Females	66	235859.43	94558	46743	14.45	2	0.001
No E Moderation by Age for Females	66	235868.75	94558	46753	23.77	2	<.001
No A Moderation by Age for Males	66	235884.09	94558	46768	39.11	2	<.001
No C Moderation by Age for Males	66	235846.81	94558	46731	1.83	2	0.401
No E Moderation by Age for Males	66	235849.24	94558	46733	4.26	2	0.119
Equate ACE Moderation of Age Across Sex							
Equate A Moderation of Age Across Sex	66	235856.69	94558	46741	11.71	2	0.003
Equate C Moderation of Age Across Sex	66	235856.47	94558	46740	11.49	2	0.003
Equate E Moderation of Age Across Sex	66	235860.28	94558	46744	15.3	2	<.001

Note: The model described in the results is listed in bold font, which included moderation effects of age and educational attainment on the genetic (A), shared environmental (C), and nonshared environmental (E) influences on alcohol consumption separately for each sex. Some tests have 2 df because educational attainment and age are allowed to moderate the genetic/environmental paths from educational attainment to alcohol consumption as well as the unique genetic/environmental influences on alcohol consumption.