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

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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)

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During 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 Solowj, 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
Alcohol dependence (AD) and timing of first childbirth was examined as a function of substance use or disorder. Waldron et al. (2008) found the opposite pattern for regular smoking, coded with or without progression to regular smoking, 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 1964 and 1971. In women, AD was associated with a 73% reduced likelihood of first childbirth but only after age 29. 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 (Grucca 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).

Motivated to assess reproductive timing, we recruited a sample of twins 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-
**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 (3.35)
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 (9.0)
High school, no tertiary education, n (%) | 1,839 (54) | 1,571 (57.5)
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)

**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 (74.6)
Stepparent presence, n (%) | 245 (7) | 170 (6.9)
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)
Physical abuse, n (%) | 141 (4) | 77 (3)
Age at onset, mean (SD) | 7.03 (3.34) | 7.86 (3.07)

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aGender difference not significant at p = .05; b p = .03; 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
Across risk periods, illicit drug use was associated with 23% likelihood of first childbirth 2.32 times that of never users. Between cannabis use and early childbearing in women, with Before age 20, there remains a strong association between cannabis use and early childbearing in women, with 26% 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 3. Hazard ratios (and 95% confidence intervals) from Cox proportional hazards models: Substance use or disorder in women

<table>
<thead>
<tr>
<th>Predictor (risk period)</th>
<th>Unadjusted</th>
<th>Adjusted F</th>
<th>Adjusted II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking experimenters</td>
<td>0.89 (0.75-1.06)</td>
<td>0.99 (0.84-1.18)</td>
<td>1.12 (0.94-1.33)</td>
</tr>
<tr>
<td>Nondependent RS, &lt;20</td>
<td>3.67 (2.44-5.51)</td>
<td>2.21 (1.75-2.78)</td>
<td>1.64 (1.28-2.11)</td>
</tr>
<tr>
<td>Nondependent RS, 20-24</td>
<td>1.61 (1.26-2.05)</td>
<td>1.27 (1.02-1.58)</td>
<td>1.25 (0.99-1.58)</td>
</tr>
<tr>
<td>Nicotine dependence, &lt;20</td>
<td>4.95 (2.83-8.68)</td>
<td>2.80 (2.15-3.65)</td>
<td>2.17 (1.61-2.93)</td>
</tr>
<tr>
<td>Nicotine dependence, 20-24</td>
<td>1.86 (1.42-2.43)</td>
<td>1.22 (0.98-1.52)</td>
<td>1.41 (1.12-1.79)</td>
</tr>
<tr>
<td>Nicotine dependence, ≥25</td>
<td>0.85 (0.69-1.05)</td>
<td>0.74 (0.66-0.84)</td>
<td>0.84 (0.73-0.96)</td>
</tr>
<tr>
<td>Cannabis use, &lt;20</td>
<td>3.07 (2.18-4.31)</td>
<td>2.32 (1.65-3.28)</td>
<td>1.89 (1.29-2.77)</td>
</tr>
<tr>
<td>Cannabis use, 20-24</td>
<td>1.10 (0.91-1.32)</td>
<td>0.74 (0.66-0.84)</td>
<td>0.84 (0.73-0.96)</td>
</tr>
<tr>
<td>Other illicit drug use, &lt;20</td>
<td>1.61 (0.99-2.62)</td>
<td>1.25 (1.07-1.46)</td>
<td>1.21 (1.02-1.43)</td>
</tr>
<tr>
<td>Other illicit drug use, 20-24</td>
<td>0.93 (0.73-1.17)</td>
<td>0.77 (0.66-0.89)</td>
<td>0.90 (0.77-1.05)</td>
</tr>
<tr>
<td>Other illicit drug use, ≥25</td>
<td>0.64 (0.54-0.76)</td>
<td>0.56 (0.47-0.67)</td>
<td>0.56 (0.47-0.67)</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Predictor (risk period)</th>
<th>Unadjusted</th>
<th>Adjusted F</th>
<th>Adjusted II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking experimenters</td>
<td>0.79 (0.62-1.00)</td>
<td>0.90 (0.70-1.15)</td>
<td>0.84 (0.65-1.09)</td>
</tr>
<tr>
<td>Nondependent RS, &lt;20</td>
<td>2.11 (1.52-2.93)</td>
<td>2.60 (1.84-3.68)</td>
<td>1.47 (1.04-2.09)</td>
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<tr>
<td>Nondependent RS, ≥25</td>
<td>1.10 (0.84-1.45)</td>
<td>1.44 (1.07-1.93)</td>
<td>1.05 (0.77-1.42)</td>
</tr>
<tr>
<td>Nicotine dependence, &lt;20</td>
<td>1.95 (1.34-2.84)</td>
<td>2.62 (1.78-3.87)</td>
<td>1.89 (1.39-2.59)</td>
</tr>
<tr>
<td>Nicotine dependence, ≥25</td>
<td>1.01 (0.77-1.32)</td>
<td>1.34 (1.00-1.79)</td>
<td>1.05 (0.77-1.42)</td>
</tr>
<tr>
<td>Cannabis use, &lt;25</td>
<td>1.12 (0.89-1.42)</td>
<td>0.79 (0.68-0.92)</td>
<td>0.87 (0.74-1.03)</td>
</tr>
<tr>
<td>Cannabis use, ≥25</td>
<td>0.86 (0.74-1.00)</td>
<td>0.87 (0.75-1.02)</td>
<td>1.15 (0.97-1.37)</td>
</tr>
<tr>
<td>Other illicit drug use, &lt;25</td>
<td>1.25 (0.97-1.62)</td>
<td>0.87 (0.75-1.02)</td>
<td>1.15 (0.97-1.37)</td>
</tr>
<tr>
<td>Other illicit drug use, ≥25</td>
<td>0.80 (0.68-0.94)</td>
<td>0.87 (0.75-1.02)</td>
<td>1.15 (0.97-1.37)</td>
</tr>
</tbody>
</table>

Notes: Bold indicates statistical significance. RS = regular smoking. *Risk period in years of age; model without control variables; controlling for other substance use or disorder, including alcohol dependence; controlling for other substance use or disorder, alcohol dependence, and sociodemographic, psychiatric, and family and childhood risks.
The possibility is that drug use has a cumulative effect on reproductive onset. Gender differences in the association with delayed reproduction. The association of other illicit drug use with reproductive delay during early risk periods, for example, before age 24. What could account for this “mixed” pattern, particularly in women? One possibility is that drug use has a cumulative effect on reproductive 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, comorbidly 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...
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 childbirth (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 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.

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