Alcohol Dependence and Reproductive Timing in African and European Ancestry Women: Findings in a Midwestern Twin Cohort

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ABSTRACT. Objective: We examined associations between reproductive onset and history of alcohol dependence (AD) in 475 African ancestry (AA) and 2,865 European or other ancestry (EA) female twins. **Method:** Participants were drawn from a U.S. midwestern birth cohort study of like-sex female twin pairs born between 1975 and 1985, ages 21–32 as of last completed assessment. Cox proportional hazards regression models were estimated predicting age at first childbirth from history of AD, separately by race/ethnicity, without and with adjustment for sociodemographic characteristics, body mass index, history of other substance involvement, psychopathology, and family and childhood risks.

Results: Among EA twins, AD predicted early childbearing through age 17 and delayed childbearing from age 25 onward; in adjusted models, AD was associated with overall delayed childbearing. Among AA twins, reproductive timing and AD were not significantly related in either unadjusted or adjusted models. **Conclusions:** Findings for twins of European ancestry are consistent with well-documented links between early alcohol mis/use and teenage parenting as well as delays in childbearing associated with drinking-related reproductive and relationship difficulties. Extension of analyses to other racial/ethnic groups of sufficient sample size remains important. (*J. Stud. Alcohol Drugs*, 75, 235–240, 2014)

DESPITE WELL-DOCUMENTED ASSOCIATIONS between alcohol use during early adolescence and risky sexual behaviors predictive of teenage pregnancy (CASA, 1999), reproductive and relationship difficulties observed among individuals with alcohol dependence (AD) may result in overall delayed childbearing. Even moderate alcohol consumption by women is associated with gynecological and obstetric problems, including infertility and fetal loss (Emanuele et al., 2002). Because partners of alcoholic women are also more likely to drink (Grant et al., 2007), and heavy or chronic drinking men have on average lower sperm count and higher rates of impotence (Emanuele and Emanuele, 2001), reproductive risks may be compounded. In addition, alcoholics are more likely to be single because they either never marry or divorce early (Kessler et al., 1998; Waldron et al., 2011), and thus opportunities for childbearing may be limited regardless of biological dysfunction.

In the only study to date of timing of childbearing and alcohol use disorder, Waldron and colleagues (2008) examined associations between age at first childbirth and lifetime history of AD using data drawn from two volunteer Australian twin cohorts, both almost exclusively of European ancestry. Among men, little to no effect of AD on reproductive timing was observed. However, AD in women was a strong predictor, associated with between 23% and 73% reduced likelihood of childbearing. Although genetic influences on risk of AD are well documented (Heath et al., 1997; Kendler et al., 1994; Knopik et al., 2004; McGue, 1994), with heritable variation also reported for age at first childbirth (Kirk et al., 2001; Neiss et al., 2002), genetic covariation between AD and reproductive timing was statistically nonsignificant in genetically informed analyses.

In the present study, we examined timing of childbearing as a function of AD in a midwestern birth cohort of female twins of African and European ancestry, including tests of genetic influences on observed associations. Replication in a sample that is better representative of the U.S. population and more diverse is critical given differences by race/ethnicity in both prevalence of AD (Grant, 1997; Hasin et al., 2007) and timing of childbearing (Martin et al., 2003), with African Americans exhibiting lower rates of dependent drinking and earlier childbearing than individuals of European ancestry. Cross-national replication is also important. Although international comparisons of alcohol

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use disorder are sometimes difficult, in part because of differences in diagnostic assessment and whether lifetime versus past-year disorder is assessed (World Health Organization, 2004), age at first childbirth varies considerably even among developed countries (Organisation for Economic Cooperation and Development, 2012).

Method

Participants

Data were drawn from the Missouri Adolescent Female Twin Study (Heath et al., 1999, 2002), a prospective study of female like-sex twin pairs, born in Missouri to Missouri-resident parents, identified from 1975–1985 birth records ($N = 370$ African ancestry [AA], 1,999 European or other ancestry [EA] pairs; the latter total includes 26 pairs of Asian/Pacific Islander or other ancestry). In addition to baseline telephone diagnostic interviews conducted with parents, all available twins were targeted for three waves of telephone interviews (Waves 1, 4, and 5, at median ages 15, 22, and 24 years, respectively). Subsamples of twins completed a brief 1-year follow-up (Wave 2) or a 3-year retest interview (Wave 3). For each wave, participants gave verbal consent (or assent if minors) following procedures approved by the institutional review board at Washington University (St. Louis, MO).

Lifetime history of AD was last assessed at Wave 4, with past-2-year assessments conducted at Wave 5. Dates of birth of biological children were queried in Wave 5 only. Thus, twins who participated at both Waves 4 and 5 comprise the current sample. Of 3,787 individual twins (553 AA, 3,234 EA) completing Wave 4 interviews, 3,349 were also interviewed at Wave 5 (479 AA, 2,870 EA). Analyses were limited to 3,340 individual twins (475 AA, 2,865 EA) with nonmissing data on variables necessary to code both reproductive timing and lifetime history of AD. Analyses of genetic covariation were further limited to complete pairs of monozygotic (MZ) and dizygotic (DZ) twins (AA: $n_{MZ} = 97$, $n_{DZ} = 110$; EA: $n_{MZ} = 729$, $n_{DZ} = 551$). At Wave 5, the selected sample ranged in age from 21 to 32 years, with AA twins slightly older, $t(1) = 2.23$, $p = .03$.

Measures

Parents and twins completed telephone adaptations of the Semi-Structured Assessment of the Genetics of Alcoholism (Bucholz et al., 1994; Hesselbrock et al., 1999), a semi-structured interview developed for the Collaborative Study on the Genetics of Alcoholism (Begleiter et al., 1995). Individual variables, described below, derive from twin self-report measures unless otherwise indicated.

Reproductive onset. For twins reporting biological children at Wave 5, age at first childbirth was computed by

subtracting twin's date of birth from the date of birth of her firstborn child.

Alcohol dependence. Lifetime history of AD as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV, American Psychiatric Association, 1994), was assessed at Wave 4, as was AD onset (age at first 12-month clustering of three or more dependent symptoms). New onsets only were coded at Wave 5.

Control variables. To ensure specificity of observed effects, important correlates of both reproductive timing and AD were included in adjusted models. Control variables were selected based on review of the literature and for consistency with prior publications (Waldron et al., 2008, 2009). Current educational attainment, religious practice, and marital status were included among sociodemographic variables, each assessed at Wave 5. Dummy variables for dropping out of high school and attending at least some college were computed, with completion of high school only (via diploma or General Educational Development [GED] credential) comprising the reference group. Weekly or more frequent religious practice was coded from time spent on religious attendance or spiritual practice. Dummy variables for having never married (nor lived as though married) and having separated from a marital or marriage-like partner were computed, with continuously married twins comprising the reference group.

We examined body mass index (BMI) at Wave 5 as one indicator of health status. Dummy variables for underweight ($BMI < 18.5$), overweight ($BMI = 25\text{--}29.9$), and obese ($BMI \geq 30$) were computed; twins having normal BMI ($18.5\text{--}24.9$) comprised the reference group. Given potential confounding of BMI with childbearing (e.g., weight gain related to recent pregnancy), sensitivity analyses were conducted using BMI derived from Wave 1 versus Wave 5 reports of height and weight. Results (not shown) revealed few differences with respect to reproductive timing such that associations with Waves 1- and 5-derived BMI were of similar magnitude.

To control for other substance involvement, we examined lifetime history of smoking and cannabis use. Onset of smoking (having ever "tried" a cigarette), regular smoking (having smoked 100 or more cigarettes or having smoked at least once per week for 2 months or longer, 21–99 cigarettes total), and DSM-IV nicotine dependence were assessed at Waves 4 and 5. Dummy variables for dependent smokers, nondependent regular smokers, and smoking experimenters (who never smoked regularly) were computed, with never smokers comprising the reference group. Onset of cannabis use was queried at Waves 4 and 5, with DSM-IV cannabis dependence assessed at Wave 5 only. Dummy variables for dependent cannabis users and nondependent users were computed, with twins who denied ever using cannabis comprising the reference group.

History of DSM-IV childhood conduct disorder (CD) and major depressive disorder (MDD) were included as psychi-

atric control variables along with nondiagnostic measures of prior suicide attempt and history of panic attack (not limited to panic disorder). CD was assessed at Waves 1, 3, and 4. Given the low prevalence of CD in women, we examined a broadly defined phenotype of three or more CD symptoms each with onset before age 18. Onset of MDD and suicide attempt were assessed at Waves 4 and 5, with panic attack onset assessed at Wave 4 only.

Family and childhood risk factors included maternal educational attainment, parental separation, parental alcoholism, and childhood sexual abuse (CSA). Maternal education was coded from parental report and, if missing, twin report at Wave 5. Dummy variables for mothers who dropped out of high school and who attended at least some college were computed, with completion of high school only comprising the reference group. Parental separation was assessed as part of parental and Waves 1, 3, 4, and 5 twin interviews, with twins' age at separation coded from year parents' marriage ended or, if missing, age last lived with both parents. Parental alcoholism was coded from parental self-report of AD, parental ratings of coparent AD symptoms, and twin ratings of each parent as a problem and excessive drinker, the latter assessed at Waves 1 and 4. Consistent with earlier work, a parent was considered alcoholic based on positive self-report or any family history rating (see Waldron et al., 2012, 2013). CSA was queried at Waves 1 and 4 and defined as unwanted or forced sexual activity before age 18.

Zygosity. Zygosity was diagnosed based on twins' responses to standard questions regarding similarity and the degree to which others confused them (Nichols and Bilbro, 1966). If Waves 1 or 4 twin report was missing, parental responses to comparable questions were used.

Analytic strategy

Because not all respondents had aged through periods of highest likelihood of childbearing, time-to-event data were analyzed using survival analysis. In preliminary analyses, cumulative failure curves were estimated using the Kaplan–Meier survivor function (Kaplan and Meier, 1958), with log-rank tests to examine differences by race/ethnicity. Although MZ twinning occurs at random, DZ twinning has been linked to both maternal age and socioeconomic status (Bulmer, 1970); thus, to identify limitations to the generalizability of twin data, differences by zygosity were also examined using Kaplan–Meier log-rank tests. To examine reproductive onset as a function of AD without and with adjustment for control variables, Cox proportional hazards (PH) regression (Cox, 1972) was conducted, with the Huber–White robust variance estimator used to compute confidence intervals [CIs] adjusted for nonindependence of twin data. AD was modeled as a time-varying predictor to ensure onset before or at the same age as first reproduction, as were control variables with available ages at onset (smoking, cannabis

use, MDD, suicide attempt, panic attack, parental separation, CSA). Cox analyses of genetic influences contributing to observed associations were conducted without covariate adjustment. The following variables modeled as predictors in genetically informed Cox analyses: AD, zygosity, co-twin AD and the interaction between zygosity and co-twin AD, the latter a test of genetic covariation. For all Cox analyses, the Grambsch and Therneau test of Schoenfeld residuals (Grambsch and Therneau, 1994) was used to examine potential violation of the PH assumption, and where appropriate, age interactions were modeled to correct observed PH violations (Cleves et al., 2004). Analyses were conducted using STATA Version 12.1 (StataCorp LP, College Station, TX).

Results

More than half (58%, $n = 276$) of AA twins reported biological children, compared with 34% of EA twins ($n = 982$), with the differences in cumulative probability of first childbirth highly significant by Kaplan–Meier log-rank tests, $\chi^2(1) = 143.69$, $p < .0001$. Of AA and EA twins, 10% ($n = 46$) and 13% ($n = 359$) met criteria for AD, respectively. Racial/ethnic differences in the cumulative probability of AD were nonsignificant, $\chi^2(1) = 3.81$, $p = .05$. Zygosity was unrelated to probability of first childbirth, AA twins: $\chi^2(1) = 2.30$, $p = .13$; EA twins: $\chi^2(1) = 0.01$, $p = .91$, and AD, AA twins: $\chi^2(1) = 0.38$, $p = .54$; EA twins: $\chi^2(1) = 0.36$, $p = .55$.

Cox analyses

In unadjusted models, the association between AD and onset of reproduction was nonsignificant for AA twins (hazard ratio [HR] = 1.06, 95% CI [0.61, 1.86]). Among EA twins, AD predicted early reproduction through age 17, with likelihood of childbearing more than three times greater than for nonalcoholic twins (HR = 3.22, 95% CI [1.47, 7.08]); over ages 18–24, little to no effect of AD was observed (HR = 1.06, 95% CI [0.80, 1.41]); and from age 25 onward, AD predicted 49% reduced likelihood of childbearing (HR = 0.51, 95% CI [0.27, 0.98]). Results from adjusted models are presented in Table 1, separately for AA and EA twins. Although effects of AD on reproductive timing were nonsignificant for AA twins, among EA twins, AD predicted overall delayed childbearing, with no differences by risk period.

Genetically informed analyses

Nonsignificant heritable covariation was observed in genetically informed Cox analyses limited to EA twins, where significant phenotypic effects were observed. For Co-Twin AD $\times$ Zygosity through age 17, HR = 0.13, 95% CI [0.02, 1.13], and from age 18 onward, HR = 1.56, 95% CI [0.86, 2.96].

TABLE 1. Hazard ratios (HRs) (and 95% confidence interval [CIs]) from multivariate Cox proportional hazards models predicting reproductive onset from alcohol dependence, sociodemographic characteristics, body mass index, other substance involvement, psychopathology, and family and childhood risk factors, by race/ethnicity

Predictor ^a	African ancestry HR [95% CI]	European ancestry HR [95% CI]
Alcohol dependence	0.67 [0.32, 1.42]	0.68 [0.50, 0.92]
Sociodemographic characteristics		
High school dropout		
<20	1.99 [1.24, 3.20]	2.44 [1.83, 3.25]
≥20	0.97 [0.27, 1.84]	1.14 [0.75, 1.75]
College attendance		
<25	0.38 [0.27, 0.55]	0.33 [0.27, 0.40]
≥25		0.58 [0.41, 0.81]
Weekly religious practice		
<20	1.15 [0.87, 1.53]	0.94 [0.74, 1.20]
≥20		1.46 [1.23, 1.73]
Never married		
<18	0.70 [0.43, 1.15]	0.33 [0.16, 0.70]
≥18	0.38 [0.24, 0.61]	0.11 [0.07, 0.16]
Separated/divorced		
<20	1.64 [1.02, 2.63]	1.21 [1.02, 1.42]
20–25	0.63 [0.36, 1.09]	
≥25		0.33 [0.21, 0.52]
Body mass index		
Underweight	^b	0.94 [0.64, 1.37]
Overweight	1.34 [0.89, 1.83]	1.12 [0.95, 1.32]
Obese	1.12 [0.79, 1.58]	1.12 [0.92, 1.36]
Other substance involvement		
Smoking experimenters	1.04 [0.77, 1.41]	1.52 [1.23, 1.87]
Nondependent regular smoking		
<16	6.06 [1.68, 21.86]	1.64 [1.29, 2.09]
≥16	0.88 [0.50, 1.57]	
Nicotine dependence		
<18	0.45 [0.18, 1.10]	3.34 [1.93, 5.77]
≥18		1.73 [1.31, 2.28]
Nondependent cannabis use	1.24 [0.93, 1.67]	0.90 [0.75, 1.07]
Cannabis dependence	4.29 [1.82, 10.10]	0.68 [0.39, 1.20]
Psychopathology		
Conduct disorder	0.79 [0.49, 1.23]	1.33 [1.07, 1.66]
Major depressive disorder	1.03 [0.69, 1.57]	1.03 [0.85, 1.25]
Suicide attempt	0.94 [0.55, 1.61]	0.86 [0.62, 1.21]
Panic attack	1.04 [0.69, 1.57]	0.88 [0.71, 1.10]
Family and childhood risks		
Maternal high school dropout		
<20	1.58 [1.00, 1.49]	1.44 [1.15, 1.79]
≥20	0.74 [0.38, 1.43]	
Maternal college attendance	0.63 [0.45, 0.88]	0.89 [0.75, 1.04]
Maternal alcohol dependence		
<18	1.81 [0.88, 3.73]	1.47 [0.87, 2.48] ^c
≥18	0.75 [0.39, 1.42]	0.93 [0.71, 1.21] ^c
Paternal alcohol dependence		
<18	1.51 [0.81, 2.82] ^c	1.10 [0.94, 1.30]
≥18	0.97 [0.68, 1.39] ^c	
Parental separation		
<20	1.25 [0.87, 1.80]	1.99 [1.51, 2.62]
≥20		1.00 [0.83, 1.21]
Childhood sexual abuse		
<18	0.56 [0.28, 1.12] ^c	1.23 [1.01, 1.48]
≥18	0.86 [0.55, 1.36] ^c	

Notes: Where vertical brackets are shown for HRs [CIs], reported risk is equivalent across risk periods. ^aRisk period in years of age; ^bempty cell; ^cpost hoc test equating HRs across risk periods did not show significant heterogeneity ($p > .05$), but the proportional hazards assumption was violated, and thus an age interaction was modeled with separate HRs reported.

Discussion

We examined associations between lifetime history of AD and timing of reproduction in a midwestern birth cohort of AA and EA female twins. Our primary goal was to replicate, in a more diverse and population-representative U.S. cohort of twins, findings of delayed reproduction previously observed in an Australian sample of alcoholic women (Waldron et al., 2008). Among African Americans, effects of AD on reproductive timing were nonsignificant. In contrast, AD predicted both early and delayed reproduction in twins of European ancestry, consistent with risks for teenage childbearing associated with very early drinking, and reproductive and relational difficulties from continued and problem drinking. However, controlling for sociodemographic characteristics, BMI, and history of other substance involvement, psychopathology, and family and childhood risk factors, differences by risk period were no longer significant, with AD predicting overall delayed childbearing. We also examined heritable contributions to the relationship between AD and reproductive timing observed among EA twins. Consistent with earlier findings (Waldron et al., 2008), genetic sources of covariation were nonsignificant, although CIs were wide so as not to preclude the possibility of genetic effects.

We controlled for a range of correlated risks in adjusted models. Effects of individual control variables were largely consistent with the broader literature, particularly regarding educational and marital correlates of both early and delayed childbearing (e.g., Rindfuss et al., 1996). For example, among both AA and EA twins, high school dropout predicted higher likelihood of childbearing during adolescent years, with schooling beyond Grade 12 associated with reproductive delays. Having never married was associated with delayed childbearing. Although separation from a marital or marriage-like partner predicted early reproduction through young adulthood, among EA twins, marital separation was also predictive of childbearing delays from age 25 onward. Regarding health status, BMI was unrelated to onset of reproduction; however, we observed moderate to strong associations between smoking and early childbearing, particularly for EA twins, also consistent with prior research (Waldron et al., 2008, 2009). Among African Americans, cannabis dependence was especially predictive of early childbearing.

Although evidence of delayed reproduction was observed in alcoholic women of European ancestry, there are a number of limitations of our study that suggest the need for cautious interpretation, particularly regarding African Americans. It is possible that AD has little to no effect on timing of childbearing in African Americans, but in our relatively modest sample, limited statistical power potentially obscured important age interactions, such as those observed among EA twins. Thus, research with diverse samples of sufficient size for adequately powered analyses remains important. The current twin cohort is also relatively young, on average age

24 years as of last completed assessment, with a little more than one third of EA twins reporting any biological children. Examination in an older sample, when participants have had more time to reproduce, would provide increased confidence of observed delays associated with AD. Although results largely support the generalizability of findings from twins to singleton populations, with no significant differences by zygosity observed in the likelihood of childbearing or AD, extension to non-twin samples is also important, including direct comparison of twins to singletons where data on both are available.

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