Explaining Individual Differences in Alcohol Intake in Adults: Evidence for Genetic and Cultural Transmission?

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ABSTRACT. **Objective:** The current study aimed to describe what proportion of variation in adult alcohol intake is attributable to genetic differences among individuals and what proportion to differences in environmental experiences individuals have been exposed to. Effects of age, gender, spousal resemblance, and cultural transmission of alcohol intake from parents to offspring were taken into account. **Method:** In a twin-family design, the effects of genetic and cultural transmission and shared and nonshared environment on alcohol intake were estimated with genetic structural equation models. Data originated from adult twins, their siblings, parents (n = 12,587), and spouses (n = 429) registered with the population-based Netherlands Twin Register (63.5% female; ages 18–97 years). **Results:** Alcohol intake (grams per day) was higher among men than women and increased with age. Broad-sense heritability estimates were similar across sex and age (53%). Spousal resemblance was observed (r = .39) but did not significantly affect the heritability estimates. No effects of cultural transmission were detected. In total, 23% of the variation in alcohol intake was explained by additive genetic effects, 30% by dominant (nonadditive) gene action, and 47% by environmental effects that were not shared among family members. **Conclusions:** Individual differences in adult alcohol intake are explained by genetic and individual-specific environmental effects. The same genes are expressed in males and females and in younger and older participants. A substantial part of the heritability of alcohol intake is attributable to nonadditive gene action. Effects of cultural transmission that have been reported in adolescence are not present in adulthood. (*J. Stud. Alcohol Drugs, 75,* 201–210, 2014)

ALCOHOL USE CONVEYS RISK for medical conditions (e.g., cancer) (Dawson, 2011; Rehm et al., 2003) as well as psychosocial problems (e.g., alcohol use disorders) (National Institute on Alcohol Abuse and Alcoholism [NIAAA], 2000). Despite these well-known risks, the vast majority of people consume alcohol, at least occasionally. In Western countries, the prevalence of current drinking ranges between 72% and 96% in men and between 59% and 95% in women (World Health Organization, 2011). Given the high prevalence of alcohol use in combination with the aforementioned risks, understanding the causes of individual differences in alcohol intake is important.

Twin studies can provide insight into the role of genetic and environmental factors in the variation in alcohol intake. Genetic and environmental effects on the phenotypic trait variation can be separated by the comparison of resemblance among monozygotic (MZ) twin pairs (assumed to share all their genetic material) and dizygotic (DZ) twin pairs (who share about half of their segregating genes) (Van Dongen et al., 2012). For alcohol intake, heritability estimates range

around 50% for adults (Dick et al., 2009, 2011; Hansell et al., 2008; Kendler et al., 2008; McGue, 1999), with somewhat lower heritabilities of 30% to 40% for young adults around 20–30 years of age (Dick et al., 2011; Geels et al., 2012; Hansell et al., 2008). The remainder of the variation is mostly attributable to environmental effects not shared among family members, although some studies have reported evidence for additional effects of the shared environment for young adults (Geels et al., 2012; Kendler et al., 2008). These findings leave some issues unresolved, including (a) whether parent–offspring resemblance in alcohol intake levels is fully explained by genetic resemblance, or whether parents' drinking has additional effects on the drinking behavior of their adult offspring that are not accounted for by the transmission of their genes (i.e., effects of cultural transmission); (b) whether nonrandom mating has an effect on heritability; (c) to what degree the heritability of alcohol intake reflects effects of additive versus nonadditive gene action; and (d) whether genetic and environmental influences on alcohol intake are equally important for men and women and with increasing age.

Parents can affect the drinking level of their offspring by the genes they transmit and/or the environment they provide for their children. The effect of parental alcohol intake on the alcohol intake level of their children that is not accounted for by the genes they transmit is referred to as *cultural transmission*. Effects of cultural transmission are suggested by social learning theory (Bandura and McClelland, 1977), which views parents as the role models for their children

who, consequently, when they see their parents drink, imitate that behavior (Quigley and Collins, 1999). Effects of cultural transmission can also result from parenting associated with parental drinking, such as being less inclined to enforce strict drinking rules, which is known to affect adolescent drinking (Engels and Bot, 2006). Although effects of cultural transmission have been reported for alcohol initiation in mid-adolescence (Koopmans and Boomsma, 1996), results on whether effects of cultural transmission extend into adulthood are unclear. Some studies did not detect effects of cultural transmission (Baker et al., 2012; Kendler et al., 1994; Slutske et al., 2008), whereas others did (Maes et al., 1999; Newlin et al., 2000). The latter were conducted in very large samples ($N > 14,000$), suggesting that a proper test of cultural transmission of alcohol intake requires large sample sizes, which the current study provides ($N \sim 12,500$).

Heritability estimates of alcohol intake may change if spouses choose their partner (partly) based on their drinking behavior (i.e., phenotypic assortment), for instance because they enjoy the social activity of drinking together. When there is no phenotypic assortment, the genetic similarity for DZ twins and full siblings is, on average, 50% (resulting from the possibility of inheriting zero, one, or two parental alleles in common with the respective probabilities of 25%, 50%, and 25%). Phenotypic assortment induces genetic similarity among spouses, which increases the probability of inheriting alleles in common for DZ twins and full siblings, resulting in an increased genetic similarity among these individuals. As the genetic similarity among MZ twins is not increased by the genetic similarity among spouses (because they already share ~100% of their genetic material), the DZ twin similarity will be increased relative to the MZ twin similarity, resulting in an underestimation of genetic effects and an overestimation of environmental effects that are shared among twins and siblings. Not all spousal resemblance is attributable to phenotypic assortment. Alternatively, assortative mating may be explained by mechanisms such as social homogamy and cohabitation effects, which have no effect on heritability estimates. Social homogamy results from choosing a spouse from the same stratum. Cohabitation effects refer to the process whereby spouses become more alike the longer they are together (Van Grootheest et al., 2008). Spousal resemblance for alcohol use has been attributed to all three mechanisms, but mostly to phenotypic assortment (Agrawal et al., 2006; Grant et al., 2007; Leonard and Eiden, 2007; Maes et al., 1998, for alcohol use disorder; Agrawal et al., 2006, for regular alcohol use; Ask et al., 2012; Reynolds et al., 2006, for alcohol intake levels) and cohabitation effects (Grant et al., 2007), especially during the first years of the relationship (Ask et al., 2012; Leonard and Eiden, 2007). Effects of social homogamy have also been detected (Maes et al., 1998; Reynolds et al., 2006), but those were smaller than the effects of phenotypic assortment (Maes et al., 1998).

Genetic resemblance among relatives can result from additive and nonadditive gene action. If the joint genetic effect is equal to the sum of the separate effects, gene action is additive. To the extent that allelic effects interact within loci (dominance) or between loci (epistasis), nonadditive gene action is present. Nonadditive effects have been reported for genes involved in alcohol metabolism (Chen et al., 1999; Kuo et al., 2008), but their effects in explaining differences in alcohol intake levels have not previously been explored.

The large sex differences in alcohol use (Holmila and Raitasalo, 2005) can have their origin in cultural factors and biological factors. Cultural factors influencing drinking behavior include gender roles. Biological factors include sex differences in the breakdown and elimination of alcohol. Women have higher amounts of body fat and lower amounts of body water, as well as lower activity of the enzyme alcohol dehydrogenase in the stomach, which has been hypothesized to reduce alcohol intake among women through lower "first pass" alcohol metabolism and higher peak blood alcohol levels (Wilsnack et al., 2000). The current study examines whether the sources of variation in alcohol intake, including that of additive versus nonadditive gene action, differ by sex. The latter were detected for frequency of alcohol use (Maes et al., 1999) but have not been studied yet for alcohol intake levels.

A means to estimate the magnitude of additive and nonadditive genetic effects and environmental effects (individual-specific or shared within the offspring generation) is provided by an extended twin design that includes data from parents and siblings of twins. This design can take effects of nonrandom assortment into account and allows for the estimation of cultural transmission effects. The current study examined the genetic architecture of alcohol intake by analyzing data from 13,016 twins, siblings, parents, and spouses registered with the Netherlands Twin Register (NTR) (Boomsma et al., 2002) and estimated the amount of variation that can be ascribed to additive and nonadditive genetic effects, to shared and nonshared environment, cultural transmission, and to assortative mating, allowing for differences in the importance of genetic and environmental effects across sex and age.

Method

Participants

Data on alcohol intake originated from adult twins and their family members registered with the NTR who participated in the longitudinal survey research on health, personality, and lifestyle (Boomsma et al., 2002; Willemsen et al., 2013). For this study, we analyzed data on alcohol intake collected in the eighth NTR survey, which was sent out between 2009 and 2011. The study protocol was approved by the Central Ethics Committee on Research Involving Human

TABLE 1. Number of participants as a function of zygosity and sex of the twins within the family

	Number of participants					
Zygosity by sex group	Twins[a] n (%)	Brothers n	Sisters n	Fathers n	Mothers n	Spouses n
MZM	945 (57%)	65	84	172	212	81
DZM	541 (50%)	40	61	143	159	35
MZF	2,413 (65%)	121	180	355	467	157
DZF	1,229 (57%)	75	115	203	288	69
DOS	1,491 (44%)	71	154	314	390	87
Families without twins[b]	0	176	350	663	1,110	0
Total	6,619	548	944	1,850	2,626	429

Notes: MZM = monozygotic males; DZM = dizygotic males; MZF = monozygotic females; DZF = dizygotic females, DOS = dizygotic opposite-sex twins. [a]Percentage reflects what proportion of twins is part of a complete twin pair; [b]families in which twins did not participate.

Subjects of the VU University Medical Center, Amsterdam (no. 2008/244). Data on ever alcohol use were available for 16,661 individuals, which is nearly everyone who filled out Survey 8 (total $N_{SURVEY\ 8}$ = 16,861; see Willemsen et al., 2013). Data were excluded for 376 individuals who never drank alcohol. For 1,869 individuals, data on alcohol intake were missing, and for 700 individuals, alcohol intake data were considered invalid and therefore excluded (number of drinks per day or week > 100, > 4 *SD* above the mean, and/or inconsistent with data on drinking frequency). For 1,129 individuals, data were excluded because they were not biological relatives of the twins (n = 67); zygosity was unknown (n = 24); they were part of a triplet/quadruplet (n = 89); they were a sibling in a family with more than two same-sex siblings (n = 21; a maximum of two same-sex siblings was included per family); or they had a relation to the twin other than co-twin, sibling, or parent (n = 499, including 240 spouses for whom data on the length of their relationship were not available). Hence, data on alcohol intake were analyzed for 13,016 individuals: 6,619 twins, 1,492 siblings, and 4,476 parents, as well as data on alcohol intake and relationship duration from 429 spouses of twins. Overall, 63.5% were female (year of birth: 1911–1992). Table 1 gives an overview of the number of individuals (including the percentage of twins belonging to complete twin pairs) as a function of sex and zygosity of the twins within the family. For same-sex twins, zygosity was based on DNA polymorphisms (51%) or survey questions on physical similarity. Agreement between DNA zygosity and zygosity based on survey questions was greater than 96% (Willemsen et al., 2013) (sensitivity > 96%; specificity > 94%).

Measures

Respondents were asked to report the number of glasses of beer, wine, and distilled spirits they drank for each day of the week, keeping the past 12 months in mind. In the analyses described below, alcohol intake was analyzed as the average amount (in grams) of alcohol consumed per day.

This was calculated by summing the number of drinks per week, multiplied by 14 g of alcohol per glass, divided by 7 (days in the week).

Statistical analyses

All analyses were performed by fitting structural equation models to raw data based on maximum likelihood estimation, using the statistical software package Mx (version 1.54) (Neale et al., 2006) in five zygosity-by-sex family groups. First, a saturated model was specified containing 16 sex-specific familial correlations to describe the resemblance in alcohol intake among family members (Model 1). There were five twin correlations (for MZ males and females [MZM and MZF], DZ males and females [DZM and DZF], and DZ opposite sex [DOS]), three twin–sibling and three sibling–sibling correlations (male–male, male–female, female–female), four parent–offspring correlations (father–son, mother–son, father–daughter, mother–daughter), and one spouse correlation. Separate means and variances for men and women were estimated, and sex differences were tested for significance. Age was included as a covariate, for males and females.

Differences in the familial correlations were tested in submodels: (a) presence of a special twin environment was examined by testing whether DZ twin–sibling and sibling–sibling correlations were equal; (b) sex differences in the correlations were tested by equating correlations across sex of DZ twin/sibling pairs, parent–offspring pairs, and MZ twins; (c) age effects on the correlations were tested by equating correlations for parent–offspring pairs to those for offspring (DZ twin/sibling) pairs (when correlations for both pairs can be constrained to be equal, there are no age effects on the correlations, indicating that genetic effects underlying differences in alcohol intake are similar across age); (d) spousal resemblance for alcohol intake was tested for significance, and in case of significant spousal resemblance, we explored whether this could be explained by cohabitation effects by estimating the correlation between the absolute
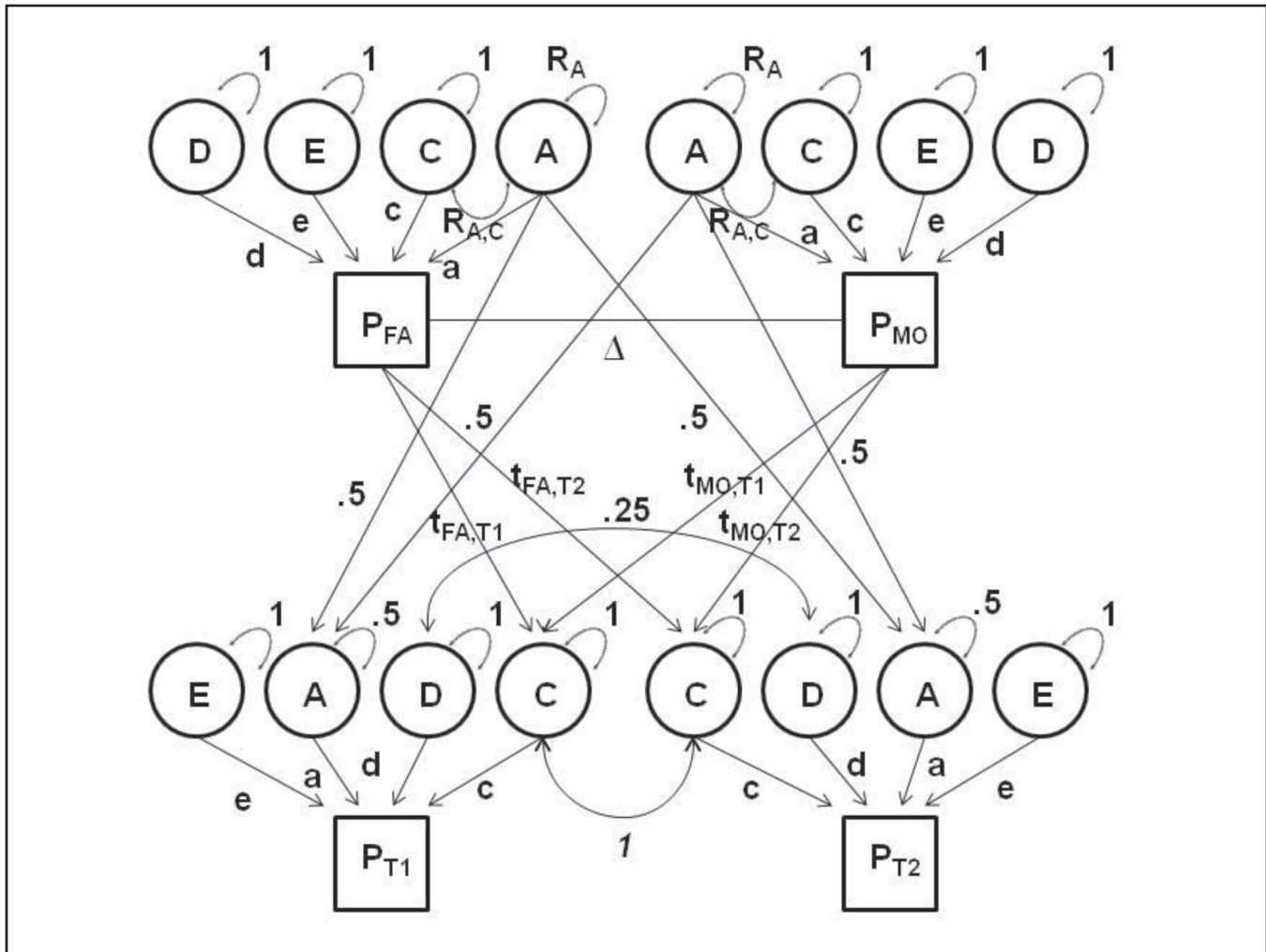
FIGURE 1. Path diagram for variance decomposition with extended twin-family design (ETFD) (shown for DZ twin/sibling pair with parents); P_{FA}, P_{MO}, P_{T1}, P_{T2} = phenotype of father, mother, twin/sibling 1, twin/sibling 2; A = additive genetic factor with variance R_A (differs from 1 in the case of phenotypic assortment); D = nonadditive genetic factor; C = shared-environmental factor with variance R_C (differs from 1 in the case of cultural [shared-environmental] transmission); E = individual-specific environmental factor a,c,d,e = path loadings (d-paths estimated in ACDE model; set to zero in ACE model with cultural [shared-environmental] transmission); $t_{FA,T1}$, $t_{FA,t2}$, $t_{MO,T1}$, $t_{MO,T2}$ = cultural (shared-environmental) transmission paths from father to twin/sibling 1, father to twin/sibling 2, mother to twin/sibling 1, mother to twin/sibling 2 (estimated in ACE model with cultural [shared-environmental] transmission; set to zero in ACDE model); $R_{A,C}$ = covariation between A and C (differs from 1 in the case of cultural [shared-environmental] transmission); Δ = path representing correlations between the latent factors induced by phenotypic assortment; Note: Possible sex differences in the a, c, d, e, and t loadings have been omitted from the figure for reasons of clarity in the presentation.

difference in alcohol intake for spouses and the duration of their relationship in months (performed on data of 429 twin–spouse pairs and 903 parental pairs with data on relationship duration). If living together influences resemblance between spouses, this correlation will be negative (i.e., smaller differences between spouses who have been together longer). The results informed the second step, in which genetic models were fitted to the data.

Genetic factor models were specified in which alcohol intake among family members was regressed on latent factors that represented the genetic and environmental contributions to alcohol intake (Neale et al., 1994) (Figure 1). The alcohol intake of fathers and mothers (depicted as P_{FA} and

P_{MO}) and their offspring (depicted as P_{T1} and P_{T2} for Twin 1 and Twin 2; siblings not depicted in the figure for clarity of presentation) was regressed on additive genetic factors (with factor loadings a), common environmental factors shared by twins and siblings (factor loadings c), and nonshared environmental factors (factor loadings e). The model is identified because family members share their genetic and environmental backgrounds to different degrees. MZ twin pairs share all of their genetic material, and DZ twin pairs/ siblings, parents, and offspring share half of their segregating genes (A factors were modeled to correlate .5 for DZ twin, sibling, and parent–offspring pairs). Shared environmental influences (C factors) were completely correlated (*r*

= 1) among the offspring generation. Spousal resemblance was modeled to run via a Δ-path that represents the correlations between the latent genetic and environmental factors influencing the phenotypes of the parents that result from phenotypic assortment. The resulting increase in the additive genetic variance (R_A) is modeled through the additive genetic variance component. The variance of the additive genetic factor in the offspring generation (.5) reflects the segregation variance that emerges because of recombination. This within-family additive genetic variance emerges because parents pass their alleles, not genotypes, giving rise to new genetic variance in the offspring generation (Keller et al., 2009).

Cultural transmission was tested in the ACE model (Additive genetics, Common environment, and unique Environment) and is indicated by significant path loadings from parents to offspring ($t_{FA,T1}$, $t_{MO,T1}$, $t_{FA,T2}$, $t_{MO,T2}$). Because parents also contribute to variation in the offspring by transmission of their genes, cultural transmission refers to the nongenetic transmission of alcohol intake. The presence of both genetic and shared environmental transmission gives rise to a correlation between the additive genetic and shared environmental factors (passive gene–environment [A-C] correlation: $r_{A,C}$). The remainder of the variance was estimated as nonshared environmental effects, E.

In the ACDE model, cultural transmission paths were constrained at zero (for model identification reasons), and dominant gene action (D) was estimated (reflecting nonadditive genetic influences; see Keller et al., 2010) (with factor loadings d). In MZ twin pairs, D factors are completely correlated ($r = 1$), and in DZ twins and sibling pairs, D factors are correlated as .25. Parent–offspring pairs share no genetic factors reflecting dominance.

If the saturated model indicated sex differences in the correlation structure, sex-specific factor loadings were estimated. If not, these were constrained to be equal across sex. Qualitative sex differences in environmental factors (shared by the offspring generation) were examined by testing whether the correlation between the shared environmental factors ($r_{C,OS}$) was less than 1 in opposite-sex offspring pairs. Along the same lines, qualitative sex differences in the genetic factors were tested by estimating the genetic correlation in opposite-sex family members (Vink et al., 2012). Model comparisons were based on the likelihood ratio test with a significance level of .01 (Bentler and Bonett, 1980).

Results

Table 2 shows the untransformed values of alcohol intake in grams per day for male and female twins, siblings, and parents. After taking the natural logarithm of alcohol intake levels, alcohol intake levels were close to normally distributed (skewness = -0.5, kurtosis = -0.5 vs. skewness = 2.2, kurtosis = 7.5 for untransformed levels). Subsequent analy-

TABLE 2. Descriptive statistics for males and females, separately for twins, and their siblings, parents and spouses[a]

Variable	Males		Females	
	M (SD)	n	M (SD)	n
Twins		2,076		4,543
Alcohol intake[b]	19.3 (18.7)		10.4 (11.7)	
Alcohol intake/kg[c]	0.25 (0.24)		0.16 (0.18)	
Age	33.0 (14.6)		33.0 (14.0)	
Siblings		548		944
Alcohol intake	20.2 (19.0)		10.1 (11.5)	
Alcohol intake/kg	0.24 (0.23)		0.15 (0.17)	
Age	38.7 (14.3)		36.9 (13.4)	
Parents		1,850		2,626
Alcohol intake	21.5 (18.9)		12.4 (12.4)	
Alcohol intake/kg	0.26 (0.23)		0.18 (0.18)	
Age	56.6 (8.1)		53.4 (8.2)	
Spouses		273		156
Alcohol intake	17.9 (15.9)		9.9 (12.0)	
Alcohol intake/kg	0.22 (0.20)		0.15 (0.17)	
Age	45.3 (12.0)		40.4 (12.7)	

[a]Data of twins, siblings, and parents were analyzed to estimate heritability and/or cultural effects by genetic models; data of spouses of twins were analyzed to study the mechanism of spousal resemblance for alcohol use; [b]untransformed values for alcohol intake in grams/day; [c]untransformed values for alcohol intake in grams/day divided by weight in kilograms.

ses were performed on log-transformed values of alcohol intake. Model fit statistics for these models are presented in Table 3.

Alcohol intake was higher among men than women and increased with age similarly for both sexes ($\beta = .11$; $r = .09$). Inspection of the scatter plots did not indicate an influence of outlier values. Variances were comparable across sex. Thus, in later models, two means were specified (males, females) along with one variance and one age regression (equal across sex).

Familial correlations as estimated in the saturated model are shown in Figure 2. DZ twin correlations were not systematically larger than sibling correlations, indicating that genetic and environmental effects make similar contributions to alcohol intake for DZ twins and siblings, rendering a special twin environment unlikely. There were no significant sex differences in the correlations. MZ correlations (r_{MZM} = .53, r_{MZF} = .54, and $r_{OVERALL}$ = .53) and DZ twin/sibling correlations ($r_{DZM/SIB}$ = .22; $r_{DZF/SIB}$ = .24; $r_{DOS/SIB}$ = .16; $r_{OVERALL}$ = .20) were equal across sex, as were all parent–offspring correlations ($r_{FATHER–SON}$ = .17; $r_{MOTHER–DAUGHTER}$ = .20; $r_{FATHER–DAUGHTER}$ = .14, $r_{MOTHER–SON}$ = .12; $r_{OVERALL}$ = .16). Thus, the same genetic risk factors seem to influence alcohol intake in males and females. Parent–offspring pairs, who differ more in age than offspring pairs (DZ twin/siblings), showed a similar resemblance in alcohol intake levels as the offspring pairs ($r_{OVERALL}$ = .18), indicating that similar genes are expressed across age. Alcohol intake correlated significantly between spouses ($r = .39$). Spousal resemblance did not increase with increasing relationship length (at $\alpha = .01$), but the correlation was close to significant, $\chi^2(1) = 6.51$, $p = .011$ ($r = -.07$, 95% CI [-.13, -.02]), suggesting that cohabitation effects may explain some

TABLE 3. Model fit statistics for genetic models of alcohol intake

Variable	NP	-2LL	df	vs.	$\Delta\chi^2$	Δdf	p	Explanation
1. Saturated model	22	37,932.49	12565					
2a. No sex differences mean alcohol intake	21	38,504.99	12566	1	572.50	1	<.001	Higher alcohol intake levels for males
2b. No age regression mean alcohol intake	20	38,040.05	12567	1	107.55	1	<.001	Alcohol intake increases with age
2c. No sex differences age regression mean alcohol intake	21	37,934.75	12566	1	2.26	1	.133	Association with age equal across sex
2d. No sex differences phenotypic variance	21	37,933.02	12566	1	0.53	1	.467	Phenotypic variance equal across sex
2e. Saturated model with constraints[a]	20	37,935.26	12567	1	2.77	2	.250	
3. DZ twin = sibling correlations	14	37,942.50	12573	2e	7.24	6	.299	Equal correlations for twin and sibling pairs; no special twin environment
4a. Male = female = opposite sex DZ twin/sibling correlation	12	37,945.85	12575	2e	10.59	8	.226	No sex difference in twin-/sibling correlations
4b. Male = female = opposite sex parent–offspring correlation	17	37,940.37	12570	2e	5.12	3	.164	No sex difference in parent-offspring correlation
4c. Male = female MZ correlation	19	37,935.30	12568	2e	0.039	1	.844	No sex difference in MZ correlations
5. DZ twin = sibling = parent–offspring correlation	8	37,953.02	12579	2e	17.76	12	.123	No age difference correlation first-degree relatives
6. Spouse correlation = 0	19	38,093.36	12568	2e	158.11	1	<.001	Significant spousal resemblance
7. ACE model with cultural transmission	11	38,002.28	12576	2e	67.02	9	<.001	ACE model with cultural transmission does not fit data
7a. Drop cultural transmission	10	38,002.28	12577	7	0	1	1	No cultural transmission effects
8. ACDE model	10	37,950.59	12577	2e	15.33	10	.121	ACDE model fits data
9. ADE model (drop C to 0)	9	37,950.59	12578	8	0	1	1	No shared environmental effects
10. ACE model (drop D to 0)	9	38,040.09	12578	8	89.51	1	<.001	Nonadditive genetic effects important

Notes: NP = number of parameters in statistical model; -2LL = -2 log likelihood, fit function, for model with df degrees of freedom; $\Delta\chi^2$ = model fit statistic: difference in -2LL of two nested models is distributed as chi-square with $df = \Delta df$, the difference in NP between the models; p value was regarded significant when < .01. [a]Constraints included two means (males/females) and one variance and beta for the age regression (equal across sex).

of the spousal resemblance for alcohol intake, although large effects are unlikely. In the genetic model, spousal resemblance for alcohol intake was therefore modeled as resulting from phenotypic assortment.

Given that the correlations did not differ across sex, path loadings and cultural transmission paths were constrained to be equal across sex. Cultural transmission of alcohol intake was not significant. A model that included genetic dominance gave a better fit to the data than the model with cultural transmission. In the final model, 23.4% of the variance in alcohol intake was explained by additive genetic effects (95% CI [19.1%, 27.5%]), 29.9% by dominant gene action (reflecting nonadditive genetic effects) (95% CI [23.9%, 36.0%]), and 46.7% by nonshared individual-specific environmental effects (95% CI [43.1%, 50.7%]). Quantifying the effect of spousal resemblance on the heritability indicated that 0.1% of the broad-sense heritability could be ascribed to effects of phenotypic assortment.

Discussion

We examined the genetic architecture of alcohol intake in a large sample of adult twins, siblings, and parents. Specifically, we tested (a) whether there were effects of cultural transmission (no), (b) if heritability estimates were affected by nonrandom mating (very little), (c) if nonadditive gene action was of importance (yes), and (d) if the importance of genetic and environmental risk factors differed across sex and age (no).

Effects of cultural transmission or the shared environment on adult alcohol intake were not found. Spouses resemble each other in their alcohol intake levels ($r = .39$). Large cohabitation effects were not detected, however, suggesting that most of the spousal resemblance is attributable to effects of phenotypic assortment. However, taking into account phenotypic assortment as the process underlying spousal resemblance did not significantly affect the heritability estimates. Alcohol intake is higher among men than women and increases with age, suggesting that increased welfare standards and healthy life years among the Dutch elderly lead to more drinking (Geels et al., 2013). Previous research has pointed at a lower heritability of alcohol intake among women (Dick et al., 2009; McGue, 1999), but the current study shows that the genetic architecture underlying differences in alcohol intake is similar across sex (broad-sense $h^2 = 53\%$) and age. The absence of sex differences in heritability in this study and other recent studies (Dick et al., 2009, 2011; Geels et al., 2012; Sartor et al., 2010) may be explained by the growing convergence in male and female alcohol use due to earlier initiation and augmented alcohol intake by women (Geels et al., 2013; Keyes et al., 2011), which has been associated with changes in gender roles (Keyes et al., 2011; Rahav et
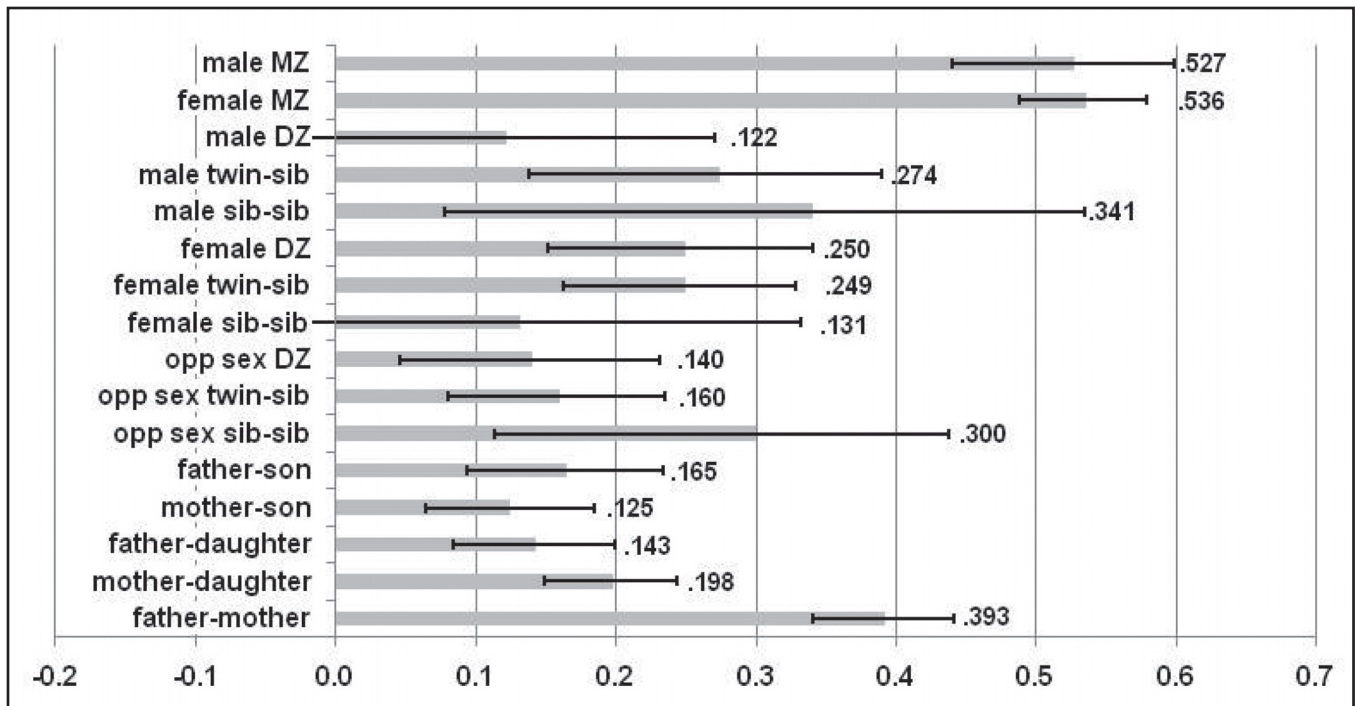
FIGURE 2. Familial correlations for alcohol intake (with 95% confidence intervals); MZ = monozygotic; DZ = dizygotic; sib = sibling; opp = opposite.

al., 2006). Interestingly, a substantial part of the underlying genetics of alcohol intake is due to genes that act in a nonadditive manner (30%).

Genes have been hypothesized to affect variation in alcohol use via two broad pathways (Kendler et al., 2012). Genetic effects specific to alcohol intake can reflect those on alcohol metabolism (Hurley and Edenberg, 2011; van Beek et al., 2010) and sensitivity to the response to alcohol (Heath et al., 1999; Schuckit, 2009). A second pathway through which genes can have their effect on alcohol intake is by personality characteristics such as impulsivity, disinhibition, sensation seeking (Schuckit, 2009), and externalizing psychopathology (Kendler et al., 2011; Krueger, 1999), which are traits that influence risk for substance use in general (Kendler et al., 2012). Interestingly, for both alcohol metabolism (Chen et al., 1999; Kuo et al., 2008) and personality (e.g., novelty seeking) (Keller et al., 2005), nonadditive genetic effects have been detected.

It is tempting to speculate about the underlying mechanism generating the nonadditive genetic effects. Nonadditive genetic effects were modeled to result from dominant gene action (D). As indicated in a simulation study by Keller et al. (2010), variance captured by D can reflect effects due to dominant gene action as well as epistasis and Gene × Age interaction (a different expression of genes across age). Gene × Age interaction effects are unlikely given that the offspring and parent–offspring correlations were not significantly different from each other. The nonadditive genetic effects therefore more likely result from dominant gene action and/or epistasis. Given sufficient power, nonadditivity due to dominance and that due to additive-by-additive epistasis can be disentangled by model fitting (Heath et al., 1984). Dominant gene action requires that individuals share both alleles at a locus. This is the case for MZ twin pairs and for one quarter of the DZ twin/sibling pairs, but not for parent–offspring pairs, because parents transmit only one of their alleles to their children. Effects of dominant gene action are thus suggested when DZ twin/sibling correlations are higher than those among parent–offspring pairs. Epistasis represents the effects of interacting risk alleles from different loci, which is equal for all first-degree relatives. In the presence of additive-by-additive epistasis, all first-degree relatives share 25% of the nonadditive genetic variation. For higher-order epistasis, this correlation is less than .25 (Posthuma et al., 2003). Higher-order epistasis would thus predict that model fit improves when the correlation among nonadditive genetic factors in the offspring correlation is lowered (Keller et al., 2005). When exploring possible effects of dominance and epistasis for the current study, clear effects were not seen, which may be due to low power to detect these effects for a moderately heritable trait such as alcohol intake. Parent–offspring correlations and offspring correlations were similar, suggesting additive-by-additive epistasis rather than dominance. Evidence for higher-order epistasis could not detected. That is, assuming that the correlation between nonadditive genetic factors for DZ twins and siblings was .20 or .15 did not improve model

fit. Regardless of the precise mechanism, however, a clear effect of nonadditive gene action is evident. Future gene-finding studies may benefit when taking this nonadditivity into account, for instance, by using prediction models that involve complex interactions among genetic markers, such as random forests (Molinaro et al., 2011).

There was no evidence for cultural transmission of alcohol intake. Previously, two other large studies found effects of cultural transmission of alcohol use (Maes et al., 1999; Newlin et al., 2000). Differences in results may be explained by differences in methodology, at least for those with Newlin et al. (2000). In the latter, similarity between probands and their biological parents was estimated as effects resulting from both cultural and genetic transmission. For probands from adoptive or step families, however, any (reported) similarity in the proband's alcohol use behavior and that of his or her parents was a direct measure of cultural transmission. Thus, to the extent rater effects were present, these were incorporated in the estimate of cultural transmission. However, this cannot explain differences in results from the study by Maes et al. (1999), because in that study, similar to ours, self-report data on alcohol use were analyzed.

The absence of effects of cultural transmission of alcohol intake does not mean that parents cannot influence the drinking behavior of their children, but their influence may be limited to childhood and adolescence. For younger adolescents, cultural transmission of alcohol use patterns from parents to children seems to play a role, although peer influences on adolescent alcohol use are generally greater than parental influences (Allen et al., 2003; Hopfer et al., 2003). For adolescents ages 15–16 years, it might explain up to 10% of the variation in alcohol use (Koopmans and Boomsma, 1996). In addition, parents can influence adolescent drinking through certain styles of parenting that may be unrelated to the parents' own drinking behavior (Petrie et al., 2007; Smit et al., 2008; van den Eijnden et al., 2011).

We examined one aspect of gene–environment correlation, namely passive gene–environment (A-C) correlation. There are other means by which genes and environment can work together to affect alcohol use that were not explicitly modeled in this study, for instance, through active or reactive gene–environment (A-E) correlation or gene–environment (A × E or A × C) interaction. Reactive *gene–environment correlation* refers to the phenomenon whereby individuals are reacted to based on their genetic propensity. A "wild" adolescent (e.g., because of his or her externalizing personality traits) may be sent to a sports club by his or her parents, which gives him or her ample time to drink after the games. Active gene–environment correlation arises when an individual creates or seeks out an environment based on his or her genotype. A person with a genetic predisposition to use alcohol may seek out friends who use alcohol (Plomin et al., 1977). When not modeled, a positive correlation between genes and the nonshared environment will increase the ad-

ditive genetic variance (Purcell, 2002). *Gene–environment interaction* refers to a different reaction to different environments for individuals with the same genotype or to different reactions to the same environment depending on the genotype. When not explicitly incorporated in the model, positive interactions will be estimated as variance due to nonshared environment, whereas positive A × C interactions will be estimated as variance due to additive genetic effects (Purcell, 2002). The additive genetic effects underlying alcohol intake detected in this study thus may partly reflect processes of active or reactive gene–environment correlation or A × C interaction. Similarly, the nonshared individual-specific environmental effects may include effects of A × E interaction.

It might be argued that including the group of not-current drinkers in the study has introduced bias if these include individuals who have stopped drinking because of their propensity to indulge in heavy drinking (which is likely to be reflective of a high genetic risk for heavy drinking). This seems unlikely. For 1,426 of 1,714 not-current drinkers, data were available on their reasons for not drinking, and only 0.8% stopped drinking because of problems with alcohol use. Most individuals reported they did not drink any alcohol because they did not like the taste (52.9%), because they did not feel the need to drink (16.3%), or for health reasons (17.5%). Some drank only at special occasions (2.1%). Other reasons for not drinking were (unpleasant) side effects (3.3%), principles or reasons of belief (2.0%), fear of alcohol problems because of what occurred in their surroundings (2.4%), or other reasons (2.6%).

To conclude, the current study showed that 53% of the variation in adult alcohol intake is explained by genes, taking the significant spousal resemblance into account. Effects of cultural transmission were not significant. The substantive amount of nonadditive genetic variation representing effects of dominant gene action and/or epistasis presents an important venue for further study.

Acknowledgments

References

Agrawal, A., Heath, A. C., Grant, J. D., Pergadia, M. L., Statham, D. J., Bucholz, K. K., . . . Madden, P. A. F. (2006). Assortative mating for cigarette smoking and for alcohol consumption in female Australian twins and their spouses. *Behavior Genetics, 36,* 553–566.

Allen, M., Donohue, W. A., Griffin, A., Ryan, D., & Turner, M. M. M. (2003). Comparing the influence of parents and peers on the choice to use drugs: A meta-analytic summary of the literature. *Criminal Justice and Behavior, 30,* 163–186.

Ask, H., Rognmo, K., Torvik, F. A., Røysamb, E., & Tambs, K. (2012). Non-random mating and convergence over time for alcohol consumption, smoking, and exercise: The Nord-Trøndelag Health Study. *Behavior Genetics, 42,* 354–365.

Baker, J. H., Maes, H. H., & Kendler, K. S. (2012). Shared environmental contributions to substance use. *Behavior Genetics, 42,* 345–353.

Bandura, A., & McClelland, D. C. (1977). *Social learning theory.* Englewood Cliffs, NJ: Prentice-Hall.

Bentler, P. M., & Bonett, D. G. (1980). Significance tests and goodness of fit in the analysis of covariance structures. *Psychological Bulletin, 88,* 588–606.

Boomsma, D. I., Vink, J. M., van Beijsterveldt, T.C. E. M., de Geus, E. J. C., Beem, A. L., Mulder, E. J. C. M., . . . van Baal, G. C. M. (2002). Netherlands Twin Register: A focus on longitudinal research. *Twin Research, 5,* 401–406.

Chen, C. C., Lu, R. B., Chen, Y. C., Wang, M. F., Chang, Y. C., Li, T. K., & Yin, S. J. (1999). Interaction between the functional polymorphisms of the alcohol-metabolism genes in protection against alcoholism. *American Journal of Human Genetics, 65,* 795–807.

Dawson, D. A. (2011). Defining risk drinking. *Alcohol Research & Health, 34,* 144–156.

Dick, D. M., Meyers, J. L., Rose, R. J., Kaprio, J., & Kendler, K. S. (2011). Measures of current alcohol consumption and problems: Two independent twin studies suggest a complex genetic architecture. *Alcoholism: Clinical and Experimental Research, 35,* 2152–2161.

Dick, D. M., Prescott, C. A., & McGue, M. (2009). The genetics of substance use and substance use disorders. In Y.-K. Kim (Ed.), *Handbook of behavior genetics* (pp. 433–453). New York, NY: Springer.

Engels, R. C. M. E., & Bot, S. M. (2006). Social influences on adolescent substance use: Insights into how parents and peers affect adolescent's smoking and drinking behavior. In D. de Ridder & J. de Wit (Eds.), *New perspectives on health behavior: Self-regulation in health behavior* (pp. 71–95). New York, NY: Wiley.

Geels, L. M., Bartels, M., van Beijsterveldt, T. C., Willemsen, G., van der Aa, N., Boomsma, D. I., & Vink, J. M. (2012). Trends in adolescent alcohol use: Effects of age, sex and cohort on prevalence and heritability. *Addiction, 107,* 518–527.

Geels, L. M., Vink, J. M., van Beek, J. H. D. A., Bartels, M., Willemsen, G., & Boomsma, D. I. (2013). Increases in alcohol consumption in women and elderly groups: Evidence from an epidemiological study. *BMC Public Health, 13,* 207.

Grant, J. D., Heath, A. C., Bucholz, K. K., Madden, P. A. F., Agrawal, A., Statham, D. J., & Martin, N. G. (2007). Spousal concordance for alcohol dependence: Evidence for assortative mating or spousal interaction effects? *Alcoholism: Clinical and Experimental Research, 31,* 717–728.

Hansell, N. K., Agrawal, A., Whitfield, J. B., Morley, K. I., Zhu, G., Lind, P. A., . . . Martin, N. G. (2008). Long-term stability and heritability of telephone interview measures of alcohol consumption and dependence. *Twin Research and Human Genetics, 11,* 287–305.

Heath, A. C., Madden, P. A. F., Bucholz, K. K., Dinwiddie, S. H., Slutske, W. S., Bierut, L. J., . . . Martin, N. G. (1999). Genetic differences in alcohol sensitivity and the inheritance of alcoholism risk. *Psychological Medicine, 29,* 1069–1081.

Heath, A. C., Martin, N. G., Eaves, L. J., & Loesch, D. (1984). Evidence for polygenic epistatic interactions in man? *Genetics, 106,* 719–727.

Holmila, M., & Raitasalo, K. (2005). Gender differences in drinking: Why do they still exist? *Addiction, 100,* 1763–1769.

Hopfer, C. J., Crowley, T. J., & Hewitt, J. K. (2003). Review of twin and adoption studies of adolescent substance use. *Journal of the American Academy of Child and Adolescent Psychiatry, 42,* 710–719.

Hurley, T. D., & Edenberg, H. J. (2011). Genes encoding enzymes involved in ethanol metabolism. *Alcohol Research: Current Reviews, 34,* 339–344.

Keller, M. C., Coventry, W. L., Heath, A. C., & Martin, N. G. (2005). Widespread evidence for non-additive genetic variation in Cloninger's and Eysenck's personality dimensions using a twin plus sibling design. *Behavior Genetics, 35,* 707–721.

Keller, M. C., Medland, S. E., & Duncan, L. E. (2010). Are extended twin family designs worth the trouble? A comparison of the bias, precision, and accuracy of parameters estimated in four twin family models. *Behavior Genetics, 40,* 377–393.

Keller, M. C., Medland, S. E., Duncan, L. E., Hatemi, P. K., Neale, M. C., Maes, H. H. M., & Eaves, L. J. (2009). Modeling extended twin family data I: Description of the Cascade model. *Twin Research and Human Genetics, 12,* 8–18.

Kendler, K. S., Aggen, S. H., Knudsen, G. P., Røysamb, E., Neale, M. C., & Reichborn-Kjennerud, T. (2011). The structure of genetic and environmental risk factors for syndromal and subsyndromal common DSM-IV axis I and all axis II disorders. *American Journal of Psychiatry, 168,* 29–39.

Kendler, K. S., Chen, X., Dick, D. M., Maes, H. H., Gillespie, N. A., Neale, M. C., & Riley, B. (2012). Recent advances in the genetic epidemiology and molecular genetics of substance use disorders. *Nature Neuroscience, 15,* 181–189.

Kendler, K. S., Neale, M. C., Heath, A. C., Kessler, R. C., & Eaves, L. J. (1994). A twin-family study of alcoholism in women. *American Journal of Psychiatry, 151,* 707–715.

Kendler, K. S., Schmitt, E., Aggen, S. H., & Prescott, C. A. (2008). Genetic and environmental influences on alcohol, caffeine, cannabis, and nicotine use from early adolescence to middle adulthood. *Archives of General Psychiatry, 65,* 674–682.

Keyes, K. M., Li, G., & Hasin, D. S. (2011). Birth cohort effects and gender differences in alcohol epidemiology: A review and synthesis. *Alcoholism: Clinical and Experimental Research, 35,* 2101–2112.

Koopmans, J. R., & Boomsma, D. I. (1996). Familial resemblances in alcohol use: Genetic or cultural transmission? *Journal of Studies on Alcohol, 57,* 19–28.

Krueger, R. F. (1999). The structure of common mental disorders. *Archives of General Psychiatry, 56,* 921–926.

Kuo, P.-H., Kalsi, G., Prescott, C. A., Hodgkinson, C. A., Goldman, D., Van Den Oord, E. J., . . . Riley, B. P. (2008). Association of ADH and ALDH genes with alcohol dependence in the Irish Affected Sib Pair Study of Alcohol Dependence (IASPSAD) sample. *Alcoholism: Clinical and Experimental Research, 32,* 785–795.

Leonard, K. E., & Eiden, R. D. (2007). Marital and family processes in the context of alcohol use and alcohol disorders. *Annual Review of Clinical Psychology, 3,* 285–310.

Maes, H. H. M., Neale, M. C., Kendler, K. S., Hewitt, J. K., Silberg, J. L., Foley, D. L., . . . Eaves, L. J. (1998). Assortative mating for major psychiatric diagnoses in two population-based samples. *Psychological Medicine, 28,* 1389–1401.

Maes, H. H., Neale, M. C., Martin, N. G., Heath, A. C., & Eaves, L. J. (1999). Religious attendance and frequency of alcohol use: Same genes or same environments: A bivariate extended twin kinship model. *Twin Research, 2,* 169–179.

McGue, M. (1999). Behavioral genetic models of alcoholism and drinking. In K. E. Leonard & H. T. Blane (Eds.), *Psychological theories of drinking and alcoholism* (2nd ed., pp. 372–421). New York, NY: Guilford Press.

Molinaro, A. M., Carriero, N., Bjornson, R., Hartge, P., Rothman, N., & Chatterjee, N. (2011). Power of data mining methods to detect genetic associations and interactions. *Human Heredity, 72,* 85–97.

National Institute on Alcohol Abuse and Alcoholism. (2000). Health risks and benefits of alcohol consumption. *Alcohol Research & Health, 24,* 5–11.

Neale, M. C., Boker, S. M., Xie, G., & Maes, H. H. (2006). *Mx: Statistical modeling* (7th ed.). Richmond, VA: Department of Psychiatry, VCU.

Neale, M. C., Walters, E. E., Eaves, L. J., Maes, H. H., & Kendler, K. S. (1994). Multivariate genetic analysis of twin-family data on fears: Mx models. *Behavior Genetics, 24,* 119–139.

Newlin, D. B., Miles, D. R., van den Bree, M. B. M., Gupman, A. E., & Pickens, R. W. (2000). Environmental transmission of DSM-IV substance use disorders in adoptive and step families. *Alcoholism: Clinical and Experimental Research, 24,* 1785–1794.

Petrie, J., Bunn, F., & Byrne, G. (2007). Parenting programmes for preventing tobacco, alcohol or drugs misuse in children <18: A systematic review. *Health Education Research, 22,* 177–191.

Plomin, R., DeFries, J. C., & Loehlin, J. C. (1977). Genotype-environment interaction and correlation in the analysis of human behavior. *Psychological Bulletin, 84,* 309–322.

Posthuma, D., Beem, A. L., de Geus, E. J. C., van Baal, G. C. M., von Hjelmborg, J. B., Iachine, I., & Boomsma, D. I. (2003). Theory and practice in quantitative genetics. *Twin Research, 6,* 361–376.

Purcell, S. (2002). Variance components models for gene-environment interaction in twin analysis. *Twin Research, 5,* 554–571.

Quigley, B. M., & Collins, R. L. (1999). The modeling of alcohol consumption: A meta-analytic review. *Journal of Studies on Alcohol, 60,* 90–98.

Rahav, G., Wilsnack, R., Bloomfield, K., Gmel, G., & Kuntsche, S. (2006). The influence of societal level factors on men's and women's alcohol consumption and alcohol problems. *Alcohol and Alcoholism, 41, Supplement 1,* i47–i55.

Rehm, J., Room, R., Graham, K., Monteiro, M., Gmel, G., & Sempos, C. T. (2003). The relationship of average volume of alcohol consumption and patterns of drinking to burden of disease: An overview. *Addiction, 98,* 1209–1228.

Reynolds, C. A., Barlow, T., & Pedersen, N. L. (2006). Alcohol, tobacco and caffeine use: Spouse similarity processes. *Behavior Genetics, 36,* 201–215.

Sartor, C. E., Grant, J. D., Bucholz, K. K., Madden, P. A. F., Heath, A. C., Agrawal, A., . . . Lynskey, M. T. (2010). Common genetic contributions to alcohol and cannabis use and dependence symptomatology. *Alcoholism: Clinical and Experimental Research, 34,* 545–554.

Schuckit, M. A. (2009). An overview of genetic influences in alcoholism. *Journal of Substance Abuse Treatment, 36,* S5–S14.

Slutske, W. S., D'Onofrio, B. M., Turkheimer, E., Emery, R. E., Harden, K. P., Heath, A. C., & Martin, N. G. (2008). Searching for an environmental effect of parental alcoholism on offspring alcohol use disorder: A genetically informed study of children of alcoholics. *Journal of Abnormal Psychology, 117,* 534–551.

Smit, E., Verdurmen, J., Monshouwer, K., & Smit, F. (2008). Family interventions and their effect on adolescent alcohol use in general populations; a meta-analysis of randomized controlled trials. *Drug and Alcohol Dependence, 97,* 195–206.

van Beek, J. H. D. A., Willemsen, G., de Moor, M. H. M., Hottenga, J. J., & Boomsma, D. I. (2010). Associations between ADH gene variants and alcohol phenotypes in Dutch adults. *Twin Research and Human Genetics, 13,* 30–42.

van den Eijnden, R., van de Mheen, D., Vet, R., & Vermulst, A. (2011). Alcohol-specific parenting and adolescents' alcohol-related problems: The interacting role of alcohol availability at home and parental rules. *Journal of Studies on Alcohol and Drugs, 72,* 408–417.

van Dongen, J., Slagboom, P. E., Draisma, H. H. M., Martin, N. G., & Boomsma, D. I. (2012). The continuing value of twin studies in the omics era. *Nature Reviews Genetics, 13,* 640–653.

van Grootheest, D. S., van den Berg, S. M., Cath, D. C., Willemsen, G., & Boomsma, D. I. (2008). Marital resemblance for obsessive-compulsive, anxious and depressive symptoms in a population-based sample. *Psychological Medicine, 38,* 1731–1740.

Vink, J. M., Bartels, M., van Beijsterveldt, T. C. E. M., van Dongen, J., van Beek, J. H. D. A., Distel, M. A., . . . Boomsma, D. I. (2012). Sex differences in genetic architecture of complex phenotypes? *PLoS ONE, 7*(12), e47371. Retrieved from doi:10.1371/journal.pone.0047371

Willemsen, G., Vink, J. M., Abdellaoui, A., den Braber, A., van Beek, J. H. D. A., Draisma, H. H. M., . . . Boomsma, D. I. (2013). The Adult Netherlands Twin Register: Twenty-five years of survey and biological data collection. *Twin Research and Human Genetics, 16,* 271–281.

Wilsnack, R. W., Vogeltanz, N. D., Wilsnack, S. C., & Harris, T. R. (2000). Gender differences in alcohol consumption and adverse drinking consequences: Cross-cultural patterns. *Addiction, 95,* 251–265.

World Health Organization. (2011). *Global Status Report on Alcohol and Health 2011.* Retrieved from http://www.who.int/substance_abuse/publications/global_alcohol_report/en/index.html