SOCIO-ENVIRONMENTAL FACTORS ASSOCIATED WITH PUBERTAL DEVELOPMENT IN FEMALES: THE ROLE OF PREPUBERTAL TOBACCO AND ALCOHOL USE

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Abstract

Purpose—Alcohol administered to laboratory animals has been shown to suppress puberty-related hormones and delay puberty by interfering with ovarian development and function. The effects of early substance use on human pubertal development are relatively unexplored.

Methods—This cross-sectional study of 3106 females, ages 11-21, evaluates the association between prepubertal alcohol and tobacco use and onset of puberty. Ages at initial breast development, body hair growth and menarche were self-reported. Prepubertal alcohol and tobacco use were defined as age at first use preceding the age of pubertal development and accompanied by regular use. Hazard ratios and 95% confidence intervals were calculated using Cox proportional hazard models. Logistic regression was used to estimate the association between substance use and delayed puberty, defined as lack of breast development by age 13.

Results—Unadjusted models indicated prepubertal tobacco use was associated with longer time to breast development (HR=0.74; 95% CI 0.65-0.85) and body hair growth (HR=0.81; 95% CI 0.71-0.93). Prepubertal alcohol use was associated with later breast development (HR=0.71; 95% CI 0.57-0.88). The direction of the observed associations remained consistent after adjusting for covariates, but the magnitude of effects were attenuated and the upper bound of the 95% CIs exceeded the null value. Girls who used alcohol before puberty had four times the odds of having delayed puberty (OR=3.99; 95% CI 1.94-8.21) compared to non-users.

Conclusion—The results of this study suggest the endocrine-disrupting effects of alcohol and tobacco use may alter the timing of pubertal development. These cross-sectional findings warrant further investigation.

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Keywords

puberty; alcohol; tobacco

INTRODUCTION

Early alcohol and tobacco use has become alarmingly common among youth in the US, with up to 35% of 7th graders reporting alcohol use before the age of 13 [1] and 26% of high schoolers reporting current tobacco use [2]. In a survey of 8th, 10th and 12th grade students, 10.3%-25.9% reported consuming ≥5 alcoholic drinks in a row within the previous two weeks, whereas 1.1%-5.7% reported smoking half a pack or more of cigarettes per day [3]. Alcohol and tobacco use have been associated with a variety of adverse reproductive effects including known or suspected influences on fetal development, fertility, circulating hormone levels, menstrual cycle function, and even the timing of menopause [4,5]. Studies assessing the effects of alcohol and tobacco use on pubertal development, however, are lacking.

Research in laboratory animals indicates that alcohol delays puberty in female rats by altering the puberty-related hormones estradiol, luteinizing hormone (LH) and growth hormone and interfering with ovarian development and function [6]. The anti-estrogenic effects of smoking are well-established in human studies [5], but hormonal responses to alcohol are less consistently reported [7,8]. Reproductive maturation in females is controlled by the hypothalamic-pituitary-gonadal axis [9]. During normal development, the hypothalamus secretes gonadotropin-releasing hormone (GnRH) which regulates LH and follicle stimulating hormone (FSH) secretion from the pituitary. The pituitary gonadotropins stimulate ovarian development and the maturing ovaries secrete increasing levels of estradiol which promote the development of secondary sexual characteristics [10]. The appearance of breast tissue is considered to be the most reliable sign of the activation of the hypothalamic-pituitary-gonadal axis in females [11]. Pubic hair, which generally appears shortly thereafter, is a result of increased androgen secretion by the adrenal glands, and thus may not correlate with the maturation of the hypothalamic-pituitary-gonadal axis [12]. Menarche follows approximately two to three years later on average [13,14]. The age at onset of puberty varies across individuals, with average ages at initial breast development (entry into Tanner stage 2) in the US reported to range from 9.96-10.38 in whites and 8.87-9.5 in African Americans [13-15].

Delayed puberty, defined as the absence of breast development by age 13 in girls [9], is associated with significant health consequences including long-term effects on attained height [16], bone density [17], irregular menses [18], infertility [18], fetal loss [18] and psychological distress [19]. Given the extent of substance use among young school-age populations, there is a need to understand the effects of alcohol and tobacco use on reproductive maturation. This study examines whether prepubertal alcohol and tobacco exposures influence the timing of pubertal development.

METHODS

Sample

We hypothesize that the endocrine active effects of early alcohol and tobacco use may disrupt the timing of pubertal onset. To address this hypothesis, the study utilizes existing cross-sectional data collected from the offspring participating in the Adaptations to Stress Study [20]. The parent cohort was recruited in 1971 from 18 of the 36 junior high schools in the Houston Independent School District and was followed into their mid-thirties (n=5,469 (71.8% response)). Children (n=7,177) of the original study participants (i.e., biological,

adopted, step, and foster children) who were 11 years of age or older were interviewed between 1993-2002.

Informed consent was obtained from all participants prior to enrollment. The study protocol was reviewed and approved by the Texas A&M University Institutional Review Board. A total of 3106 girls between the ages of 11 and 21 were included in these analyses, after excluding 151 over the age of 21 at the time of the interview, 105 reporting precocious pubertal development before the age of 8, and 198 with missing data on the exposure, outcome and covariates of interest.

Measurements

Puberty Assessment—We analyzed the effects of prepubertal alcohol and tobacco use on timing of breast development, body hair growth and menarche. To assess the timing of pubertal events, females were asked if they had ever experienced body hair growth, breasts beginning to grow or having a period (menstruating). If yes, they were asked to report the age when each occurred. No additional description of body hair growth was provided; thus this variable represents the appearance of either axillary or pubic hair.

Alcohol and Tobacco Use—Information on alcohol and tobacco use was collected as age at first use and peak frequency of use. Participants were asked, "How old were you the first time you ever … used chewing tobacco, snuff or dip? Smoked cigarettes? Drank beer? Drank wine? Drank hard liquor?" Those who had not used alcohol or tobacco were coded "never." Peak frequency was assessed by asking, "When you were using this, what was the most that you ever used it?" Subjects selected from the following options: about every day, about once a week, a few times a month, a few times a year or less, only once or sporadically. When operationally defining alcohol and tobacco exposure, we gave consideration to the fact that selecting a cutpoint for a biologically meaningful age at exposure was problematic given the specific timing of etiologically relevant exposures is unknown and given temporally relevant exposures (i.e., exposures preceding the outcome) would likely occur at different ages for individuals who experience pubertal changes at different ages. Thus, prepubertal alcohol consumption was defined broadly as first reported use of beer, wine or liquor before onset of the pubertal characteristic of interest and use of at least "a few times a month" or more. By identifying only those with more than occasional use, we avoid classifying as exposed those who simply tried alcohol or tobacco at an early age and never used regularly. Because the exposure and outcome data were reported in whole years, there is some uncertainty concerning the temporal relationship between exposures and outcomes reported during the same year of age. Thus, we analyzed the data using two definitions of prepubertal exposure among regular users: age at first alcohol use < or ≤ the age at onset of each pubertal characteristic. The results using the two definitions were not substantively different. Therefore, we report results for age at first use < age at onset of each pubertal characteristic. Prepubertal tobacco use was similarly defined as regular users with first reported use of cigarettes, chewing tobacco, snuff or dip before the age reported for breast development, body hair growth or menarche.

Subanalyses were conducted to evaluate exposure defined by age at first use. We examined first reported alcohol and tobacco use ≤ age 11 among more than occasional users, selecting the age cut-point representing the mean age of pubertal events among the non-users. To avoid the erroneous inclusion of substance use initiated after the outcome, substance use must have also preceded the puberty event.

Covariates—Age at interview, race, household income, and parent's education were evaluated as potential confounders. Age and race were obtained from the adolescent's self

report; household income and parental education were obtained from the parent's interview. When all covariates were added to the model individually or combined, age was the only variable that met the criteria for confounding by changing the point estimates for prepubertal alcohol or tobacco use by more than 10% when controlled in the analysis. Thus, results are presented for unadjusted models, models adjusted for age at interview, and models adjusted for all measured covariates.

Statistical analysis—To evaluate the relationship between prepubertal alcohol or tobacco use and the timing of pubertal onset, we began by comparing mean ages at pubertal events. Cohen's d, calculated as the difference between two means divided by the pooled standard deviation, estimated the magnitude of the difference after accounting for the variability in the data. Hazard ratios and 95% confidence intervals were calculated using Cox proportional hazards models to compare the hazard of puberty onset for those with prepubertal alcohol or tobacco consumption to those without such exposures. Hazard ratios < 1.0 indicate a reduced hazard of puberty (i.e., longer time to puberty) whereas hazard ratios > 1.0 indicate an increased hazard of puberty (i.e., shorter time to puberty). Separate models were estimated for each puberty characteristic. The time-varying variables were the reported ages at onset for each puberty characteristic. Girls who had not experienced the puberty event were censored at the age of interview (6.8% without breast development, 9.3% without body hair growth, 29.4% without menarche).

We used logistic regression models to examine associations with delayed puberty, defined as lack of breast development by age 13. These analyses were restricted to girls 14 years of age or older at the time of the interview (n=1305). Odds ratios and 95% confidence intervals are reported.

All analyses were estimated using STATA 9.0.2 (College Station, TX). Standard errors in all models were adjusted to account for the lack of independent observations (clustering) among siblings [21].

RESULTS

Participant Characteristics

The characteristics of the study participants are described in Table 1. The participants were interviewed at a mean age of 14 years (sd 2.7; range 11-21) and were predominately non-Hispanic white (53%) or non-Hispanic black (33%). Most (96%) reported having experienced one or more of the three indicators of puberty. A total of 93.2% reported experiencing breast growth (mean age 11.0 years (sd 1.3)), 90.7% reported body hair growth (mean age 11.1 years (sd 1.2)) and 70.6% reported menarche (mean age 11.7 years (sd 1.3)). Alcohol and tobacco use occurred before the reported pubertal events in 1.9% to 2.8% of the sample (Table 2).

Time to Onset of Puberty

Table 2 compares mean age at breast development, growth of body hair and menarche by prepubertal alcohol and tobacco use. Girls reporting prepubertal alcohol and tobacco use were older at onset of all pubertal characteristics, but mean differences were not statistically significant for alcohol and body hair. The largest mean differences (0.9 years) were observed when comparing age at breast development by alcohol and tobacco use (Cohen's d effect size=-0.73).

The unadjusted, age-adjusted and fully adjusted Cox proportional hazards models are presented in Table 3. In the unadjusted models, prepubertal alcohol use was associated with

an increased time to breast development (HR=0.71; 95% CI 0.57-0.88). Prepubertal tobacco use was associated with a longer time to breast development (HR=0.74; 95% CI 0.65-0.85) and body hair growth (HR=0.81; 95% CI 0.71-0.93). Controlling for age attenuated the associations with prepubertal tobacco and alcohol use. The direction of the associations remained consistent, but the upper bound of the 95% CIs included or slightly exceeded 1.0 for all associations except tobacco and breast development. Adjusting for the additional covariates (prepubertal tobacco or alcohol use, race, and parental income and education) did not cause the point estimates to differ meaningfully from the unadjusted measures, but the confidence intervals had less precision and excluded the null value. Unadjusted and adjusted associations with menarche were not statistically significant, but age-adjusted models reflected marginal statistical significance.

When exposure was operationalized as prepubertal alcohol or tobacco use ≤ age 11, the hazard ratios were stronger in all models for breast development and body hair growth. In the fully adjusted models, a longer time to breast development was observed for girls with alcohol (HR=0.54; 95% CI 0.41-0.70) and tobacco use (HR=0.77; 95% CI 0.66-0.89) by age 11 compared to those not exposed by this age. Similar associations were observed for body hair (HR for alcohol=0.61; 95% CI 0.47-0.80 and HR for tobacco=0.76; 95% CI 0.62-0.93). Time to menarche was also greater among early alcohol users (HR=0.70; 95% CI 0.56-0.86) but not among early tobacco users (HR=1.03; 95% CI 0.84-1.26).

Delayed Puberty

A subanalysis among those ≥ age 14 examined associations with delayed puberty onset, as indicated by lack of breast development by age 13. When compared to girls who did not engage in prepubertal use of alcohol, girls who did had four times the odds of having delayed breast development (OR=3.99; 95% CI 1.94-8.21). Prepubertal tobacco use was not statistically associated with the outcome of delayed puberty (OR=2.00; 95% CI 0.86-4.66).

DISCUSSION

Early pubertal development has been associated with an increased prevalence of *subsequent* tobacco and alcohol use during adolescence [22]. While the social and behavioral consequences of early pubertal timing have been well explored, the possible impact of early substance use on the timing of pubertal development has not been sufficiently assessed in human studies. As a whole, environmental influences on pubertal development remain poorly understood and inadequately explored [9]. A growing body of evidence suggests that exposures to endocrine-disrupting chemicals such as lead and pesticides may alter the timing of pubertal development (reviewed in [9]). Thus, it is plausible that substances such as alcohol and tobacco, which may display similar endocrine-disrupting properties, could influence reproductive. Our study provides evidence that substance use during pivotal stages of reproductive development may alter the progression of puberty. Alcohol and tobacco use at any age prior to the puberty event were modestly associated with later onset, but adjusted HRs did not maintain statistical significance. However, alcohol and tobacco use initiated ≤ age 11 were each associated with prolonged time to breast development and body hair growth. Alcohol use at early ages was also associated with later menarche, but early tobacco use was not. Among those who were age 14 and older, the odds of delayed puberty onset were increased 4-fold among girls who initiated alcohol use at any time before breast development.

The deficit of human research in this area is likely attributed to the difficulty of conducting research in adolescent populations on the sensitive topic of sexual development. The few studies that have addressed the effects of substance use on reproductive maturation have been largely limited to assessments of puberty-related hormones, which are less useful for

determining pubertal stage because the range of values overlaps across the stages of puberty [23]. Our findings of prolonged time to breast development among early prepubertal alcohol users are consistent with the anti-estrogenic effect of alcohol observed by Block et al. who reported lower serum estrogen concentrations among 21 adolescent females who abused alcohol compared to 114 young females without alcohol use [24]. These results are consistent with reports of alcohol-related reproductive disturbances that occur throughout the female lifecycle, including effects on circulating hormone levels, fertility, and timing of menopause [8,25,26]. Diamond et al. reported decreased serum testosterone, LH and FSH concentrations in teenage males being treated for drug and alcohol abuse, but observed no differences in the Tanner stages of sexual development [27]. Given that pubarche is controlled by androgen secretion, our observation of prolonged time to onset of body hair growth among alcohol users is compatible with the anti-androgenic effects of alcohol observed by Diamond et al.

Alcohol use during childhood has been hypothesized to delay puberty among girls by interfering with regulatory systems within the ovary such as the insulin-like growth factor-1 (IGF-1) and nitric oxide systems [28]. Secretion of puberty-related hormones such as IGF-1, LH and estradiol is suppressed in female rats and rhesus monkeys following chronic exposure to alcohol [29-33]. Additionally, laboratory studies have linked alcohol exposure to markers of altered progression of puberty in animals, where female rats exhibited delayed vaginal opening and rhesus monkeys failed to develop regular menstrual patterns (reviewed in [4]). Furthermore, in prepubertal female rats, there is recent evidence of alcohol-induced suppression of hypothalamic *KiSS-1* gene expression, whose products occupy a critical role in the onset of puberty by stimulating LH-releasing hormone and LH secretion [34].

Cigarette smoking has been associated with anti-estrogenic effects in women, altering menstrual cycle function, decreasing fertility and reducing age at menopause [5]. Daughters of women who smoked heavily during pregnancy have menarche at later ages [35], although findings related to prenatal smoke exposure have not been consistent across studies. We are unaware of human studies that have assessed the effects of prepubertal tobacco use on reproductive maturation. Our study did not observe an association between tobacco use and menarche, but suggests evidence of potential tobacco-related influences on breast and body hair growth.

The nature of the extant data source provided a unique opportunity to explore the role of alcohol and tobacco consumption on the timing of puberty. However, several study limitations should be noted. First, the cross-sectional study design cannot establish the temporal relationship between early alcohol and tobacco use and the development of puberty characteristics. The secondary analysis of these cross-sectional data, however, offers an efficient opportunity to address this novel and challenging research question and generate hypotheses to be pursued using more definitive (and more costly) study designs. Our findings are, therefore, hypothesis-generating and should be confirmed by prospective studies. Other limitations of this study are predominantly those intrinsic to secondary data analyses. The exposure and outcome measurements are limited to those previously obtained in the course of the original study. Hence, the retrospective assessment of pubertal development is based on self-reported ages at developmental milestones rather than clinical examination of stages of sexual maturation (i.e., Tanner staging) and may be susceptible to reporting errors. Self reported age at menarche is commonly used as a readily available marker of pubertal development. Some reports suggest short term recall of age at menarche is reasonably reliable [36], but others have noted discrepancies as large as 18 months when recalled over a period of one year [37].

Self-reports are the most common source of measurement for alcohol consumption and tobacco use among adolescents and adults. Given the sensitive nature of substance use and abuse, studies that rely on self-reported use are vulnerable to exposure misclassification due to recall errors or deception. We anticipate that errors in self-reported substance use reflect the tendency to underreport true use. To the extent that recall errors are not differential with regard to timing of reproductive development, the observed associations would likely underestimate the true magnitude of the association, in the absence of other biases. Studies examining the validity and reliability of self-reported alcohol and tobacco use among adolescents have generally shown good agreement [38]. Among adolescents, agreement for reports of alcohol use has been estimated at 94% after two years with agreement for other substance use such as cigarettes over 80% [38].

Exposure classification was limited to the available data pertaining to age at first use and peak frequency of use and dose-response could not be assessed. Although exposure was assigned only to those who reported use "more than a few times per month," exposure misclassification may have occurred among those who tried alcohol or tobacco before puberty but did not use the substances regularly until after puberty. To the extent these errors may have occurred more commonly among those with early development (given the social influences of early puberty on increased substance use), the associations may be overestimated if regular substance use were a consequence of earlier pubertal development

Defining exposure as substance use initiated at any time prior to pubertal development resulted in varying windows of opportunity for exposure for earlier versus later maturers. Thus, it is possible that the observed associations with prolonged time to puberty events could be explained by social norms of increased substance use initiation at later ages. Accordingly, girls who develop later would have more time to begin using alcohol or tobacco before puberty. Alternatively, girls who experience puberty later than their peers may be inclined to initiate substance use at the same time as their more mature peers, leading to classifications of prepubertal exposure that are spuriously related to pubertal events. To address these concerns, we also explored substance use defined by age at initiation. Comparing girls who began using alcohol or tobacco ≤ age 11 to those who did not resulted in associations of greater magnitude.

Data on constitutional delay of growth and puberty (family history) or causes of pubertal delay secondary to chronic illness such as malnutrition, asthma, endocrine disease or gastrointestinal disease were not available in this study. Unless the genetic or pathologic conditions that delay puberty are also associated with alcohol or tobacco consumption, these characteristics would not be expected to confound the observed associations. Measures addressing nutritional factors such as body fat, weight, height or self-perceived estimate of body size relative to others were also not available for analysis. Higher body mass index has been associated with earlier onset of puberty [39] and reduced alcohol use [40]. Therefore, an unequal distribution of obesity among prepubertal substance users and nonusers could possibly confound the observed associations. Thus, future studies investigating substance use and puberty onset should evaluate the potential confounding effects of obesity.

In conclusion, our findings are consistent with the hypothesis that female reproductive maturation may be disturbed by prepubertal use of alcohol and tobacco products. The clinical significance of modest delays in development are not understood and warrant further investigation. Studies are needed to replicate these findings using improved measurements of exposure and puberty events. Similar studies of prepubertal males would also be beneficial to determine if such patterns are applicable to both genders. If replicated, the findings of endocrine-disrupting effects of early alcohol and tobacco use could have

implications for health education and clinical practice by identifying modifiable behaviors that could be targeted at early ages to protect reproductive health.

Acknowledgments

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Table 1

Characteristics of the study population (n=3106).

	N	%
Age at Interview		
11 - 13	1801	58.0
14 - 17	839	27.0
18 - 21	466	15.0
Race/Ethnicity		
Non-Hispanic White	1645	53.0
Non-Hispanic Black	1010	32.5
Hispanic/Other	451	14.5
Household Income		
Less than $35,000	1088	35.0
$35,000-$49,999	636	20.5
$50,000 or more	1382	44.5
Parent's Education		
Less than High School	447	14.4
High School Graduate	2050	66.0
College Graduate	609	19.6
Age at Breast Development		
8 - 10	922	29.7
11 - 13	1870	60.2
≥ 14	102	3.3
Not occurred	212	6.8
Age at Body Hair Growth		
8 - 10	730	23.5
11 - 13	2008	64.6
≥ 14	78	2.5
Not occurred	290	9.3
Age at Menarche		
8 - 10	306	9.9
11 - 13	1709	55.0
≥ 14	179	5.8
Not occurred	912	29.3

Table 2

Mean age (standard deviations) at puberty events by early tobacco and alcohol use.

	Breast Development		Body Hair Growth		Menarche	
	n	Mean (sd)	n	Mean (sd)	n	Mean (sd)
Early Alcohol Use						
No	2835	11.0 (1.25)	2756	11.1 (1.16)	2119	11.7 (1.29)
Yes	59	11.9 (2.25)	60	11.5 (1.38)	75	12.5 (1.65)
p-value[†]		<0.001		0.07		<0.001
Early Tobacco Use						
No	2832	11.0 (1.28)	2758	11.1 (1.16)	2107	11.7 (1.29)
Yes	62	11.9 (1.32)	58	11.8 (1.15)	87	12.5 (1.52)
p-value[†]		<0.001		<0.001		<0.001

[†]Differences in mean age at pubertal event were assessed using t-tests with standard errors corrected using heteroskedasticity-consistent covariance matrix estimator that does not assume independent cases within clusters (families).

Table 3

Hazard ratios (95% confidence intervals) for onset of breast development, pubic hair growth, and menarche.[†]

	Model 1 Unadjusted	**Model 2[a] Age Adjusted**	**Model 3[b] Adjusted**
Breast Development			
Tobacco Use	0.74 (0.65-0.85)	0.86 (0.74-0.98)	0.91 (0.79-1.06)
Alcohol Use	0.71 (0.57-0.88)	0.81 (0.66-1.00)	0.84 (0.67-1.05)
Body Hair Growth			
Tobacco Use	0.81 (0.71-0.93)	0.91 (0.80-1.04)	0.92 (0.79-1.06)
Alcohol Use	0.97 (0.81-1.16)	1.07 (0.89-1.29)	1.12 (0.91-1.37)
Menarche			
Tobacco Use	0.90 (0.76-1.06)	0.85 (0.72-1.01)	0.94 (0.78-1.14)
Alcohol Use	0.90 (0.75-1.07)	0.85 (0.71-1.02)	0.92 (0.75-1.12)

[†] In all models, standard errors are corrected using heteroskedasticity-consistent covariance matrix estimator that does not assume independent cases within clusters (families).

[a] Adjusted for age.

[b] Adjusted for the other substance, age, and race, parental income, parental education.