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ASSOCIATIONS BETWEEN EARLY ALCOHOL AND TOBACCO USE AND PROLONGED TIME TO PUBERTY IN MALES

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Abstract

Background—Previous research has demonstrated a relationship between prepubertal alcohol and tobacco use and delayed pubertal characteristics in females. Although, laboratory research indicates that alcohol and tobacco use inhibits sexual maturation in male rats, human research in this area is lacking. To address this question among males, we conducted a study to explore the association between early use of alcohol and tobacco and time to development of secondary sexual characteristics.

Methods—The study population included 3,199 males interviewed between the ages of 11 and 21. Participants reported the ages at which they first experienced body hair growth, deepening of the voice, and facial hair growth. Early alcohol and tobacco use were defined as first use preceding the age of pubertal development among those reporting regular consumption patterns. Hazard ratios and 95% confidence intervals were calculated using Cox proportional hazard models.

Results—Early alcohol use was associated with longer time to body hair growth (HR 0.77; 95% CI 0.69–0.87), voice changes (HR 0.72; 95% CI 0.64–0.82), and facial hair growth (HR 0.77; 95% CI 0.68–0.86), after adjusting for tobacco use and age at interview. Tobacco use was not independently associated with the puberty indicators after controlling for alcohol use and age at interview.

Conclusions—Our findings are consistent with the hypothesis that alcohol may inhibit puberty onset in males, an association that has been previously observed among young females. Thus, alcohol may be an exposure deserving more scrutiny as a disruptor to normal pubertal development.

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INTRODUCTION

Among American youth, alcohol and tobacco use continues to be a prominent public health issue. Results from the Monitoring the Future survey (2013) suggest that across the US approximately 28% of students consume alcohol by the eighth grade, with nearly half reporting drinking enough alcohol to become drunk at least once in the past (Johnston *et al.* 2014). The same study reports that 15% of students have experimented with cigarettes by the eighth grade, although only 2% of eighth graders label themselves as current smokers (Johnston *et al.* 2014) The Surgeon General's Report refers to tobacco use as a "pediatric epidemic," noting that almost all tobacco use begins in childhood or adolescence (U.S. Department of Health and Human Services 2012). Historically, males have initiated substance use at earlier ages and at higher proportions than females, making substance-related health outcomes in boys a relevant point of concern (Westling *et al.* 2008). Previous studies have demonstrated that adverse reproductive outcomes are associated with alcohol and tobacco use among males, including altered hormone levels (Field *et al.* 1994, Venkat *et al.* 2009), reduced sperm count and motility (Villalta *et al.* 1997, Ramlau-Hansen *et al.* 2007, Soares and Melo 2008), increased risk for sperm anomalies (Pajarinen *et al.* 1996), decreased fecundity (Hull *et al.* 2000, Hassan and Kilick 2004), and multiple congenital anomalies among offspring (Zhang *et al.* 1992). However, little research exists regarding early use of alcohol and tobacco and altered development of pubertal characteristics.

Laboratory research indicates that alcohol and tobacco use inhibits sexual maturation in male rats. Chronic administration of ethanol to prepubertal rats alters several pubertal indices by reducing serum testosterone (Anderson *et al.* 1987, Cicero *et al.* 1990, Salonen *et al.* 1992), testicular weight (Anderson *et al.* 1987, Cicero *et al.* 1990), and the growth of secondary sexual organs, (seminal vesicles and epididymis) (Anderson *et al.* 1987, Cicero *et al.* 1990, Salonen *et al.* 1992). The oral administration of nicotine to prepubertal rats has also been demonstrated to reduce testicular and secondary sexual organ weight (seminal vesicles, epididymis, prostate gland, and vas deferens), suggesting delayed reproductive development (Londonkar *et al.* 2000). Thus, the alcohol and tobacco-related deviations from the expected physiology of pubertal development in laboratory animals suggest that delayed onset of puberty should be explored as a potential health-related outcome of early substance use.

In typical development, the pubertal period is marked by changes in hormone levels, increased growth, initiation of secondary sexual characteristics, and subsequent achievement of reproductive capacity (Buck Louis *et al.* 2008). The pubertal period begins with the reactivation of the hypothalamic-pituitary-gonadal (HPG) axis, which releases gonadotropin releasing hormone (GnRH), which then initiates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) (Emanuele and Emanuele 1998, Buck Louis *et al.* 2008, Schoeters *et al.* 2008). In males, the release of LH stimulates androgen secretion, such as testosterone (Buck Louis *et al.* 2008). The influence of these hormones as well as the hypothalamic-pituitary-adrenal (HPA) axis activated hormones of androstenedione and dehydroepiandrosterone (DHEA) results in the development of secondary sexual changes, including acne and pubic, axillary, and facial hair (Buck Louis *et al.* 2008, Schoeters *et al.* 2008). In boys, testicular enlargement (Tanner stage II), typically precedes the development

of pubic hair by approximately one year (Marshall and Tanner 1970). The most abrupt change in the adolescent male voice occurs during the transition from Tanner stage III to IV (Harries *et al.* 1997), therefore occurring approximately two years after testicular enlargement (Marshall and Tanner 1970). Among boys, delayed puberty may be clinically defined by the absence of one of the first signs of puberty (having a testicular volume <4 mL) by 14 years of age (Buck Louis *et al.* 2008). Delayed puberty may result from familial constitutional delay, chronic disease, primary hypothalamic-pituitary dysfunction, primary gonadal failure, or may be of unknown etiology (Traggiai and Stanhope 2002, Buck Louis *et al.* 2008) and can result in in psychological distress, reduced bone mass, and reduced potential height (Traggiai and Stanhope 2002).

To our knowledge, the only human study to date evaluating the relationship between prepubertal alcohol and tobacco use and delayed indications of puberty was conducted in females (Peck et al. 2011). In this cross-sectional study, girls initiating alcohol use before the age of 11 had longer time to breast development (HR = 0.54; 95% CI: 0.41–0.70), growth of body hair (HR=0.61; 95% CI 0.47–0.80; and menarche (HR =0.70; 95% CI: 0.56–0.86) compared to girls without early alcohol exposure. Similar associations with breast development and body hair growth, but not menarche, were observed for early tobacco use. When analyses were restricted to those who were 14 years of age or older when completing the interview, girls reporting pre-pubertal alcohol use had four times the odds of delayed puberty onset as measured by lack of breast development by the age of 13 (OR=3.99; 95% CI: 1.94–8.21). However, in males the potential effects of early substance use on pubertal development remain poorly understood due to the limited research in this area. Thus, in this study we aim to address this knowledge gap by exploring the relationship between prepubertal alcohol and tobacco use and time to pubertal development in males as indicated by the appearance of secondary sexual characteristics including the body hair growth, deepening of the voice, and facial hair growth.

METHODS

Study Population

Our study analyzed cross-sectional data collected as part of a longitudinal, multigenerational cohort study of adaptations to stress (Kaplan 1980). The study population includes the offspring of a cohort that was originally recruited from 18 junior high schools in Houston, Texas, in 1971 and followed into adulthood for psychosocial outcomes. The children (n=7,177) of the original study participants (i.e., biological, adopted, step, and foster children) were 11 years of age or older when they were interviewed between 1993–2002. These offspring comprise the study population for the present study. The study was reviewed and approved by the Texas A&M University Institutional Review Board.

The sample included a total of 3,617 male offspring; 3,199 boys between the ages of 11 and 21 are included in the present analyses. Of the 418 boys excluded, 163 were over the age of 21 at the time of the interview, 31 reported pubertal development before the age of 9, and 224 had data missing on the exposure, outcome or covariates of interest.

Measurements

Puberty Indicators—During the offspring interview, males were asked to report if they had ever experienced body hair growth, voice changing or deepening, or facial hair growth. If yes, they were queried about the age when each occurred. Age was recorded in whole years. Body hair growth was not defined further, so it is interpreted as the appearance of either axillary or pubic hair.

Alcohol and Tobacco Use—Alcohol and tobacco use were recorded as age at first use and the frequency at which the substance was used most. During the interview, 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.” Greatest frequency of use was addressed by asking, “When you were using this, what was the most that you ever used it?” The response options included: about every day, about once a week, a few times a month, a few times a year or less, only once or sporadically. Selecting a specific age to define early use for all subjects is problematic because the sensitive window of exposure is unknown and would be expected to vary across individuals who experience normal pubertal changes at different ages. Thus, with consideration for the fact that exposures must precede the outcome in order to be relevant determinants, we defined prepubertal alcohol consumption as first reported use of beer, wine or liquor before the age at onset of the pubertal characteristic of interest. Prepubertal tobacco use was similarly defined as first reported use of cigarettes, chewing tobacco, snuff or dip before the age reported for body hair growth, voice changes or beard growth.

Exposure was limited to those who reported substance use at least “a few times a month” or more to avoid including those who tried alcohol or tobacco at an early age but never used regularly. To address uncertainty concerning the temporal sequence of exposure and outcomes reported during the same year of age, we explored two definitions of prepubertal exposure among regular users: (1) age at first use less than the age at onset of the pubertal characteristic and (2) age at first use less than or equal to the age at onset of the pubertal characteristic. Because the results of analyses using the two definitions did not substantively differ, we report results for age at first use less than age at onset of each pubertal characteristic.

Statistical Analysis

Mean age at appearance of body hair, voice change, and development of facial hair was compared between early alcohol users and nonusers and between early tobacco users and nonusers using t-tests with standard errors corrected using heteroscedasticity-consistent covariance matrix estimator that does not assume independence. Hazard ratios and 95% confidence intervals were calculated using Cox proportional hazards models to compare the hazard of onset of each pubertal characteristic for those with prepubertal alcohol or tobacco consumption to those without exposure. Hazard ratios less than 1.0 indicate longer time to puberty (i.e., a reduced hazard of puberty) while hazard ratios greater than 1.0 indicate shorter time to puberty (i.e., increased hazard of puberty). The time-varying variables are the reported ages at onset for each puberty characteristic. Boys who had not experienced the

puberty event were censored at the age of interview (19.5 percent without body hair growth, 34.7 percent without voice change, 53.8 percent without facial hair growth). Potential confounders assessed in these analyses included other substance use (alcohol or tobacco), age at interview and race, which were collected from the offspring interview, and household income and parent's education, which were obtained from the parent's interview. Only age at interview and other substance use altered the hazard ratios for the exposure of interest by more than ten percent; thus, these factors were controlled in the final models. All analyses were estimated using STATA 11.0. (College Station, TX). Because the data include siblings, we present corrected standard errors in all models to account for the lack of independent observations (clustering) among children in the same household (Hayes and Cai 2007).

RESULTS

Study population characteristics are described in Table 1. Interviews were conducted at the average age of 14 (sd 2.7; range 11–21). Overall, 84 percent had experienced one or more of the puberty indicators. A total of 80.5 percent reported growth of body hair (mean age 11.9 years, sd 1.4), 65.3 percent reported experiencing deepening of the voice (mean age 12.6 years, sd 1.6) and 46.2 percent reported growth of facial hair (mean age 13.7 years, sd 2.0). Among those reporting puberty characteristics, patterns of the frequency of early alcohol and tobacco use were similar. A total of 7.7 and 7.2 percent reported alcohol and tobacco use, respectively, before the age at which body hair growth occurred, 12.1 and 11.2 percent reported using before experiencing voice changes and 23.3 and 20.4 percent using before facial hair growth.

Boys reporting prepubertal alcohol and tobacco use were older at onset of all pubertal characteristics (Table 2). The largest mean differences were for facial hair growth by alcohol use (2.0 years), voice change by alcohol use (1.6 years), and facial hair growth by tobacco use (1.4 years).

In unadjusted Cox proportional hazards models, tobacco use and alcohol use were each associated with increased time to all pubertal characteristics (Table 3). Adjusting for alcohol use and age at interview, however, attenuated associations between tobacco use and the puberty indicators and the upper bound of the confidence intervals exceeded 1.0. The associations between prepubertal alcohol use and the puberty indicators remained statistically significant after adjustment for tobacco use and age at interview, with alcohol use associated with longer time to body hair growth (HR 0.77; 95% CI 0.69–0.87), voice change (HR 0.72; 95% CI 0.64–0.82), and facial hair growth (HR 0.77; 95% CI 0.68–0.86).

DISCUSSION

Our study provides evidence that alcohol use during early stages of reproductive development may prolong time to puberty in males. Boys who reported prepubertal alcohol use were older at the time of appearance of body hair, voice changes, and facial hair growth. The associations persisted after controlling for tobacco use and age at interview. Tobacco use before puberty was not associated with the timing of the onset of these pubertal characteristics after adjusting for alcohol use and age at interview.

Due to the cross-sectional nature of these data, the temporal sequence between alcohol exposure and pubertal changes cannot be confirmed in this study. However, these results are consistent with the limited human and animal data linking alcohol to pubertal or hormonal alterations in males. For example, a small study assessing serum testosterone, LH, and FSH concentrations among teenage males being treated for drug and alcohol abuse noted significantly lower mean hormone concentrations among treated boys (n=22) when compared to boys with no history of substance use (n=10). (Diamond *et al.* 1986). When a subset of six boys were followed up to a year after drug and alcohol withdrawal, mean testosterone levels significantly increased post-treatment, suggesting that the drug and alcohol abuse had a suppressive effect on the HPG axis. The authors noted, however, that all participants had "adult genital development" prior to entering the study, thus no significant differences were observed concerning testicular volume, penile length or Tanner stage of pubic hair development. Given that body hair, facial hair, and larynx growth is androgen-dependent, our observation of prolonged time to onset of secondary sexual characteristics among alcohol users is compatible with the observed hormonal patterns (Diamond *et al.* 1986), although their study did not directly evaluate the timing of alcohol consumption in relation to puberty onset.

Laboratory studies have demonstrated that alcohol use has a direct inhibitory effect at all points on the HPG axis in rats (Anderson *et al.* 1987). In particular, among prepubertal rats, chronic alcohol exposure decreases testosterone levels by 65 to 80% (Cicero *et al.* 1990) and acute and chronic alcohol use is associated with low concentrations of LH in adults (Cicero *et al.* 1990, Salonen *et al.* 1992), as well as inhibition of testosterone secretions by the testes (Little *et al.* 1992). Mechanisms for these relationships suggest that both acute and chronic alcohol exposure may induce cell necrosis and apoptosis of testicular germ cells, lowering levels of testosterone, (Zhu *et al.* 2000, Emanuele and Emanuele 2001) or may induce elevated levels of prolactin and cytokines, which may contribute to the suppression of testosterone release from the gonads (Emanuele and Emanuele 2001). Alternatively, alcohol may cause disturbances in adrenal gland functioning in the HPA axis, which may contribute to gonadal and testosterone suppression (Emanuele and Emanuele 2001). While the exact mechanism relating alcohol use and potential pubertal delays remains unknown, the proposed anti-androgenic effects of alcohol are consistent with the subsequent delay in the development of secondary sexual characteristics observed in our study.

Studies of the effect of tobacco use on testosterone and LH levels have been conducted mainly among adult males, with inconsistent results (Simon *et al.* 1992, Field *et al.* 1994, Al-Matubsi *et al.* 2011, Svartberg *et al.* 2003, Funabashi *et al.* 2006). For instance, a study conducted by Richtoff et al. examined the effect of tobacco use on reproductive factors among Swedish male adolescents (Richthoff *et al.* 2008). However, the study failed to observe differences in testicular volume, testosterone levels, or LH concentrations between smokers and non-smokers (Richthoff *et al.* 2008). The lack of association between tobacco use and testicular volume or hormone levels (testosterone and LH) suggests that smoking may not affect the timing of onset of pubertal characteristics in males; findings supported by our study.

The use of secondary data optimized the opportunity to address this challenging, understudied question, but limited the study to existing measurements. Thus, limitations that should be considered when interpreting the study results include the potential for measurement error in the exposure and outcome variables, unmeasured confounders, and the inability of a cross-sectional study to establish temporality. The exposure and outcome measurements are limited to retrospective reporting of events. Clinical examination of the stages of sexual maturation (i.e., Tanner staging) was not conducted during the original study. Furthermore, the sensitive nature of substance use renders it vulnerable to under-reporting. Additionally, exposure assessment was restricted to available information on age at first use and amount most used. Thus, exposure misclassification may have occurred if those who reported early initiation of use and using “more than a few times per month” did not become habitual users until after pubertal development. Such errors could have overestimated the observed association if they occurred more frequently among those with earlier pubertal onset. Potential confounders such as obesity and family related factors, including parental traits, prenatal environment, or stressful home environment, were not available for evaluation in this study. However, although both obesity and stressful home environment have been associated with earlier puberty in girls, this relationship has not been consistently observed in boys (Ellis *et al.* 1999, Kaplowitz 2008), suggesting that these two factors may not meet the criteria for confounding in this study. In contrast, other familial factors such as parental traits and prenatal environment have been demonstrated to influence both substance use and pubertal development, and as unmeasured variables in this study may serve to confound the observed associations (Cornelius *et al.* 2000, Traggiai and Stanhope 2002, Lan *et al.* 2013, Patrick *et al.* 2014). Furthermore, this cross-sectional study design cannot establish the temporal sequence between prepubertal substance use and delayed development. Thus, alternative explanations for the observed associations cannot be ruled out. It is possible that young males lacking the physical maturity of their peers may increase substance use as a result of depression or in an attempt to fit in with others who are more developed.

This study reports associations between alcohol use and increased time to body hair growth, voice changes and facial hair growth. These observed associations are consistent with the hypothesis that the effects of alcohol may inhibit puberty onset in males. While causal inference is limited by the nature of these data, these hypothesis-generating results are suggestive of potential adverse effects of substance use among youth that should be investigated further in epidemiologic studies. The clinical significance of the one to two-year delays in the reported appearance of pubertal indicators is unknown and also deserving of further study. Future confirmation of these findings would have important implications for adolescent health and for public health practitioners working in areas of substance abuse, health education, and preventive health.

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KEY MESSAGES

1. Boys reporting prepubertal alcohol and tobacco use were older at onset of all pubertal characteristics. Mean ages at facial hair growth and voice change were 2.0 and 1.6 years greater, respectively, for early alcohol users compared to non-users. Average age at facial hair growth was 1.4 years greater among early tobacco users compared to non-users.
2. Adjusting for tobacco use and age at interview, early alcohol use was associated with delayed pubertal development in boys, including a longer time to body hair growth (HR 0.77; 95% CI 0.69–0.87), voice changes (HR 0.72; 95% CI 0.64–0.82), and facial hair growth (HR 0.77; 95% CI 0.68–0.86).
3. Crude associations between early tobacco use and delays in pubertal development were observed; however, these associations were attenuated after adjusting for alcohol use and age at interview.

Table 1

Characteristics of the study participants (n=3199).

	N	%
Age at Interview		
11 – 13	1914	59.8
14 – 17	843	26.4
18 – 21	442	13.8
Race/Ethnicity		
Non-Hispanic White	1760	55.0
Non-Hispanic Black	979	30.6
Hispanic/Other	460	14.4
Household Income		
Less than $35,000	1038	32.4
$35,000–$49,999	694	21.7
$50,000 or more	1467	45.9
Parent's Education		
Less than High School	409	12.8
High School Graduate	2136	66.8
College Graduate	654	20.4
Age at Body Hair Growth		
9 – 10	318	9.9
11 – 13	1976	61.8
≥ 14	280	8.8
Not occurred	625	19.5
Age at Voice Change		
9 – 10	116	3.6
11 – 13	1453	45.4
≥ 14	521	16.3
Not occurred	1109	34.7
Age at Facial Hair Growth		
9 – 10	58	1.8
11 – 13	655	20.5
≥ 14	765	23.9
Not occurred	1721	53.8

Table 2

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

	Body Hair Growth		Voice Change		Facial Hair Growth	
	n	**Mean (sd)**	**n**	**Mean (sd)**	**n**	**Mean (sd)**
Early Alcohol Use						
No	2377	11.8 (1.3)	1837	12.4 (1.4)	1134	13.2 (1.8)
Yes	197	13.0 (1.7)	253	14.0 (1.7)	344	15.2 (1.7)
p-value*		<.001		<.001		<.001
Early Tobacco Use						
No	2388	11.8 (1.3)	1867	12.5 (1.5)	1177	13.4 (2.0)
Yes	186	12.7 (1.4)	223	13.6 (1.5)	301	14.8 (1.6)
p-value*		<.001		<.001		<.001

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

Table 3

Hazard ratios (95% confidence intervals) for onset of body hair growth, voice change, and facial hair growth.*

	Unadjusted HR (95% CI)	Adjusted HR ** (95% CI)
Body Hair Growth		
Tobacco Use	0.75 (0.67–0.84)	0.94 (0.84–1.01)
Alcohol Use	0.63 (0.56–0.70)	0.77 (0.69–0.87)
Voice Change		
Tobacco Use	0.72 (0.65–0.80)	0.95 (0.85–1.07)
Alcohol Use	0.58 (0.52–0.64)	0.72 (0.64–0.82)
Facial Hair Growth		
Tobacco Use	0.77 (0.69–0.84)	0.98 (0.88–1.10)
Alcohol Use	0.61 (0.55–0.67)	0.77 (0.68–0.86)

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

** Adjusted for the other substance and age at interview.