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Adolescent alcohol use is a risk factor for adult alcohol and drug dependence: evidence from a twin design

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ABSTRACT

Background. Early alcohol use is associated with abuse and dependence of licit and illicit substances later in life. The role of genetic and environmental factors in this association is not conclusive.

Method. In 1992, data on substance use, abuse/dependence and psychiatric disorders were collected from 8169 male twin members of the Vietnam Era Twin Registry. The interview obtained age of onset of regular drinking (one drink/month for 6 or more months). Regression analyses of twin pairs discordant for early alcohol use tested whether the association between early drinking (before age 17) and adult substance use and abuse/dependence remained after controlling for genetic factors, family environment and covariates. Twin models tested for common genetic and/or environmental influences on early drinking and adult alcohol dependence and ever use and abuse/dependence on marijuana and other drugs.

Results. Co-twin analyses suggested the association between early regular alcohol use and adult alcohol dependence, marijuana and other drug use, and marijuana and other drug abuse/dependence could not be entirely explained by common genetic and shared family environmental factors. Genetic contributions to early regular drinking were significantly correlated with those on use of marijuana ($r_A = 0{\cdot}59$), use of other drugs ($r_A = 0{\cdot}64$), alcohol dependence ($r_A = 0{\cdot}54$) and abuse/dependence of marijuana and other drugs ($r_A = 0{\cdot}63$ and $0{\cdot}66$). Small but significant unique environmental correlations (r_E range $0{\cdot}11$–$0{\cdot}22$) indicated that familial factors could not entirely explain the association between early alcohol use and later substance use, abuse and dependence.

Conclusions. Early regular drinking is associated with later alcohol dependence and use, abuse/dependence on drugs. The association is not entirely explained by genetic or shared family environmental factors. This suggests unique environmental factors contribute to transitions from early regular alcohol drinking to use, abuse and dependence on alcohol and other substances.

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INTRODUCTION

Early alcohol use in adolescence is a risk factor for adult alcohol and drug abuse/dependence. In US and European studies, there is evidence

that earlier alcohol use is associated with a greater likelihood of developing problem drinking, alcohol dependence (Grant & Dawson, 1997; DeWit *et al.* 2000; Kraus *et al.* 2000; Guo *et al.* 2001), and drug and psychiatric disorders (McGue *et al.* 2001). Longitudinal studies provide evidence that use of illicit drugs is often preceded by use of alcohol and tobacco (Kandel, 2002). While several researchers (Bucholz, 1990; Bullers *et al.* 2001; Barkley *et al.* 2004) have shown negative peer influences and childhood psychiatric disorders contribute to use of illicit drugs, it is not certain if these influences are sufficient to explain this transition without consideration of the genetic contributions to drug use, abuse and dependence.

Evidence from twin studies has established that genetic factors contribute to licit and illicit substance use, abuse and dependence (Heath *et al.* 1997; True *et al.* 1999; Kendler *et al.* 2000, 2003), and to initiation and persistence of substance use. Genetic influence has been found to range from 33% to 60% for smoking initiation (Heath & Martin, 1993; True *et al.* 1997), and from 58% to 74% for smoking persistence (Heath & Madden, 1995; True *et al.* 1997). Genetic factors account for 14–40% of the variance in initiation of alcohol and between 20% and 35% of the variance in regular use (reviewed by Hopfer *et al.* 2003). Tsuang *et al.* (1999) in a study of transitions from use to abuse/dependence, reported substantial heritabilities for ever use, more than casual use, and regular use of marijuana. Recently, Agrawal *et al.* (2005) reported that there are common genetic and environmental contributions to illicit drug use and abuse/dependence with evidence of factors specific to abuse/dependence. Kendler and colleagues (2003), studying the genetic specificity to drug use and abuse/dependence, found most of the liability to use and having problems with one drug *versus* another are due to unique environmental experiences.

From a public health standpoint, a transition of particular interest which has not been analyzed in many genetically informative samples is the transition from early use of alcohol to adult substance use problems. Grant & Dawson (1997) have demonstrated a relationship between decreasing age of onset and risk of alcohol dependence. For each year onset of drinking was delayed, a 14% reduction in risk was observed. Prescott & Kendler (1999) reported the association between early drinking and later risk for alcoholism in twins could be explained by familial (i.e. genetic and/or shared environmental) factors.

Two recent publications have elucidated the role of early marijuana use and later illicit drug problems. Lynskey and colleagues (2003) using a discordant twin paradigm in an Australian young adult twin sample, reported that transitions from early marijuana use to abuse/dependence on a variety of licit and illicit drugs were not entirely accounted for by genes or shared environment. From co-twin analyses among middle-aged members of the Virginia Twin Registry, Agrawal and colleagues (2004) were able to conclude a causal relationship between early cannabis use and later illicit drug abuse/dependence. In the same work, Agrawal *et al.* (2004) also fitted a biometrical twin model that suggests the association between early use and later drug problems could be attributed to correlated genetic and environmental factors.

We combined both approaches here to study the influence of early alcohol use on adult substance use problems. Because genetic factors make a contribution to substance initiation, regular use, abuse and dependence, it is logical to test whether early alcohol use (before age 17) is associated with later alcohol dependence and illicit drug use, abuse and dependence *after* accounting for genetic and shared environmental influences. In addition, we sought to determine whether common genetic and/or environmental vulnerability contributes to early alcohol use and adult substance use problems.

Using data from the Vietnam Era Twin (VET) Registry, we tested if an association remained between early regular drinking and adult abuse/dependence after adjusting for familial (including genetic) factors in a co-twin control design. Second, we fitted biometric models to test for genetic and environmental correlations between early regular drinking and adult alcohol dependence and between early regular drinking and adult drug use and abuse/dependence.

METHOD

Subjects and variable definitions

The VET Registry is a national registry of male–male twin pairs, both of whom served in the

military during the Vietnam Era (1965–1975). Construction of the registry (Eisen *et al*. 1987; Henderson *et al*. 1990) and method of determining zygosity have been previously reported (Eisen *et al*. 1989).

Data collection for the present analyses was conducted in 1987 and 1992. In 1987, twins were mailed a survey that included questions about their military service. In 1992, twins were administered a computerized telephone interview (CATI) in which data on substance use, abuse, and dependence and other psychiatric disorders were collected via the *Diagnostic Interview Schedule, Version III Revised* (DIS-3R; Robins *et al*. 1989). The DIS-3R is a structured interview from which DSM-III-R lifetime diagnoses may be obtained.

Experienced staff from the Institute for Survey Research (ISR) at Temple University, who were trained by senior investigators and DIS developers, conducted the telephone interviews. All twins gave verbal consent prior to being interviewed, as approved by the Institutional Review Boards at the participating universities.

Eligibility for interview in 1992 required that twins both had a Department of Defense military record, and identifying and locating information. Of 10 300 eligible individuals (5150 pairs) from the VET Registry, 8169 (79·3%) were successfully interviewed, with a pairwise response rate of 66·1% (3372 pairs). The mean age of respondents in 1992 was 44·6 years (S.D. = 2·8, range 36–55 years); 90·4% were non-Hispanic white, 4·9% African-American, 2·7% Hispanic, 2·0% 'other'; 31% were high-school graduates and 65% had some college or greater; and 92·6% were employed full-time.

Definition of early regular alcohol use

Regular alcohol use was defined as having consumed alcohol at least once a month for 6 months or more. Early use was defined as having been a regular alcohol drinker before 17 years of age. We selected the threshold of age 17 because empirically it was a deviant behavior in that only 19·4% of the members of the VET Registry were early regular drinkers. Among those who ever drank regularly, 4·4% began regular use between 5 and 14 years of age, 4·7% began at age 15 and 10·2% at age 16. In addition, many US states reduced the legal drinking age in the United States to age 18 between the 1960s and 1970s, thus many early drinkers were drinking illegally. Furthermore, drinking before age 17 is of theoretical interest in light of adult problems associated with adolescent drinking.

Reliability of onset of early regular alcohol use

A subset of 146 participants were re-interviewed by an ISR staff member who did not perform the original interview. The mean interval between interviews was 466 days (S.D. = 50·5 days, range 357–601). The reliability analyses included 103 individuals who were from pairs that were in both the baseline and reliability interview. We found good reliability for age of onset for regular drinking among lifetime regular drinkers ($r = 0{\cdot}78$, $n = 84$) and for early alcohol use classification (tetrachoric correlation 0·78, $n = 103$). For the reliability analyses, subjects who never drank regularly were included with the non-early user classification.

Primary outcome variables

We used logistic regression analyses to compute the odds of developing alcohol dependence and of ever use and lifetime DSM-III-R drug abuse and dependence on any of the following substances: marijuana, stimulants/cocaine, sedatives, opiates and hallucinogens/phencyclidine (PCP) as a function of early alcohol use. Because our focus is on early use as a predictor of later substance use problems, only respondents with drug use onsets that occurred after the onset of regular alcohol use were included in the present analyses.

Exploratory logistic regression analyses predicting specific drug use, abuse, and dependence from early alcohol use yielded large odds ratios (ORs) accompanied by very broad confidence intervals (CIs) inclusive of unity for stimulants/cocaine, sedatives, opiates, and hallucinogens/PCP. Therefore, we created the following composite drug variables: (1) ever use of marijuana, (2) marijuana abuse/dependence, (3) ever use of other drugs (i.e. stimulants/cocaine, sedatives, opiates or hallucinogens/PCP) and (4) abuse/dependence on other drugs.

Covariates

Covariates included early regular smoking (smoking 100 plus cigarettes before age 17, or smoking daily for 1 month before age 17,

or having one nicotine dependence symptom before age 17) and lifetime diagnoses of DSM-III-R depression, post-traumatic stress disorder (PTSD) and childhood conduct disorder. These covariates were selected because they have been associated with early regular drinking and with adult substance use, abuse and dependence in other studies (Fergusson *et al.* 1995; Jackson *et al.* 2002; Liu *et al.* 2004). We also adjusted for service in Vietnam because of evidence that combat exposure is associated with substance dependence (Koenen *et al.* 2003).

Early alcohol use prevalence

We computed the prevalence of substance use disorders for twins concordant for early use ($n=177$ pairs), discordant for ($n=622$ pairs) and concordant for no early use ($n=2039$ pairs) in order to test whether familial influences partly explain the association between early and later substance use, abuse, and dependence. Familial influence would be suggested if early users from discordant pairs had less substance use than early users from concordant pairs (i.e. a protective effect from having a non-early-using co-twin), and if non-early-users from discordant pairs had higher rates of substance use than pairs concordant for not using alcohol early (i.e. heightened risk associated with an early-using co-twin).

Analytic approach: co-twin analyses

Discordant pairs were studied to determine if early alcohol use was associated with later substance use, abuse/dependence after accounting for genetic and family environmental influences. In our analyses, one twin used alcohol early but the co-twin did not. ORs for later dependence on alcohol and on other drugs for the early-using twin *versus* the non-early-using twin were computed separately for MZ and DZ pairs. Results from MZ pairs are especially enlightening because MZ pairs share 100% of their genes and family environment. Therefore, any difference between twin pairs is attributed to non-shared environment (e.g. early alcohol use). In contrast, DZ twins share 50% of their genes, so that differences in DZ pairs could be due to genes and/or non-shared environment.

Conditional logistic regression was used to test for zygosity differences in the impact of early alcohol use on other substance use among discordant pairs following the methods described by Lynskey *et al.* (2003). The interaction between early alcohol use and zygosity was not significant indicating that the risks associated with an early-using MZ co-twin compared to a DZ co-twin are not significantly different. For completeness, we analyzed discordant MZ pairs alone.

Twin pairs were eligible for co-twin analyses if they (1) were discordant for early regular alcohol use and (2) never used drugs or used them only after becoming regular alcohol users. Pairs were discordant for early alcohol use if one twin reported onset of regular alcohol use at age 16 or younger and the other twin reported onset of regular drinking at age 17 or later which resulted in 752 pairs. In 130 of these pairs, one or both twins used drugs before alcohol and thus were not eligible for analyses predicated on alcohol use preceding drug use. Therefore, the co-twin analyses included data from 622 pairs; 302 MZ and 320 DZ pairs.

Logistic regressions conditional on twins' early alcohol use status were computed separately for each outcome. Analyses were adjusted for depression, PTSD, childhood conduct disorder, early tobacco use and service in Southeast Asia. All regression analyses were computed using STATA (Stata Corp, 1997), a statistical package that uses a robust variance estimator to account for the non-independence of twin observations.

Bivariate twin models

Standard univariate quantitative genetic model-fitting procedures were used to obtain estimates of the proportions of variance attributable to additive genetic (annotated 'A'), shared environmental (annotated 'C'), and non-shared environmental (annotated 'E') factors for each outcome. The best-fitting univariate models were selected for use in bivariate Cholesky models (Neale & Cardon, 1992) to examine the extent to which the sources of variation in early alcohol use overlapped with those on marijuana and other drug use, alcohol dependence, and marijuana and other drug abuse/dependence. Models were fitted to the data using methods of maximum-likelihood estimation as implemented in the statistical package Mx (Neale *et al.* 2003).

Table 1. *Lifetime prevalence of substance use, abuse and dependence among monozygotic and dizygotic twin pairs concordant and discordant for early alcohol use*

Substance use	Individuals in twin pairs concordant for early use ($n=177$ twin pairs)	Early user from pairs discordant for early use ($n=622$ index twins)	Non early user from pairs discordant for early use ($n=622$ co-twins)	Individuals in twin pairs concordant for no early use ($n=2039$ pairs)
Alcohol				
Dependence	63%[a]†	54%[b]	41%[c]	28%[d]
Marijuana				
Ever used	69%[a]	60%[b]	49%[c]	33%[d]
Abuse/dependence	15%[a]	12%[a]	8%[b]	4%[c]
Other drug*				
Ever used	45%[a]	36%[b]	27%[c]	14%[d]
Abuse/dependence	16%[a]	9%[b]	4%[c]	2%[d]

* Other drug = cocaine/stimulants, sedatives, opiates, hallucinogens/PCP.
† Superscripts with different letters indicate prevalences are significantly different ($p<0{\cdot}05$).

RESULTS

Phenotypic ORs in the full sample of twins who used alcohol before using illicit drugs ($n=7097$) confirmed that early alcohol use was a significant predictor of later alcohol dependence as well as of drug use, abuse, and dependence. Risk of alcohol dependence was significantly increased among those who started using alcohol early (OR 3·47, 95% CI 3·06–3·94). Marijuana use, and marijuana abuse/dependence risk were also increased among early alcohol users (use: OR 3·29, 95% CI 2·86–3·71; abuse/dependence: OR 3·35, 95% CI 2·73–4·10). Finally, the risk of other drug use and other drug abuse/dependence was also increased (use: OR 3·57, 95% CI 3·12–4·09; abuse/dependence: OR 4·97, 95% CI 3·94–6·26).

Table 1 displays the prevalences of alcohol dependence and ever use and abuse/dependence of marijuana and other drugs. Prevalences are reported for twins concordant for early alcohol use, for early-alcohol-using index twins, for non-early-alcohol-using co-twins, and for twins concordant for no early alcohol use. Overall, the prevalence of substance use, abuse and dependence is highest for concordant early users, lower for the early-alcohol-using member of discordant twin pairs, lower still for the non-early-using member of discordant pairs and lowest for concordant non-early users. The prevalence of alcohol dependence, ever use of marijuana, and ever use and abuse/dependence for other drugs significantly decreases at each step from the concordant early users to the early users from discordant pairs to the non-early-users from discordant pairs to the concordant non-early users. A similar pattern was observed for abuse/dependence on marijuana with the exception that concordant early users did not differ from the early-using twin in discordant pairs.

Tests of differences in covariates revealed that lifetime DSM-III-R criteria conduct disorder (OR 1·72, 95% CI 1·2–2·5), major depression (OR 1·57, 95% CI 1·1–2·3) and early tobacco use (OR 3·20; 95% CI 2·3–4·5) were significantly associated with early alcohol use. Service in Southeast Asia and PTSD were not associated with early regular use of alcohol.

The associations between early regular alcohol use and later alcohol dependence, marijuana and other drug use, abuse/dependence are shown in the left-hand portion of Table 2 for the 622 discordant pairs. Because inclusion of covariates did not markedly change the estimates, results are only discussed for adjusted analyses. Early alcohol use was significantly associated with later alcohol dependence (OR 2·11, 95% CI 1·54–2·90), with ever use of marijuana (OR 2·04, 95% CI 1·46–2·86) with ever use of other drugs (OR 1·80, 95% CI 1·30–2·55), with marijuana abuse/dependence (OR 2·36, 95% CI 1·28–4·34), and with abuse/dependence for other drugs (OR 2·23, 95% CI 1·24–3·99).

Although the above results indicate that early alcohol use does contribute to later drug use/abuse/dependence independent of genetic and family environmental influences, the inclusion of DZ pairs does allow for the possibility that

Table 2. *Odds ratios (and 95% confidence intervals) showing the association between early alcohol use and later substance use, abuse and dependence in discordant twin pairs from the Vietnam Era Twin Registry*

	MZ and DZ pairs ($n=622$)			MZ pairs only ($n=302$)		
Substance outcome	Unadjusted conditional odds ratio	Adjusted conditional odds ratio	Covariates[a]	Unadjusted conditional odds ratio	Adjusted conditional odds ratio	Covariates[a]
Alcohol dependence	2·03* (1·55–2·65)	2·11* (1·54–2·90)	PTSD*, SEA+	2·69* (1·76–4·12)	2·70* (1·67–4·35)	—
Marijuana						
Ever used	1·87* (1·42–2·46)	2·04* (1·46–2·86)	MD*, CD*, PTSD*	1·94* (1·26–2·97)	1·59+ (0·98–2·59)	CD*
Abuse/dependence	1·73* (1·11–2·72)	2·36* (1·28–4·34)	MD*, SEA+	1·71 (0·89–3·32)	1·80 (0·83–3·90)	—
Other drug[b]						
Ever used	1·85* (1·37–2·50)	1·80* (1·28–2·55)	PTSD*	1·93* (1·23–3·02)	2·04* (1·24–3·36)	—
Abuse/dependence	2·25* (1·39–3·64)	2·23* (1·25–3·99)	MD*	1·92+ (0·98–3·76)	1·82 (0·87–3·79)	—

[a] Regular smoking (smoked daily for 1 month or more) before age 16; PTSD, DSM-III-R post-traumatic stress disorder; CD, DSM-III-R conduct disorder; MD, DSM-III-R major depression; SEA, Service in Southeast Asia.

[b] Other drug = cocaine/stimulants, sedatives, opiates, hallucinogens/PCP.

* $p<0·05$, + $p<0·10$.

inheritance of different genes is contributing to DZ pair dissimilarity on early alcohol use and later drug use/abuse/dependence. Thus, because MZ twins are genetically identical, the prediction of adult substance use, abuse/dependence in MZ pairs discordant for early alcohol use is an even more powerful test of the hypothesis that the association cannot be accounted for by genetic and shared family environmental factors that predispose to both early onset alcohol use and adult substance problems. The right-hand portion of Table 2 shows results from the discordant MZ twin pairs ($n=302$ pairs). In these analyses early regular drinking remained significantly associated with subsequent alcohol dependence (OR 2·7, 95% CI 1·7–4·4), and with ever use of any non-marijuana drug (OR 2·0, 95% CI 1·2–3·4). The remaining ORs were suggestive of an association but did not reach statistical significance. The ORs obtained in the MZ only analyses are comparable to those obtained in the analyses with both MZ and DZ pairs, suggesting that the reduced significance levels may stem from loss of power with the reduced sample size.

Although the preceding analyses have shown that familial factors do not entirely explain the association between early alcohol use and later substance use, abuse, and dependence, the pattern of prevalences in Table 1 suggested that familial influences (i.e. genes and shared environment) do contribute to the rates of substance use and abuse/dependence because the early-using twins from discordant pairs have drug use and abuse/dependence rates lower than the pairs concordant for early alcohol use, and the non-early-using twins from discordant pairs have drug use and abuse/dependence rates higher than the pairs concordant for not using alcohol early. That the rates of other drug use and abuse/dependence are lower in early users from discordant pairs compared to concordant early users suggests a protective effect (either genetic or environmental) conveyed by having a non-early-using co-twin. Similarly, having an early-using co-twin is associated with vulnerability (either genetic or environmental) to the non-early users.

We used traditional bivariate genetic models to estimate the contributions of genetic and environmental influences to the association between early alcohol use and later alcohol dependence and other drug use, abuse and dependence (see Table 3 *a*, *b*). In keeping with previous research, bivariate model-fitting results indicated a substantial genetic contribution to early alcohol use, with 53% of the variance in liability for early alcohol use due to heritable factors. There were also substantial genetic influences on alcohol dependence, marijuana and other drug use, and marijuana and other drug abuse/dependence. In addition, there were high genetic correlations (ranging from 0·54 to 0·66) between early alcohol use and the other measures. This suggests a large portion of the association between early alcohol use and adult

Table 3. *Variance components and correlations for bivariate genetic models*

(*a*) Between early alcohol use and ever use of drugs ($n = 1583$ monozygotic and 1255 dizygotic pairs)

Early alcohol use[a]			Ever use			Correlations	
A^2	E^2	Substance used	A^2	C^2	E^2	r_A	r_E
0·53*	0·47*	Marijuana	0·60*	0·08 N.S.	0·32*	0·59*	0·15*
0·53*	0·47*	Other drug[b]	0·54*	0·16 N.S.	0·30*	0·64*	0·15*

(*b*) Between early alcohol use and drug dependence

Early alcohol use[a]			Abuse/dependence			Correlations	
A^2	E^2	Substance abuse/dependence	A^2	C^2	E^2	r_A	r_E
0·53*	0·47*	Alcohol[c]	0·57*	— [d]	0·43*	0·54*	0·22*
0·53*	0·47*	Marijuana	0·39*	0·20 N.S.	0·40*	0·63*	0·11*
0·53*	0·47*	Other drug[b]	0·48*	0·00 N.S.	0·52*	0·66*	0·20*

[a] For alcohol, an AE model provided a better fit than the full ACE model.
[b] Other drug = cocaine/stimulants, sedatives, opiates, hallucinogens/PCP.
[c] Alcohol = dependence only.
[d] Parameter not estimated. A, Additive genetic factor; C, shared family environmental factor; E, unique environmental factor.
* Indicates $p < 0·05$ based on 95% confidence intervals around estimates.

substance problems can be attributed to the influence of shared or correlated genetic vulnerabilities predisposing to both early alcohol use and later use, abuse and dependence. Finally, we found small, yet significant, non-shared environmental correlations (ranging from 0·11 to 0·22). Finding significant unique environmental correlations is consistent with the co-twin analyses, in that genes and family environment do not entirely explain the association between early alcohol use and adult substance problems. The unique environmental correlations suggest early alcohol use itself is associated with adult substance use, abuse and dependence.

DISCUSSION

The prevalence of ever using marijuana and other drugs was elevated in early (before age 17) regular alcohol-using twins compared to their non-early-using twin brothers in a co-twin design that controlled for genetic and shared environmental influences. In models including both MZ and DZ twin pairs, early regular alcohol use was significantly associated with all outcome measures (alcohol dependence, ever use of marijuana, ever use of other drugs, and marijuana and other drug abuse/dependence), even after controlling for covariates. The magnitude of these effects was minimally changed when only MZ pairs were modeled, although several CIs included 1·0, suggesting that the decreased significance might be due to a loss of power. Results from bivariate genetic models suggest that the association between early regular alcohol use and alcohol dependence, marijuana and other drug use, and abuse/dependence is partly due to significant genetic and small but significant unique environmental correlations. We conclude from these results that genes and shared environment contribute to, but do not completely account for, the association between early alcohol use and later adult alcohol, marijuana, and other drug abuse/dependence. Unique environmental factors must contribute to the transition from early use to abuse and dependence.

Our results are consistent with previous studies reporting decreased risk of lifetime alcohol dependence (Grant & Dawson, 1997) and drug use disorders (McGue *et al.* 2001) when onset of drinking is delayed. However, our findings appear to differ with the behavioral genetic analyses of Prescott & Kendler (1999) in which they infer that the association between early drinking and lifetime alcohol dependence can be accounted for by genes and or shared environmental factors. Different definitions of early alcohol use may account for the disagreement. Our analyses used a relatively stringent definition of early alcohol use, drinking at least once a month for 6 months or more, and DSM-III-R lifetime alcohol dependence. In contrast,

Prescott & Kendler (1999) used age onset of first full drink and DSM-IV alcohol dependence. Although we controlled for several covariates, it is possible that the vulnerability for adult alcohol dependence, ever use and abuse and dependence of marijuana and other drugs may be due to other unmeasured covariates thought to contribute to substance use and abuse/dependence, such as childhood psychiatric disorders (e.g. ADHD), or to unmeasured psychosocial variables such as peer and societal influences. Although twins are very similar, different pathways to drug use may be partially due to differences in the domains mentioned above. For instance, MZ twins have identical genetic and shared environmental vulnerability for drug dependence, but non-shared experiences such as one twin having ADHD, experimenting with alcohol and developing negative peer associations will put that twin at greater risk for problems with drug abuse/dependence. Alcohol-using peer groups and access to alcohol in school and work environments may predispose one twin to initiate drinking at an earlier age compared to his twin brother who has a non-drinking social network. This is plausible given the considerable evidence that actual and perceived peer substance involvement are correlated with adolescent and young adult alcohol use and abuse (Bucholz, 1990; Bullers *et al.* 2001; Arata *et al.* 2003), and exposure to deviant social environments is associated with adolescent drinking (Bucholz, 1990; Guo *et al.* 2001).

Our study findings should be interpreted in light of the following limitations. Our results may not generalize to female or to minority populations. The minimum requirements for military service may have excluded those with adolescent alcoholism, thus our results may not generalize to more severely affected early alcohol users. The exposure to illicit substances during the Vietnam Era might have increased the likelihood that both index and co-twins had the chance to use drugs; however, this would have attenuated the magnitude of the association between early alcohol use and ever use of drugs. The retrospective method of data collection may have increased measurement error and limited our ability to detect differences between twin pairs. Assuming error in reporting age of onset is random we expect this to limit the true discordance for early regular drinking thereby decreasing our power to detect an association with adult use, abuse and dependence. Therefore, it is possible that our estimates are conservative. The validity of the present analyses is also dependent on the assumptions of quantitative genetic theory (see Rutter *et al.* 1993), with the equal environments assumption being the most debatable for the present analyses. This assumption takes as its basis that the environment is no more similar for MZ twins than it is for DZ twins. Although this assumption is frequently questioned, there is scant evidence of its being violated in other twin studies (Kendler & Gardner, 1998; Xian *et al.* 2000). Of most relevance to the present report, Xian and colleagues (2000) found no evidence of violation in the data under study from the VET Registry.

Our results were similar to those reported by Lynskey *et al.* (2003) in a study of young adult Australian twins discordant for early marijuana use. Both provide evidence that genes and shared environment are not sufficient to explain the transition from early substance use to later abuse and dependence. Although we recognize the weakness of retrospective age of onset data, we note that age of onset of regular drinking differed by more than 1 year in 86% of discordant pairs. Recall bias is probably minimal as we found good test–retest reliability for reported age onset of regular drinking. Other strengths of the present paper include data that were collected from a non-clinical sample for whom the researchers and interviewers had no prior knowledge of respondent's lifetime history of drug use and use of standardized data collection methods and structured interviews to obtain data on use, abuse and dependence of licit and illicit substances and psychiatric disorders. Finally, the large sample size, lack of association between early regular drinking and service in Southeast Asia, and the national distribution of participants suggest these data should generalize to most middle-aged males.

Evidence from the co-twin design and the biometric models point to common genetic and unique environmental contributions to the association between early drinking and later drug involvement. Our data do not support a role for shared family environmental factors in this association. Common genetic vulnerability and unique environmental influences such as peers

and/or possible physiological effects of early alcohol exposure increase risk for later and more severe substance involvement. Yet, we cannot conclude that the association is causal. Although it is biologically plausible for early alcohol exposure to lead to later substance use problems, our data fall short of satisfying rigorous criteria for causality. However, when we consider the evidence from both the MZ discordant design and the biometric modeling results, we are able to conclude that despite the large shared genetic contributions to early regular drinking and later drug use problems, unique environmental factors also impact the association between early alcohol use and later alcohol dependence, ever use, and abuse/dependence on other drugs. Longitudinal research in adolescent twins is warranted to identify specific unique environmental influences that may contribute to transitions in substance use. Because our results implicate potentially modifiable environmental factors in later drug use, it may be prudent to emphasize delayed alcohol use and avoidance of environmental risk factors, such as peer influences, known to be associated with early alcohol use. Recent media campaigns designed to motivate young people to discourage each other from smoking may serve as an example of a public health intervention. Having school teachers, parents, and physicians counsel adolescents about the risk of early alcohol use may also reduce the risk of subsequent drug involvement.

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DECLARATION OF INTEREST

None.

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