Smoking and Illicit Drug Use Associations With Early Versus Delayed Reproduction: Findings in a Young Adult Cohort of Australian Twins*

MARY WALDRON, PH.D.,† ANDREW C. HEATH, D.PHIL.,† MICHAEL T. LYNSKEY, PH.D.,† ELLIOT C. NELSON, M.D.,†
KATHLEEN K. BUCHOLZ, PH.D.,† PAMELA A.F. MADDEN, PH.D.,† AND NICHOLAS G. MARTIN, PH.D.†

School of Education, Indiana University, 201 N. Rose Avenue, Bloomington, Indiana 47405

ABSTRACT. Objective: This article examines relationships between reproductive onset and lifetime history of smoking, regular smoking, and nicotine dependence, and cannabis and other illicit drug use. **Method:** Data were drawn from a young adult cohort of 3,386 female and 2,751 male Australian twins born between 1964 and 1971. Survival analyses were conducted using Cox proportional hazards regression models predicting age at first childbirth from history of substance use or disorder separately by substance class. Other substance use or disorder, including alcohol dependence, as well as sociodemographic characteristics, history of psychopathology, and family and childhood risks, were included as control variables in adjusted models. **Results:** Regular smoking and nicotine dependence were associated with earlier reproduction, with pronounced effects for women. For women, use of

cannabis was associated with early reproduction before age 20, and with delayed reproduction among women who have not reproduced by age 20 or 25. Adjustment for control variables only partially explained these associations. **Conclusions:** Consistent with research linking adolescent use with sexual risk taking predictive of early childbearing, regular smokers and nicotine-dependent individuals show earlier reproductive onset. In contrast, delays in childbearing associated with use of cannabis are consistent with impairments in reproductive ability and/or opportunities for reproduction. Continued research on risks both upstream and downstream of substance-use initiation and onset of substance-use disorder is needed for causal mechanisms to be fully understood. (*J. Stud. Alcohol Drugs* **70:** 786-796, 2009)

D URING ADOLESCENCE, drinking, smoking, and use of illicit drugs are associated with risky sexual behaviors strongly predictive of teenage childbearing (for a review, see National Center on Addiction and Substance Abuse at Columbia University [CASA], 1999). Compared with abstaining peers, substance-using adolescents initiate sexual intercourse at younger ages (Harvey and Spigner, 1995; Kowaleski-Jones and Mott, 1998; Mott et al., 1996; Mott and Haurin, 1988; Small and Luster, 1994), have more frequent sexual intercourse (Poulin and Graham, 2001) with more sexual partners (Duncan et al., 1999; Howard and Wang, 2004; Lowry et al., 1994; Santelli et al., 1998; Shrier et al., 1997), and are less consistent in use of contraception (Fergusson and Lynskey, 1996; Fortenberry et al., 1997;

Hingson et al., 1990; Poulin and Graham, 2001; Richter et al., 1993).

Although risks for very early reproduction are well documented, reproductive impairments associated with continued substance use may work to delay reproduction. Even moderate alcohol consumption by women is associated with menstrual disruptions, such as irregular and anovulatory cycles, sexual difficulties, and gynecological and obstetrical problems, including infertility and fetal loss (Abel, 1997; Hakim et al., 1998; Jensen et al., 1998; Kesmodel et al., 2002; Mendelson and Mello, 1998; Ryback, 1977; Wilsnack et al., 1984). In addition to menstrual disruptions (Windham et al., 1999), women who smoke show delayed conception or time to pregnancy and are at increased risk for infertility and fetal loss (Augood et al., 1998; Baird and Wilcox, 1985; Bolumar et al., 1996; Hughes and Brennan, 1996; Hull et al., 2000; Joffe and Zhimin, 1994). Similar risks from illicit drug use are also reported (Gold, 1997; Hall and Solowji, 1997; Jaffe et al., 1997).

To the extent that partners of substance-using women are also more likely to drink, smoke, or use illicit drugs (Agrawal et al., 2006; Labouvie, 1996; Yamaguchi and Kandel, 1993), such risks may be compounded. Reproductive impairments are observed in men who drink but often at higher levels of consumption. Heavy- or chronic-drinking

men have lower sperm count and sperm motility, higher numbers of abnormal sperm, and higher rates of impotence (O'Farrell et al., 1998; Wright et al., 1991). Smoking reduces sperm count and sperm motility and also is associated with sperm abnormalities and impotence (Feldman et al., 1994; Vine, 1996), with similar risks observed in men who use illicit drugs (Buffum, 1982; Gold, 1997; Grinspoon and Bakalar, 1997; Jaffe et al., 1997; Wilson, 1991).

In addition, interpersonal difficulties associated with substance use may limit opportunities for reproduction regardless of reproductive impairments. Compared with light drinkers or abstainers, heavy or problem drinkers report more partner conflict and relationship dissatisfaction (Leonard and Eiden, 2007; Whisman, 2007); they are less likely to marry and, if they do, more likely to divorce, as are users of illicit drugs (Amato and Rogers, 1997; Chilcoat and Breslau, 1996; Hajema and Knibbe, 1998; Newcomb, 1994; Power et al., 1999; Temple et al., 1991; Yamaguchi and Kandel, 1997). Individuals who smoke are also more likely to divorce (Doherty and Doherty, 1998), especially those who initiate smoking during adolescence (Chassin et al., 1992).

To date, a single study has examined reproductive timing as a function of substance use or disorder. Waldron et al. (2008) examined associations between lifetime history of alcohol dependence (AD) and timing of first childbirth using data from two Australian twin cohorts, including 5,514 respondents born between 1893 and 1964 and 6,129 respondents born between 1964 and 1971. Little to no effect of AD on reproductive timing was found in men. However, for women in the older cohort, AD was associated with a 73% reduced likelihood of first childbirth but only after age 29. For women in the young cohort, AD was associated with delayed reproduction after age 24, with 40% reduced likelihood of first childbirth. Adjusting for sociodemographic characteristics, history of regular smoking, psychopathology, and family and childhood risks reduced effects only slightly.

Although findings of reproductive delay in alcoholic women are consistent with impairments to reproductive ability and/or opportunity, results are striking given that early alcohol use is a strong predictor of future alcohol problems, including AD (Grant and Dawson, 1997), and, as reviewed, adolescent substance use is associated with risk for early childbearing. Also striking are results for regular smoking, included as a control variable. Despite high comorbidity between problem use of alcohol and cigarettes (Grucza and Beirut, 2006; Madden et al., 2000), Waldron et al. (2008) found the opposite pattern for regular smoking coded without regard to nicotine dependence (ND). Regular smoking was associated with earlier reproduction in women from both cohorts and in men from the younger cohort, adjusting for the effects of AD and other control variables.

Although many regular smokers meet criteria for ND, whether the same pattern of earlier childbearing holds for ND or smoking without progression to regular smoking is unknown. In the present study, we examine unique effects of ever smoking, regular smoking, and ND on age at first childbirth in models unadjusted and adjusted for important correlates of both substance use and reproductive timing, including other substance use or disorder. We further extend previous work by examining effects of cannabis and other illicit drug use on reproductive onset.

Method

Participants

Respondents were twins born between 1964 and 1971 who were drawn from a broadly representative volunteer twin panel that is maintained by the Australian National Health and Medical Research Council. Twins are of primarily European descent and reflect the predominantly white Australian population from which the cohort was ascertained (see Heath et al., 2001; Knopik et al., 2006). Twins were ascertained through their parents in response to flyers distributed throughout Australian schools during 1980-1982 (Heath et al., 2001). During the period 1990-1992, 8,536 twins were contacted and asked to complete a brief self-report questionnaire. Questionnaires were returned by 5,058 individual twins (59% individual response rate), including 2,270 pairs (53% pairwise response rate). Excluding pairs that could not be located or in which either twin was deceased or too impaired to give informed consent, 8,020 twins (4,010 pairs) were contacted again between 1996 and 2000 for interview assessment. During this period, structured diagnostic interviews were administered to 6,257 twins, including 2,723 pairs (78% individual and 68% pairwise response rates).

Twins were selected for analysis if they had data on (1) variables used to code reproductive onset and (2) lifetime substance use or disorder, specifically, history of smoking, regular smoking, ND, and/or cannabis and other illicit drug use. Of 6,257 interviewed twins, 6,137 (98%) had data on both reproductive onset and at least one substance class, including 3,386 female and 2,751 male respondents. Age at interview of selected twins ranged from 22 to 36 years (mean [SD] = 30.42 [2.45]).

Measures

Twins completed an abbreviated telephone adaptation of the Semi-Structured Assessment of the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994; Hesselbrock et al., 1999). The SSAGA was developed for the Collaborative Study on the Genetics of Alcoholism (COGA) to assess physical, psychological, and social manifestations of alcohol abuse or dependence and related psychiatric disorders in adults and is based on previously validated research interviews. Trained interviewers, who were supervised by a project coordinator and clinical psychologist, administered all interviews. Inter-

TABLE 1.   Descriptive statistics, by respondent gender

Variable	Women (n = 3,386)	Men (n = 2,751)
Biological children, n (%)	1,604 (47)	1,032 (38)
Age at first childbirth, mean (SD)	25.17 (3.77)	26.15 (3.33)
Smoking, n (%)	2,966 (88)	2,505 (91)
Age at onset, mean (SD)	14.25 (3.29)	13.58 (3.36)
Nondependent regular smoking, n (%)	1,644 (49)	1,450 (53)
Age at onset, mean (SD)	16.49 (2.78)	16.37 (3.11)
Nicotine dependence, n (%)	979 (29)	896 (33)
Age at onset, mean (SD)	22.17 (3.95)	21.80 (4.00)
Cannabis use, n (%)	1,791 (53)	1,877 (69)
Age at onset, mean (SD)	19.17 (3.45)	18.60 (3.22)
Other illicit drug use, n (%)	900 (27)	996 (36)
Age at onset, mean (SD)	20.25 (4.17)	20.15 (4.11)
Control variables		
Alcohol dependence, n (%)	522 (15)	842 (31)
Age at onset, mean (SD)	21.74 (3.80)	21.32 (3.59)
Sociodemographic characteristics		
Educational attainment		
High school drop-out, n (%)	347 (10)	255 (9)[NS]
High school, no tertiary education, n (%)	1,839 (54)	1,571 (57)[a]
Weekly church attendance, n (%)	375 (11)	213 (8)
Never married, n (%)	1,313 (39)	1,330 (48)
Separated/divorced, n (%)	257 (8)	150 (5)
Current physical health		
Underweight	225 (7)	19 (< 1)
Overweight	586 (18)	1,059 (39)
Obese	269 (8)	231 (8)[a]
History of psychopathology		
Childhood conduct disorder, n (%)	261 (8)	548 (20)
Major depressive disorder, n (%)	1,130 (34)	627 (23)
Age at onset, mean (SD)	22.48 (5.52)	22.41 (5.43)
Family and childhood risks		
Maternal education		
High school drop-out, n (%)	1,383 (43)	914 (35)
High school, no tertiary education, n (%)	1,315 (41)	1,196 (46)
Parents married n (%)	2,479 (73)	2,044 (74)[NS]
Stepparent presence, n (%)	245 (7)	170 (6)[NS]
Parental alcoholism, n (%)	720 (22)	511 (19)
Childhood sexual abuse, n (%)	573 (17)	155 (6)
Age at onset, mean (SD)	11.03 (5.52)	10.81 (3.40)[b]
Physical abuse, n (%)	141 (4)	77 (3)
Age at onset, mean (SD)	7.03 (3.34)	7.86 (3.07)[NS]

[NS]Gender difference not significant at $p = .05$; [a]$p = .03$; [b]$p = .02$.

views were tape-recorded and a random sampling of tapes was reviewed for quality control and coding inconsistencies. Informed consent was obtained from all participants before their participation using procedures approved by the institutional review boards at both Washington University School of Medicine and Queensland Institute of Medical Research. A summary of individual measures follows, with descriptive statistics presented in Table 1 by respondent gender.

Reproductive onset. For respondents reporting biological children, age at first childbirth was computed by subtracting respondent's date of birth from the date of birth of his or her firstborn child.

Smoking history. Dummy variables for ever smoking, regular smoking, and ND were computed, with never

smokers comprising the reference group. Respondents who reported having "tried" a cigarette were coded positive for ever smoking, with age at onset (in years) defined as age at first cigarette. Regular smoking was coded if respondents reported ever in their lifetime (1) having smoked 100 or more cigarettes or (2) smoking less than 100 but more than 20 cigarettes, and having smoked at least 1 or 2 days per week for a period of 3 weeks or more. Age at onset of regular smoking was defined as age first smoked at least 1 or 2 days per week for a period of 3 weeks or more. ND was directly assessed using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994), as was ND onset (age at first 12-month clustering of three or more DSM-IV ND symptoms). Smoking variables were coded hierarchically as (1) nicotine-dependent smokers, (2) nondependent regular smokers, and (3) smoking experimenters, who never smoked regularly.

Cannabis and other illicit drug use. Although DSM-IV cannabis abuse was assessed as part of the SSAGA interview, age at onset of cannabis abuse was not. Thus, onset of first use of illicit drugs was examined. Lifetime use of cannabis or other illicit drugs was assessed from self-report use of cannabis, sedatives and stimulants (more than prescribed or when not prescribed), opiates, cocaine, hallucinogens, solvents, or inhalants. Age at onset was defined as age at first use of cannabis and for other illicit drug use, the youngest age reported for other illicit drug classes, excluding cannabis.

Control variables. To ensure specificity of observed effects, important correlates of both substance use or disorder and reproductive timing were included in adjusted models. In addition to smoking and illicit drug use, AD was examined along with other substance use or disorder control variables. DSM-IV AD was directly assessed, as was AD onset (age at first 12-month clustering of three or more AD symptoms). A range of sociodemographic, health, psychiatric, and family and childhood risks were also examined. These variables were initially selected based on review of the literature and availability in both older and young adult cohorts of Australian twins examined previously (Waldron et al., 2008). Sociodemographic, health, psychiatric, and family and childhood risks associated ($p < .10$) with age at first childbirth in the younger cohort were included as control variables in the present study.

Educational attainment, current church attendance, and marital history were among sociodemographic control variables. Dummy variables for dropping out of and completing only high school were computed, with any tertiary education comprising the reference group. Weekly or more frequent church attendance was coded from respondent report of frequency of church attendance using a scale ranging from 1 = "more than once a week" to 6 = "never," with 3 = "every month or so." Dummy variables for having never married

and history of marital separation or divorce were computed, with married twins comprising the reference group.

Body mass index (BMI) was included as an index of current physical health. BMI was calculated from respondent's report of height and weight at interview. Dummy variables for "underweight" (BMI < 18.5), "overweight" (BMI 25-29.9), and "obese" (BMI ≥ 30) were computed, with twins having "normal" BMI (18.5-24.9) comprising the reference group.

Childhood conduct disorder (CD) and lifetime history of major depressive disorder (MDD) were among psychiatric control variables, each assessed as part of the SSAGA. Relaxed criteria were used to diagnose CD, defined as 3 or more (of 15) DSM-IV CD symptoms, each with onset before age 18. DSM-IV MDD and MDD onset (age at first clustering of five or more DSM-IV major depressive symptoms in an episode of at least 2 weeks' duration) were directly assessed.

Family and childhood risks include maternal education, parental separation or divorce during childhood, presence of a stepparent during childhood, parental alcohol problems, and childhood sexual abuse and physical abuse. Parental alcohol problems were coded from respondent's report of maternal or paternal history of alcohol-related problems with health, family, job, or police or other problems. Childhood sexual abuse was defined as unwanted or forced sexual activity before age 18. Physical abuse during childhood was coded from a single item ("Did event 8 ever happen to you [You were physically abused as a child]?"). Ages at onset of childhood sexual abuse and physical abuse were also assessed.

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). Diagnoses derived from extensive blood sampling have been shown to demonstrate 95% agreement with similar questionnaire-based zygosity determination (Martin and Martin, 1975; Ooki et al., 1990).

Analytic strategy

The present study analyzes data from individual twins to examine phenotypic associations between reproductive timing and substance use or disorder. Because not all respondents had aged through periods of highest likelihood of childbearing, time-to-event data were analyzed using survival analysis. Analyses were conducted in STATA Version 8.2 (StataCorp LP, College Station, TX), with the Huber-White robust variance estimator used to compute standard errors and confidence intervals (CIs) adjusted for nonindependence (i.e., the correlated nature) of data on twin pairs.

In preliminary analyses, cumulative failure curves were estimated using the Kaplan-Meier survivor function (Kaplan and Meier, 1958), with log-rank tests to identify significant differences in equality of survivor functions by respondent gender. Kaplan-Meier failure probabilities were also estimated to examine first childbirth as a function of respondent age and history of substance use or disorder. Consistent with recent reports of female fertility (Dye, 2008), we examined first childbirth during the teen years (before age 20), between ages 20 and 24, and from age 25 onward. In addition, we tested for zygosity differences that might identify limitations to the generalizability of twin data. Because monozygotic twinning occurs at random, monozygotic twins will represent a near-random sample of genotypes in the general population. In contrast, dizygotic twinning shows weak associations with factors, including maternal age and socioeconomic status (Bulmer, 1970).

To examine reproductive onset as a function of substance use or disorder without and with adjustment for important correlates, Cox proportional hazards regression (Cox, 1972) was used. Substance use or disorder was modeled as a time-varying predictor to ensure onset before or at the same time of first reproduction, with the Efron approximation (Efron, 1977) used for survival ties. Separate models were first run for each substance class without control variables. All substance classes were next modeled simultaneously to control for other substance use or disorder, with AD included. A third and final model included other substance use or disorder and sociodemographic, health, psychiatric, and family and childhood risks as control variables. Control variables with available ages at onset (all substance use or disorder variables, MDD, childhood sexual abuse, physical abuse during childhood) were modeled as time-varying predictors.

Results from Cox regression models are presented as hazard ratios (HRs). In Cox regression, the dependent variable is called the *hazard,* which describes event occurrence over time or the rate of event occurrence. A hazard rate is a conditional instantaneous event rate, calculated as a function of time. For dichotomous predictors, HRs represent a ratio of hazard rates for two groups, that is, the ratio of rates at which events are occurring in one group relative to a reference group. HRs greater than 1.0 indicate a higher rate of event occurrence; thus, in the context of the present study, earlier childbearing compared with the reference group. HRs less than 1.0 indicate a lower rate, suggesting later or delayed childbearing compared with the reference group. HRs equal to 1.0 indicate no difference in rates or risk related to onset of childbearing.

To examine potential violation of the proportional hazards assumption, such as might be the case if the effects of substance use or disorder on reproductive onset differ for earlier versus later age periods, the Grambsch and Therneau test of Schoenfeld residuals (Grambsch and Therneau, 1994) was employed. Following Cleves et al. (2004), interactions between age or risk period and predictor variables were modeled to correct observed proportional hazards violations. Consistent with census reporting, risk periods of less than

20, 20-24, and 25 or more years were chosen. Where there was no violation in proportional hazards, risk periods were collapsed.

Results

Preliminary analyses

As shown in Table 1, more women than men reported biological children. Results of log-rank tests in this relatively young cohort indicate significant gender differences in the cumulative probability of first childbirth, with women reproducing earlier on average than men. Consistent with previous reports, rates of substance use or disorder, including AD, were higher for men than women across all substance classes. Onset of substance use or disorder also occurred earlier on average for men across substance classes. For control variables, gender differences were significant at $p < .01$ unless otherwise noted.

Cumulative probabilities of first childbirth as a function of respondent's age and smoking history are presented in Table 2 for women. Results suggest that 2% of smoking experimenters, 10% of nondependent regular smokers, and 3% of nicotine-dependent smokers report first childbirth before age 20. By the time they are 24 years old, 13%, 32%, and 16% of women who are smoking experimenters, nondependent regular smokers, and nicotine-dependent smokers, respectively, report first childbirth. From age 25, probability of first childbirth ranged from 54% (nicotine-dependent smokers) to 73% (nondependent regular smokers). Cumulative probabilities of first childbirth as a function of respondent's age and marijuana and other illicit drug use are also presented, with equivalent estimates for men in Table 2.

Tests for zygosity differences in substance use or disorder and age at first childbirth largely support generalizability of twin data. Importantly, differences by zygosity in the cumulative probability of first childbirth were nonsignificant (women: $\chi^2_1 = 3.38$, $p = .07$; men: $\chi^2_1 = 0.09$, $p = .77$). For women, zygosity was unrelated to cannabis use ($\chi^2_1 = 2.26$, $p = .13$) and other illicit drug use ($\chi^2_1 = 2.38$, $p = .12$), with small to moderate differences by zygosity for ever smoking ($\chi^2_1 = 17.42$, $p < .0001$), regular smoking ($\chi^2_1 = 8.04$, $p = .005$), and ND ($\chi^2_1 = 18.18$, $p < .0001$). For men, zygosity was unrelated to cannabis use ($\chi^2_1 = 1.16$, $p = .28$), with differences by zygosity observed across smoking variables (ever smoking: $\chi^2_1 = 7.57$, $p = .01$; regular smoking: $\chi^2_1 = 16.57$, $p < .0001$; and ND: $\chi^2_1 = 9.49$, $p < .01$), and for other illicit drug use ($\chi^2_1 = 6.28$, $p < .05$). For both women and men, significant differences were in the direction of dizygotic twins having higher prevalence of substance use or disorder than monozygotic twins.

Cox analyses of reproductive timing and substance use or disorder

HRs and 95% CIs for substance use or disorder from models unadjusted and adjusted for other substance use or disorder (Adjusted I) and other substance use or disorder and sociodemographic, health, psychiatric, and family and childhood risks (Adjusted II) are presented in Tables 3 and 4 for women and men, respectively.

Unadjusted models. Ever smoking without progression to regular smoking or ND was not significantly related to reproductive timing for either women or men. However, nondependent regular smoking was associated with earlier reproduction. Before age 20, the likelihood of first childbirth among regular smoking women was nearly four times that of never smokers, and between ages 20 and 24, it was 61% higher. Effects of ND are especially pronounced. Before age 20, the likelihood of first childbirth among nicotine-dependent women was five times that of never smokers, and between ages 20 and 24, it was nearly twice as high. A similar pattern was found for men. Before age 25, the likelihood of first childbirth among regular smoking men was more than twice that of never smokers, and among nicotine-dependent men, the likelihood of first childbirth was nearly twice as high.

Before age 20, there was a strong association between cannabis use and early childbearing in women, with likelihood of first childbirth three times that of never users. After age 24, cannabis use was associated with delayed childbearing, with 34% reduced likelihood of first childbirth. We observed a similar pattern for other illicit drug use. After age 24, other illicit drug use was associated with 36% reduced likelihood of first childbirth in women. For men, the effect of cannabis use was nonsignificant. However, after age 24, other illicit drug use was associated with 20% reduced likelihood of first childbirth.

Models adjusting for other substance use or disorder (Adjusted I). Controlling for other substance use or disorder, including AD, regular smoking was associated with 2.21 times higher likelihood of first childbirth in women before

TABLE 2. Cumulative probabilities of first childbirth, by respondent age and substance use or disorder

	Respondent age					
	Women			Men		
Variable	<20	20-24	≥25	<20	20-24	≥25
Smoking						
Never smokers	.03	.17	.60	<.01	.09	.51
Smoking experimenters	.02	.13	.61	<.01	.07	.52
Nondependent regular smoking	.10	.32	.73	.03	.22	.65
Nicotine dependence	.03	.16	.54	<.01	.09	.49
Cannabis						
Never use	.04	.20	.69	.02	.13	.61
Use	.04	.17	.56	.01	.10	.51
Other illicit drugs						
Never use	.05	.20	.67	.01	.12	.56
Use	.03	.13	.48	.01	.10	.56

Table 3. Hazard ratios (and 95% confidence intervals) from Cox proportional hazards models: Substance use or disorder in women

Predictor (risk period)[a]	Unadjusted[b]	Adjusted I[c]	Adjusted II[d]
Smoking experimenters	0.89 (0.75-1.06)	0.99 (0.84-1.18)	1.12 (0.94-1.33)
Nondependent RS, <20	**3.67 (2.44-5.51)**		**1.64 (1.28-2.11)**
Nondependent RS, 20-24	**1.61 (1.26-2.05)**	**2.21 (1.75-2.78)**	
Nondependent RS, ≥25	0.98 (0.80-1.21)	**1.27 (1.02-1.58)**	1.25 (.99-1.58)
Nicotine dependence, <20	**4.95 (2.83-8.68)**		**2.17 (1.61-2.93)**
Nicotine dependence, 20-24	**1.86 (1.42-2.43)**	**2.80 (2.15-3.65)**	
Nicotine dependence, ≥25	0.85 (0.69-1.05)	1.22 (0.98-1.52)	**1.41 (1.12-1.79)**
Cannabis use, <20	**3.07 (2.18-4.31)**	**2.32 (1.65-3.28)**	**1.89 (1.29-2.77)**
Cannabis use, 20-24	1.10 (0.91-1.32)		**0.84 (0.73-0.96)**
Cannabis use, ≥ 25	**0.66 (0.57-0.75)**	**0.74 (0.66-0.84)**	
Other illicit drug use, <20	1.61 (0.99-2.62)		
Other illicit drug use, 20-24	0.93 (0.73-1.17)	**0.77 (0.66-0.89)**	0.90 (0.77-.1.05)
Other illicit drug use, ≥25	**0.64 (0.54-0.76)**		

Notes: **Bold** indicates statistical significance. RS = regular smoking. [a]Risk period in years of age; [b]model without control variables; [c]controlling for other substance use or disorder, including alcohol dependence; [d]controlling for other substance use or disorder, alcohol dependence, and sociodemographic, psychiatric, and family and childhood risks.

age 25, and after, 27% higher. Likelihood of first childbirth among nicotine-dependent women was nearly three times that of never smokers before age 25. For men, controlling for other substance use or disorder appears to strengthen effects of regular smoking, where likelihood of first childbirth was 2.6 times that of never smokers before age 25, and after, 44% higher. A similar pattern was observed for ND, where before age 25 the likelihood of first childbirth was 2.62 times that of never smokers.

Before age 20, there remains a strong association between cannabis use and early childbearing in women, with likelihood of first childbirth 2.32 times that of never users. After age 20, cannabis use was associated with delayed childbearing, with 26% reduced likelihood of first childbirth. Across risk periods, illicit drug use was associated with 23% reduced likelihood of first childbirth in women. For men, cannabis use was associated with 21% reduced likelihood of first childbirth, with nonsignificant effects of illicit drug use.

Consistent with previous analyses, AD, included as a control variable, was associated with delayed childbearing among women (HR = 0.76, 95% CI: 0.64-0.90); for men, the association was nonsignificant (HR = 0.90, 95% CI: 0.77-1.05).

Models adjusting for other substance use or disorder and sociodemographic, health, psychiatric, and family and childhood risks (Adjusted II). With additional adjustment for sociodemographic, health, psychiatric, and family and childhood risks, regular smoking was associated with 64% higher likelihood of first childbirth in women before age 25. The likelihood of first childbirth among nicotine-dependent women remains more than two times that of never smokers before age 25, and after, 41% higher. For men, the effect of regular smoking reduced, with likelihood of first childbirth 47% higher than for never smokers before age 25.

Before age 20, a strong association between cannabis use and earlier childbearing continues for women, with

Table 4. Hazard ratios (and 95% confidence intervals) from Cox proportional hazards models: Substance use or disorder in men

Predictor (risk period)[a]	Unadjusted[b]	Adjusted I[c]	Adjusted II[d]
Smoking experimenters	0.79 (0.62-1.00)	0.90 (0.70-1.15)	0.84 (0.65-1.09)
Nondependent RS, <25	**2.11 (1.52-2.93)**	**2.60 (1.84-3.68)**	**1.47 (1.04-2.09)**
Nondependent RS, ≥25	1.10 (0.84-1.45)	**1.44 (1.07-1.93)**	1.05 (0.77-1.42)
Nicotine dependence, <25	**1.95 (1.34-2.84)**	**2.62 (1.78-3.87)**	
Nicotine dependence, ≥25	1.01 (0.77-1.32)	1.34 (1.00-1.79)	1.19 (0.89-1.59)
Cannabis use, <25	1.12 (0.89-1.42)		0.87 (0.74-1.03)
Cannabis use, ≥ 25	0.86 (0.74-1.00)	**0.79 (0.68-0.92)**	
Other illicit drug use, < 25	1.25 (0.97-1.62)		1.15 (0.97-1.37)
Other illicit drug use, ≥ 25	**0.80 (0.68-0.94)**	0.87 (0.75-1.02)	

Notes: **Bold** indicates statistical significance. RS = regular smoking; [a]risk period in years of age; [b]model without control variables; [c]controlling for other substance use or disorder, including alcohol dependence; [d]controlling for other substance use or disorder, alcohol dependence, and sociodemographic, psychiatric, and family and childhood risks.

likelihood of first childbirth nearly twice that of never users. After age 20, cannabis use was associated with delayed childbearing, with 16% reduced likelihood of first childbirth. The effect of other illicit drug use was nonsignificant. For men, neither cannabis nor other illicit drug use was associated with reproductive timing once other substance use or disorder and sociodemographic, psychiatric, and family and childhood risks are controlled.

In models adjusting for other substance use or disorder and sociodemographic, psychiatric, and family and childhood risks, associations between AD and age at first childbearing were nonsignificant for both women (HR = 0.84, 95% CI: 0.69-1.01) and men (HR = 0.92, 95% CI: 0.77-1.09).

Discussion

This study extends previous research to examine relationships between reproductive onset and history of ever smoking, regular smoking, and ND, and cannabis and other illicit drug use in a young adult twin cohort. In a recent analysis of the same sample, an association between AD and reproductive delay was found but only after age 24 and only in women (Waldron et al., 2008); history of regular smoking, included as a control variable, was associated with earlier reproduction in both women and men. In the present study, unique effects of ever smoking and progression to regular smoking and ND were examined. Although no effect of ever smoking was observed, nondependent regular smoking and ND were both significantly associated with earlier reproduction in women and men. Such findings are consistent with research linking early smoking with future regular smoking and ND (Breslau et al., 1993) and adolescent smoking with sexual behaviors predictive of early childbearing (e.g., Duncan et al., 1999; Howard and Wang, 2004; Mott and Haurin, 1988; Poulin and Graham, 2001; Shrier et al., 1997). However, evidence of earlier childbearing among regular smokers and nicotine-dependent individuals contrasts with expectations from research on smoking-related impairments to reproductive ability and/or opportunity (e.g., Augood et al., 1998; Doherty and Doherty, 1998; Vine, 1996).

The effects of cannabis and other illicit drug use on reproductive onset were mixed. For women, use of cannabis was associated with earlier reproduction during early risk periods, for example, before age 20. However, cannabis use was also associated with delayed reproduction during later risk periods (i.e., after age 24). A similar albeit less robust pattern was found for use of other illicit drugs. For men, only in models adjusting for other substance use or disorder was the effect of cannabis use significant, with cannabis use associated with delayed reproduction. The association of other illicit drug use with reproductive delay in men was significant in unadjusted models and only after age 24. What could account for this "mixed" pattern, particularly in women? One possibility is that drug use has a cumulative effect on repro-

ductive ability, such that only after sufficient exposure does use of cannabis or other illicit drugs predict childbearing delays. Before this time, predictors of earlier childbearing (i.e., risky sexual behaviors) may be more influential. The effect of other illicit drug use on reproductive delay may be compounded by the absence of stable adult partnerships, especially for those individuals who have not reproduced by age 25.

In the present study, there was a small but nonsignificant association between AD and delayed childbearing for women once variation attributable to a number of control variables, including other substance use or disorder, was removed. Similar control variables were examined by Waldron et al. (2008), thus suggesting that comorbid smoking, cannabis and other illicit drug use together with sociodemographic, psychiatric, health, and family and childhood risks account for AD effects on reproductive timing in women. However, comorbidity alone cannot explain why AD predicts delayed childbearing in women, but nondependent regular smoking and ND are associated with earlier childbearing in both women and men.

Sexually transmitted infection associated with alcohol and illicit drug use, but not smoking, may play a role. Behavioral disinhibition and related cognitive impairments from heavy drinking or drug use increase risk for unprotected sexual intercourse and, consequently, sexually transmitted infections (Ericksen and Trocki, 1994). If untreated, sexually transmitted infections, such as chlamydia, gonorrhea, syphilis, and HIV/AIDS, are a leading cause of reproductive problems, including both female and male infertility (Grodstein et al., 1993; Ochsendorf, 2008; Pellati et al., 2008; Wallace et al., 2008).

There is also the possibility that alcoholic individuals terminate pregnancies more often than do smokers. Although rates of elective abortion are high among both licit and illicit substance-abusing women (Coleman, 2005; Fergusson et al., 2006; Mensch and Kandel, 1992; Yamaguchi and Kandel, 1987), abortion was not significantly associated with age at first childbirth in previous analyses (Waldron et al., 2008). Unfortunately, we are unable to rule out the contribution of abortion given limited assessment. In the present sample, history of abortion was assessed by questionnaire administered several years before interview, and it was not assessed of female partners of male respondents. Furthermore, no information on timing of abortion is available; thus, it is not possible to determine whether a reported abortion resulted in delayed first or subsequent childbirth. The same limitations apply to assessment of spontaneous abortion or miscarriage. Not only are assessments dated, but many miscarriages go unrecognized, especially in the very early stages of pregnancy when miscarriage is most likely to occur (Wilcox et al., 1988).

In addition, becoming a parent is associated with a significant reduction not only in drinking but also in use of

other substances (see Bachman et al., 2002; Schulenberg et al., 2003). Thus, individuals who either choose not to have children or are physically unable (e.g., because of pre-existing reproductive dysfunction) may use alcohol more frequently and in greater quantity, increasing their risk for later dependence.

Despite the fact that prevalence of ever smoking, regular smoking, and ND, and cannabis and other illicit drug use as well as AD are higher in men, with men also having earlier onset across substance classes, effects on earlier or delayed reproduction were often stronger in women. Such findings are consistent with increased vulnerability of women to the effects of substance use. Although women drink and use drugs less frequently than men, women show faster progression from use to problem use or dependence (Brady and Randall, 1999; Centers for Disease Control and Prevention, 2006; Lynch, 2006; National Institute on Alcohol Abuse and Alcoholism, 1999; Roth et al., 2004; Wilsnack et al., 2000; Zilberman et al., 2003), and consequently, to substance-abuse treatment (Hernandez-Avila et al., 2004). Compared with men, women also have earlier onset of adverse consequences, such as liver disease, brain disease, and cancer (e.g., Becker et al., 1996).

Although the results are provocative, several limitations warrant caution when interpreting the present findings, the most important of which pertains to causal mechanisms. Direction of effects are established with use of time-varying predictors (and many covariates), but causal effects are not. Nonetheless, reduction in effects by including a range of control variables, including other substance use or disorder, provides some insights. Adjusting for other substance use or disorder had a pronounced impact, at times strengthening observed effects. For example, when AD and use of cannabis and other illicit drugs were included in models of smoking, the association between early reproduction and both regular smoking and ND in men increased. However, in general, including other substance use or disorder served to reduce the magnitude of associations. Including sociodemographic, health, psychiatric, and family and childhood risks in adjusted models further explained some (but not all) of the observed relationships between reproductive timing and regular smoking, ND, and cannabis and other illicit drug use.

Further limitations are methodological. In addition to reliance on retrospective reports of substance use and dependence symptoms, the present sample was drawn from a predominantly white twin cohort from Australia. Given reported differences by race in timing of first childbearing (Martin et al., 2009) and risk of substance use or disorder (Grant, 1997; Hasin et al., 2007, Weiss et al., 2003), it is possible that observed patterns differ for other populations. Cross-national differences are also possible as reproductive onset varies widely even among developed countries, with average age at first childbirth in Australia among the oldest (Australian Bureau of Statistics, 2007). In Australia, the me-dian age at first childbirth among women is approximately 30 years (Australian Bureau of Statistics, 2008), compared with an average of 27 years in the United States (Martin et al., 2009). Although international comparisons of prevalence of substance-use disorder are also difficult because of diagnostic differences and differences in whether prevalence for lifetime versus past-year prevalence is reported, comparison of ever use and age at first use suggests significant cross-national variation, particularly among adolescents (Pirkis et al., 2003; Steptoe et al., 2003). Furthermore, some caution may be warranted in generalizing findings from twins to singleton populations given differences by zygosity, particularly for smoking variables.

Conclusion

Reproductive risks from substance use or disorder have been reported in research on adolescent use and risk for early childbearing following from early and often high-risk sexual behavior, and studies of reproductive impairments in both women and men who drink, smoke, or use illicit drugs. In the present study, we document significant associations between regular and dependent smoking and early versus delayed reproduction, and between cannabis use and both early and delayed reproduction. Although a range of important control variables was examined, including other substance use or disorder, causal mechanisms underlying observed associations remain unknown without more comprehensive assessment of risks both upstream and downstream of substance-use initiation and onset of substance use or disorder.

References

ABEL, E.L. Maternal alcohol consumption and spontaneous abortion. Alcohol Alcsm **32:** 211-219, 1997.

AGRAWAL, A., HEATH, A.C., GRANT, J.D., PERGADIA, M.L., STATHAM, D.J., BUCHOLZ, K.K., MARTIN, N.G., AND MADDEN, P.A.F. Assortative mating for cigarette smoking and for alcohol consumption in female Australian twins and their spouses. Behav. Genet. **36:** 553-566, 2006.

AMATO, P.R. AND ROGERS, S.J. A longitudinal study of marital problems and subsequent divorce. J. Marr. Fam. **59:** 612-624, 1997.

AMERICAN PSYCHIATRIC ASSOCIATION. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Washington, DC, 1994.

AUGOOD, C., DUCKITT, K., AND TEMPLETON, A. Smoking and female infertility: A systematic review and meta-analysis. Human Reproduct. **13:** 1532-1539, 1998.

AUSTRALIAN BUREAU OF STATISTICS. Australian Social Trends 2007, Catalogue. No. 4102.0, Canberra, Australia: Australian Bureau of Statistics, 2007.

AUSTRALIAN BUREAU OF STATISTICS. Births, Australia 2007, Catalogue No. 3301.0, Canberra, Australia: Australian Bureau of Statistics, 2008.

BACHMAN, J.G., O'MALLEY, P.M., SCHULENBERG, J.E., JOHNSTON, L.D., BRYANT, A.L., AND MERLINE, A.C. The Decline of Substance Use in Young Adulthood: Changes in Social Activities, Roles, and Beliefs, Mahwah, NJ: Lawrence Erlbaum, 2002.

BAIRD, D.D. AND WILCOX, A.J. Cigarette smoking associated with delayed conception. JAMA **253:** 2979-2983, 1985.

BECKER, U., DEIS, A., SORENSEN, T.I., GRONBAEK, M., BORCH-JOHNSEN, K., MULLER, C.F., SCHNOHR, P., AND JENSEN, G. Prediction of risk of liver

disease by alcohol intake, sex, and age: A prospective population study. Hepatology **23:** 1025-1029, 1996.

BOLUMAR, F., OLSEN, J., BOLDSEN, J., AND THE EUROPEAN STUDY GROUP ON INFERTILITY AND SUBFECUNDITY. Smoking reduces fecundity: A European multicenter study on infertility and subfecundity. Amer. J. Epidemiol. **143:** 578-587, 1996.

BRADY, K.T. AND RANDALL, C.L. Gender differences in substance use disorders. Psychiat. Clin. No. Amer. **22:** 241-252, 1999.

BRESLAU, N., FENN, N., AND PETERSON, E.L. Early smoking initiation and nicotine dependence in a cohort of young adults. Drug Alcohol Depend. **33:** 129-137, 1993.

BUCHOLZ, K.K., CADORET, R., CLONINGER, C.R., DINWIDDIE, S.H., HESSELBROCK, V.M., NURNBERGER, J.I., JR, REICH, T., SCHMIDT, I., AND SCHUCKIT, M.A. A new, semi-structured psychiatric interview for use in genetic linkage studies: A report on the reliability of the SSAGA. J. Stud. Alcohol **55:** 149-158, 1994.

BUFFUM, J.J. Pharmacosexology: The effects of drugs on sexual function, a review. J. Psychoact. Drugs **14:** 1-2, 5-44, 1982.

BULMER, M.G. The Biology of Twinning in Man, Oxford, England: Clarendon Press, 1970.

CENTERS FOR DISEASE CONTROL AND PREVENTION. Quick Stats. Excessive Alcohol Use and Risks to Women's Health, Atlanta, GA: Centers for Disease Control and Prevention, 2006.

CHASSIN, L., PRESSON, C.C., SHERMAN, S.J., AND EDWARDS, D.A. The natural history of cigarette smoking and young adult social roles. J. Hlth Social Behav. **33:** 328-347, 1992.

CHILCOAT, H.D. AND BRESLAU, N. Alcohol disorders in young adulthood: Effects of transitions into adult roles. J. Hlth Social Behav. **37:** 339-349, 1996.

CLEVES, M., GOULD, W.W., GUTIERREZ, R.G., AND MARCHENKO, Y. Introduction to Survival Data Analysis With Stata, Revised Edition, College Station, TX: Stata Press, 2004.

COLEMAN, P.K. Induced abortion and increased risk of substance use: A review of the evidence. Curr. Womens Hlth Rev. **1:** 21-34, 2005.

COX, D.R. Regression models and life tables (with discussion). J. Royal Stat. Soc., Series B **34:** 187-220, 1972.

DOHERTY, E.W. AND DOHERTY, W.J. Smoke gets in your eyes: Cigarette smoking and divorce in a national sample of adults. Fam. Syst. Hlth **16:** 393-400, 1998.

DUNCAN, S.C., STRYCKER, L.A., AND DUNCAN, T.E. Exploring associations in developmental trends of adolescent substance use and risky sexual behavior in a high-risk population. J. Behav. Med. **22:** 21-34, 1999.

DYE, J.L. Fertility of American Women: 2006, Population Characteristics, Washington, DC: Census Bureau, 2008.

EFRON, B. The efficiency of Cox's likelihood function for censored data. J. Amer. Stat. Assoc. **72:** 557-565, 1977.

ERICKSEN, K.P. AND TROCKI, K.F. Sex, alcohol and sexually transmitted diseases: A national survey. Fam. Plann. Perspect. **26:** 257-263, 1994.

FELDMAN, H.A., GOLDSTEIN, I., HATZICHRISTOU, D.G., KRANE, R.J., AND MCKINLEY, J.B. Impotence and its medical and psychological correlates: Results of the Massachusetts Male Aging Study. J. Urol. **151:** 54-61, 1994.

FERGUSSON, D.M., HORWOOD, L.J., AND RIDDER, E.M. Abortion in young women and subsequent mental health. J. Child Psychol. Psychiat. **47:** 16-24, 2006.

FERGUSSON, D.M. AND LYNSKEY, M.T. Alcohol misuse and adolescent sexual behaviors and risk taking. Pediatrics **98:** 91-96, 1996.

FORTENBERRY, J.D., ORR, D.P., KATZ, B.P., BRIZENDINE, E.J., AND BLYTHE, M.J. Sex under the influence: A diary self-report study of substance use and sexual behavior among adolescent women. Sex. Transm. Dis. **24:** 313-319, 1997

GOLD, M.S. Cocaine (and crack): Clinical aspects. In: LOWINSON. J.H., RUIZ, P., MILLMAN, R.B., AND LANGROD, J.G. (Eds.) Substance Abuse: A Com-

prehensive Textbook, 3rd Edition, Philadelphia, PA: Lippincott Williams and Wilkins, 1997, pp. 181-198.

GRAMBSCH, P.M. AND THERNEAU, T.M. Proportional hazards tests in diagnostics based on weighted residuals. Biometrika **81:** 515-526, 1994.

GRANT, B.F. Prevalence and correlates of alcohol use and DSM-IV alcohol dependence in the United States: Results of the National Longitudinal Alcohol Epidemiologic Survey. J. Stud. Alcohol **58:** 464-473, 1997.

GRANT, B.F. AND DAWSON, D.A. Age at onset of alcohol use and its association with DSM-IV alcohol abuse and dependence: Results from the National Longitudinal Alcohol Epidemiologic Survey. J. Subst. Abuse **9:** 103-110, 1997.

GRINSPOON, L. AND BAKALAR, J.B. Psychedelic Drugs Reconsidered, New York: Lindesmith Center, 1997.

GRODSTEIN, F., GOLDMAN, M.B., AND CRAMER, D.W. Relation of tubal infertility to history of sexually transmitted diseases. Amer. J. Epidemiol. **137:** 577-584, 1993.

GRUCZA, R.A. AND BEIRUT, L.J. Co-occurring risk factors for alcohol dependence and habitual smoking: Update on findings from the Collaborative Study on the Genetics of Alcoholism. Alcohol Res. Hlth **29:** 172-177, 2006.

HAJEMA, K.J. AND KNIBBE, R.A. Changes in social roles as predictors of changes in drinking behaviour. Addiction **93:** 1717-1727, 1998.

HAKIM, R.B., GRAY, R.H., AND ZACUR, H. Alcohol and caffeine consumption and decreased fertility. Fertil. Steril. **70:** 632-637, 1998.

HALL, W. AND SOLOWIJ, N. Long-term cannabis use and mental health. Brit. J. Psychiat. **171:** 107-108, 1997.

HARVEY, S.M. AND SPIGNER, C. Factors associated with sexual behavior among adolescents: A multivariate analysis. Adolescence **30:** 253-264, 1995.

HASIN, D.S., STINSON, F.S., OGBURN, E., AND GRANT, B.F. Prevalence, correlates, disability and comorbidity of DSM-IV alcohol abuse and dependence in the United States: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch. Gen. Psychiat. **64:** 830-842, 2007.

HEATH, A.C., HOWELLS, W., KIRK, K.M., MADDEN, P.A.F., BUCHOLZ, K.K., NELSON, E.C., SLUTSKE, W.S., STATHAM, D.J., AND MARIN, N.G. Predictors of non-response to a questionnaire survey of a volunteer twin panel: Findings from the Australian 1989 twin cohort. Twin Res. **4:** 73-80, 2001.

HERNANDEZ-AVILA, C.A., ROUNSAVILLE, B.J., AND KRANZLER, H.R. Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. Drug Alcohol Depend. **74:** 265-272, 2004.

HESSELBROCK, M., EASTON, C., BUCHOLZ, K.K., SCHUCKIT, M., AND HESSELBROCK, V. A validity study of the SSAGA—a comparison with the SCAN. Addiction **94:** 1361-1370, 1999.

HINGSON, R.W., STRUNIN, L., BERLIN, B.M., AND HEEREN, T. Beliefs about AIDS, use of alcohol and drugs, and unprotected sex among Massachusetts adolescents. Amer. J. Publ. Hlth **80:** 295-299, 1990.

HOWARD, D.E. AND WANG, M.Q. Multiple sexual-partner behavior among sexually active US adolescent girls. Amer. J. Hlth Behav. **28:** 3-12, 2004.

HUGHES, E.G. AND BRENNAN, B.G. Does cigarette smoking impair natural or assisted fecundity? Fertil. Steril. **66:** 679-689, 1996.

HULL, M.G.R., NORTH, K., TAYLOR, H., FARROW, A., AND FORD, W.C.L. Delayed conception and active and passive smoking. Fertil. Steril. **74:** 724-733, 2000.

JAFFE, J.H., KNAPP, C.M., AND CIRAULO, D.A. Opiates: Clinical aspects. In: LOWINSON, J.H., RUIZ, P., MILLMAN, R.B., AND LANGROD, J.G. (Eds.) Substance Abuse: A Comprehensive Textbook, 3rd Edition, Philadelphia, PA: Lippincott Williams and Wilkins, 1997, pp. 158-166.

JENSEN, T.K., HJOLLUND, N.H.I., HENRIKSEN, T.B., SCHEIKE, T., KOLSTAD, H., GIWERCMAN, A., ERNST, E., BONDE, J.P., SKAKKEBAEK, N.E., AND OLSEN, J. Does moderate alcohol consumption affect fertility? Follow-up study

among couples planning first pregnancy. Brit. Med. J. **317:** 505-510, 1998.

JOFFE, M. AND ZHIMIN, L. Male and female factors in fertility. Amer. J. Epidemiol. **140:** 921-929, 1994.

KAPLAN, E.L. AND MEIER, P. Nonparametric estimation from incomplete observations. J. Amer. Statistical Assoc. **53:** 457-481, 1958.

KESMODEL, U., WISBORG, K., OLSEN, S.F., HENRIKSEN, T.B., AND SECHLER, N.J. Moderate alcohol intake in pregnancy and the risk of spontaneous abortion. Alcohol Alcsm **37:** 87-92, 2002.

KNOPIK, V.S., HEATH, A.C., JACOB, T., SLUTSKE, W.S., BUCHOLZ, K.K., MADDEN, P.A.F., WALDRON, M., AND MARTIN, N.G. Maternal alcohol use disorder and offspring ADHD: Disentangling genetic and environmental effects using a children-of-twins design. Psychol. Med. **36:** 1461-1471, 2006.

KOWALESKI-JONES, L. AND MOTT, F.L. Sex, contraception and childbearing among high-risk youth: Do different factors influence males and females? Fam. Plann. Perspect. **30:** 163-169, 1998.

LABOUVIE, E. Maturing out of substance use: Selection and self-correction. J. Drug Issues **26:** 457-476, 1996.

LEONARD, K.E. AND EIDEN, R.D. Marital and family processes in the context of alcohol use and alcohol disorders. Annual Rev. Clin. Psychol. **3:** 285-310, 2007.

LOWRY, R., HOLTZMAN, D., TRUMAN, B.I., KANN, L., COLLINS, J.L., AND KOLBE, L.J. Substance use and HIV-related sexual behaviors among U.S. high school students: Are they related? Amer. J. Publ. Hlth **84:** 1116-1120, 1994.

LYNCH, W.J. Sex differences in vulnerability to drug self-administration. Exp. Clin. Psychopharmacol. **14:** 34-41, 2006.

MADDEN, P.A.F., BUCHOLZ, K.K., MARTIN, N.G., AND HEATH, A.C. Smoking and the genetic contribution to alcohol-dependence risk. Alcohol Res. Hlth **24:** 209-214, 2000.

MARTIN, J.A., HAMILTON, B.E., SUTTON, P.D., VENTURA, S.J., MENACKER, F., KIRMEYER, S., AND MATHEWS, T.J. Births: Final Data for 2006. National Vital Statistics Reports, Vol. 57, No. 7, Hyattsville, MD: National Center for Health Statistics, 2009.

MARTIN, N.G. AND MARTIN, P.G. The inheritance of scholastic abilities in a sample of twins. I: Ascertainment of the sample and diagnosis of zygosity. Ann. Human Genet. **39:** 213-218, 1975.

MENDELSON, J.H. AND MELLO, N.K. Chronic alcohol effects on anterior pituitary and ovarian hormones in healthy women. J. Pharmacol. Exp. Therapeut. **245:** 407-412, 1998.

MENSCH, B. AND KANDEL, D.B. Drug use as a risk factor of premarital teen pregnancy and abortion in a national sample of young white women. Demography **29:** 409-429, 1992.

MOTT, F.L., FONDELL, M.M., HU, P.N., KOWALESKI-JONES, L., AND MENAGHAN, E.G. The determinants of first sex by age 14 in a high-risk adolescent population. Fam. Plann. Perspect. **28:** 13-18, 1996.

MOTT, F.L. AND HAURIN, R.J. Linkages between sexual activity and alcohol and drug use among American adolescents. Fam. Plann. Perspect. **20:** 128-136, 1988.

NATIONAL CENTER ON ADDICTION AND SUBSTANCE ABUSE AT COLUMBIA UNIVERSITY (CASA). Dangerous Liaisons: Substance Abuse and Sex, New York: National Center on Addiction and Substance Abuse at Columbia University, 1999.

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM. Are women more vulnerable to alcohol's effects? Alcohol Alert, No. 46, Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism, 1999.

NEWCOMB, M.D. Drug use and intimate relationships among women and men: Separating specific from general effects in prospective data using structural equation models. J. Cons. Clin. Psychol. **62:** 463-476, 1994.

NICHOLS, R.C. AND BILBRO, W.C., JR. The diagnosis of twin zygosity. Acta Genet. Stat. Med. **16:** 265-275, 1966.

OCHSENDORF, F.R. Sexually transmitted infections: Impact on male fertility. Andrologia **40:** 72-75, 2008.

O'FARRELL, T.J., KLEINKE, C.L., AND CUTTER, H.S.G. Sexual adjustment of male alcoholics: Changes from before to after receiving alcoholism counseling with and without marital therapy. Addict. Behav. **23:** 419-425, 1998.

OOKI, S., YAMADA, K., ASADA, A., AND HAYAKAWA, K. Zygosity diagnosis of twins by questionnaire. Acta Genet. Med. Gemellol. **39:** 109-115, 1990.

PELLATI, D., MYLONAKIS, I., BERTOLONI, G., FIORE, C., ANDRISANI, A., AMBROSINI, G., AND ARMANINI, D. Genital tract infections and infertility. Europ. J. Obstet. Gynecol. Reproduct. Biol. **140:** 3-11, 2008.

PIRKIS, J.E., IRWIN, C.E., BRINDIS, C., PATTON, G.C., AND SAWYER, M.G. Adolescent substance use: Beware of international comparisons. J. Adolesc. Hlth **33:** 279-286, 2003.

POULIN, C. AND GRAHAM, L. The association between substance use, unplanned sexual intercourse and other sexual behaviours among adolescent students. Addiction **96:** 607-621, 2001.

POWER, C., RODGERS, B., AND HOPE, S. Heavy alcohol consumption and marital status: Disentangling the relationship in a national study of young adults. Addiction **94:** 1477-1487, 1999.

RICHTER, D.L., VALOIS, R.F., MCKEOWN, R.E., AND VINCENT, M.L. Correlates of condom use and number of sexual partners among high school adolescents. J. School Hlth **63:** 91-96, 1993.

ROTH, M.E., COSGROVE, K.P., AND CARROLL, M.E. Sex differences in the vulnerability to drug abuse: A review of preclinical studies. Neurosci. Biobehav. Rev. **28:** 533-546, 2004.

RYBACK, R.S. Chronic alcohol consumption and menstruation. JAMA **238:** 2143, 1977.

SANTELLI, J.S., BRENER, N.D., LOWRY, R.,BHATT, A., AND ZABIN, L.S. Multiple sexual partners among U.S. adolescents and young adults. Fam. Plann. Perspect. **30:** 271-275, 1998.

SCHULENBERG, J.E., MAGGS, J.L., AND O'MALLEY, P.M. How and why the understanding of developmental continuity and discontinuity is important: The sample case of long-term consequences of adolescent substance abuse. In: MORTIMER, J.T. AND SHANAHAN, M.J. (Eds.) Handbook of the Life Course, New York: Kluwer Academic/Plenum, 2003, pp. 413-436.

SHRIER, L.A., EMANS, S.J., WOODS, E.R., AND DURANT, R.H. The association of sexual risk behaviors and problem drug behaviors in high school students. J. Adolesc. Hlth **20:** 377-383, 1997.

SMALL, S.A. AND LUSTER, T. Adolescent sexual activity: An ecological, risk-factor approach. J. Marr. Fam. **56:** 181-192, 1994.

STEPTOE, A., WARDLE, J, CUI, W., BABAN, A., GLASS, K., PELZER, K., TSUDA, A., AND VINCK, J. An international comparison of tobacco smoking, beliefs and risk awareness in university students from 23 countries. Addiction **97:** 1561-1571, 2003.

TEMPLE, M.T., FILLMORE, K.M., HARTKA, E., JOHNSTONE, B., LEINO, V.E., AND MOTOYOSHI, M. A meta-analysis of change in marital and employment status as predictors of alcohol consumption on a typical occasion. Brit. J. Addict. **86:** 1269-1281, 1991.

VINE, M.F. Smoking and male reproduction: A review. Int. J. Androl. **19:** 323-337, 1996.

WALDRON, M., HEATH, A.C., BUCHOLZ, K.K., MADDEN, P.A.F., AND MARTIN, N.G. Alcohol dependence and reproductive onset: Findings in two Australian twin cohorts. Alcsm Clin. Exp. Res. **32:** 1865-1874, 2008.

WALLACE, L.A., SCOULAR, A., HART, G., REID, M., WILSON, P., AND GOLDBERG, D.J. What is the excess risk of infertility in women following genital chlamydia infection? A systematic review of the evidence. Sex. Transm. Infect. **84:** 171-175, 2008.

WEISS, S.R.B., KUNG, H.-C., AND PEARSON, J.L. Emerging issues in gender and ethnic differences in substance abuse and treatment. Curr. Womens Hlth Rep. **3:** 245-253, 2003.

WHISMAN, M.A. Marital distress and DSM-IV psychiatric disorders in a population-based national survey. J. Abnorm. Psychol. **116:** 638-643, 2007.

WILCOX, A.J., WEINBERG, C.R., O'CONNOR, J.F., BAIRD, D.D., SCHLATTERER, J.P., CANFIELD, R.E., ARMSTRONG, E.G., AND NISULA, B.C. Incidence of early loss of pregnancy. New Eng. J. Med. **319:** 189-194, 1988.

WILSNACK, R.W., VOGELTANZ, N.D., WILSNACK, S.C., HARRIS, T.R., AHLSTROM, S., BONDY, S., CSEMY, L., FERRENCE, R., FERRIS, J., FLEMING, J., GRAHAM, K., GREENFIELD, T., GUYON, L., HAAVIO-MANNILA, E., KELLNER, F., KNIBBE, R., KUBICKA, L., LOUKOMSKAIA, M., MUSTONEN, H., NADEAU, L., NARUSK, A., NEVE, R., RAHAV, G., SPAK, F., TEICHMAN, M., TROCKI, K., WEBSTER, I., AND WEISS, S. Gender differences in alcohol consumption and adverse drinking consequences: Cross-cultural patterns. Addiction **95:** 251-265, 2000.

WILSNACK, S.C., KLASSEN, A.D., AND WILSNACK, R.W. Drinking and reproductive dysfunction among women in a 1981 national survey. Alcsm Clin. Exp. Res. **8:** 451-458, 1984.

WILSON, B. The effect of drugs on male sexual function and fertility. Nurse Pract. **16:** 12-17, 21-24, 1991.

WINDHAM, G.C., ELKIN, E.P., SWAN, S.H., WALLER, K.O., AND FENSTER, L. Cigarette smoking and effects on menstrual function. Obstet. Gynecol. **93:** 59-65, 1999.

WRIGHT, H.I., GAVALER, J.S., AND VAN THIEL, D. Effects of alcohol on the male reproductive system. Alcohol Hlth Res. World **15:** 110-114, 1991.

YAMAGUCHI, K. AND KANDEL, D. Drug use and other determinants of premarital pregnancy and its outcome: A dynamic analysis of competing life events. J. Marr. Fam. **49:** 257-270, 1987.

YAMAGUCHI, K. AND KANDEL, D. Marital homophily and illicit drug use among young adults: Assortative mating or marital influence? Social Forces **72:** 505-528, 1993.

YAMAGUCHI, K. AND KANDEL, D.B. The influences of spouses' behavior and marital dissolution on marijuana use: Causation or selection? J. Marr. Fam. **59:** 22-36, 1997.

ZILBERMAN, M., TAVARES, H., AND EL-GUEBALY, N. Gender similarities and differences: The prevalence and course of alcohol- and other substance-related disorders. J. Addict. Dis. **22** (4): 61-74, 2003.