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Socio-Environmental Factors Associated With Pubertal Development in Female Adolescents: The Role of Prepubertal Tobacco and Alcohol Use

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Early alcohol and tobacco use has become alarmingly common among young adolescents in the United States, with up to 35\% of seventh graders reporting alcohol use before the age of 13 [1] and 26\% of high-school students reporting current tobacco use [2]. In a survey involving eighth-, 10th-, and 12th-grade students, 10.3\%–25.9\% reported consuming five or more alcoholic drinks in succession within the previous 2 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]. However, studies assessing the effects of alcohol and tobacco use on pubertal development are lacking.

Research involving laboratory animals indicates that alcohol delays puberty in female rats by altering puberty-related hormones such as estradiol, luteinizing hormone (LH), and...
growth hormone, and by interfering with ovarian development and function [6]. The anti-estrogenic effects of smoking have been well-established by studies in humans [5], but hormonal responses to alcohol have been less consistently reported [7,8]. Reproductive maturation in female adolescents is controlled by the hypothalamic–pituitary–gonadal axis [9]. During normal development, the hypothalamus secretes gonadotropin-releasing hormone, which regulates the secretion of the LH and the follicle stimulating hormone from the pituitary. The pituitary gonadotropins stimulate ovarian development and the maturing ovaries secrete increasing levels of estradiol, which promotes 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 female adolescents [11]. Pubic hair, which generally appears shortly thereafter, is a result of increased androgen secretion by the adrenal glands, and therefore may not correlate with the maturation of the hypothalamic–pituitary–gonadal axis [12]. On average, menarche follows approximately 2–3 years later [13,14]. The age at onset of puberty varies across individuals, with the average age at initial breast development (entry into Tanner stage 2) in the United States reported to range from 9.96 to 10.38 in whites and 8.87–9.5 in African Americans [13–15].

Delayed puberty, defined as the absence of breast development by the age of 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 uses cross-sectional data collected from adolescents who participated in the Adaptations to Stress Study [20]. The original parent cohort was recruited in 1971 from 18 of the 36 junior high schools in the Houston Independent School District and was followed up into their mid-30s (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 and 2002. Data from the child interviews were analyzed for this study.

Informed consent was obtained from all participants before enrollment. The study protocol was reviewed and approved by the Texas A & M University Institutional Review Board. A total of 3,106 girls between the ages of 11 and 21 were included in these analyses, after excluding 151 aged >21 years 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, or covariates of interest.

Measurements

Puberty assessment

We analyzed the effects of prepubertal alcohol and tobacco use on the timing of breast development, body hair growth, and menarche. To assess the timing of pubertal events, female adolescents were asked whether 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 at which each of the events occurred. No additional description of body hair growth was provided; therefore, 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? Drank beer? Drank wine? Drank hard liquor?” Those who had not used alcohol or tobacco were coded as “never.” Peak frequency was assessed by asking, “When were you 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 cut-point for a biologically meaningful age at exposure was problematic given that the specific timing of etiologically relevant exposures is unknown and given that temporally relevant exposures (i.e., exposures preceding the outcome) would most likely occur at different ages for individuals who experience pubertal changes at different ages. Therefore, 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 avoided classifying those who simply tried alcohol or tobacco at an early age and never used regularly as exposed. 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. Therefore, we analyzed the data using two definitions of prepubertal exposure among regular users as follows: (1) age at first alcohol use less than the age at onset of each pubertal characteristic or (2) age at first alcohol use less than or equal to 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 less than the 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 at age 11 or less among more than occasional users, selecting the age cut-point representing the mean age of pubertal events among the nonusers. To avoid the erroneous inclusion of substance use initiated after the outcome, substance use must have also the puberty event.
Covariates
Age at interview, race, household income, and parent’s education were evaluated as potential confounders. Age and race information 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. Therefore, 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 (HRs) and 95% confidence intervals (CIs) 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. HRs of <1.0 indicate a reduced hazard of puberty (i.e., longer time to puberty), whereas HRs of >1.0 indicate an increased hazard of puberty (i.e., shorter time to puberty). For each puberty characteristic, separate models were estimated and the time-varying variables were the reported ages at onset. 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, and 29.4% without menarche).

We used logistic regression models to examine associations with delayed puberty, defined as lack of breast development by the age of 13. These analyses were restricted to girls aged 14 years of age or older at the time of the interview (n = 1,305). Odds ratios (ORs) and 95% CIs are reported.

All analyses were estimated using STATA 9.0.2 (StataCorp, 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 presented 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%). The majority (96%) of participants 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 76.6% reported menarche (mean age, 11.7 years [SD, 1.3]). Alcohol and tobacco use occurred before the reported pubertal events in 1.9%–2.8% of the sample population (Table 2).

Table 1
Characteristics of the study population (n = 3,106)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at interview (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11–13</td>
<td>1,801</td>
<td>58.0</td>
</tr>
<tr>
<td>14–17</td>
<td>839</td>
<td>27.0</td>
</tr>
<tr>
<td>18–21</td>
<td>466</td>
<td>15.0</td>
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<tr>
<td>Race/Ethnicity</td>
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<td></td>
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<tr>
<td>Non-Hispanic white</td>
<td>1,645</td>
<td>53.0</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>1,010</td>
<td>32.5</td>
</tr>
<tr>
<td>Hispanic/other</td>
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<td>14.5</td>
</tr>
<tr>
<td>Household income</td>
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<tr>
<td>$35,000–$49,999</td>
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</tr>
<tr>
<td>$50,000 or more</td>
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<td>44.5</td>
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<tr>
<td>Parent’s education</td>
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<tr>
<td>Less than high school</td>
<td>447</td>
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<tr>
<td>High school graduate</td>
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<td>66.0</td>
</tr>
<tr>
<td>College graduate</td>
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<td>19.6</td>
</tr>
<tr>
<td>Age at breast development (years)</td>
<td></td>
<td></td>
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<tr>
<td>8–10</td>
<td>922</td>
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</tr>
<tr>
<td>11–13</td>
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</tr>
<tr>
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<td>102</td>
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<tr>
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<td>6.8</td>
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<tr>
<td>Age at body hair growth (years)</td>
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<td></td>
</tr>
<tr>
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<tr>
<td>11–13</td>
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<tr>
<td>≥14</td>
<td>78</td>
<td>2.5</td>
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<tr>
<td>Not occurred</td>
<td>290</td>
<td>9.3</td>
</tr>
<tr>
<td>Age at menarche (years)</td>
<td></td>
<td></td>
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<tr>
<td>8–10</td>
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<td>9.9</td>
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<td>11–13</td>
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<td>≥14</td>
<td>179</td>
<td>5.8</td>
</tr>
<tr>
<td>Not occurred</td>
<td>912</td>
<td>29.3</td>
</tr>
</tbody>
</table>

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 found to be older at onset of all pubertal characteristics, but mean differences were not statistically significant for alcohol consumption and body hair growth. 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 CIs 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 at age 11 or less, the HRs 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 with those not exposed by this age. Similar associations were observed for growth of 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 aged 14 years or more examined associations with delayed puberty onset, as indicated by lack of breast development by the age of 13. When compared with 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, 0.84–4.66).

### Discussion

Early pubertal development has been associated with an increased prevalence of subsequent tobacco and alcohol use during adolescence [22]. Although the social and behavioral consequences of early pubertal timing have been well explored, the possible effect 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]]. Therefore, it is plausible that substances such as alcohol and tobacco, which may display similar endocrine-disrupting properties, could influence reproductive functioning and development. 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 before the event of puberty were modestly associated with later onset, but adjusted HRs did not maintain statistical significance. However, alcohol and tobacco use initiated at or before the age of 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 aged 14 years and older, the odds of delayed pubertal onset were increased fourfold among girls who initiated alcohol use at any time before breast development.

The deficit of human research in this area is most 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 female adolescents who abused alcohol as compared with 114 young females who did not use alcohol [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 follicle stimulating hormone 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 and nitric oxide systems [28]. Secretion of puberty-related hormones such as insulin-like growth factor-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]). Moreover, 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]; however, 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. However, the secondary analysis of these cross-sectional data 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. Therefore, 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 that 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 1 year [37].

Self-reports are the most common sources 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 that can result from recall errors or deception. We anticipate that errors in self-reported substance use reflect the tendency to under-report true use. To the extent that recall errors are not differential with regard to timing of reproductive development, the observed associations would most 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 2 years with an agreement of over 80% for other substance use such as cigarettes [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 that 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 underestimated if regular substance use were a consequence of earlier pubertal development.

Defining exposure as substance use initiated at any time before pubertal development resulted in varying windows of opportunity for exposure for those who matured earlier versus later. Therefore, 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 by the age of 11 with 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, 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. Therefore, 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 is not fully understood and warrants further investigation. Studies are needed to replicate these findings using improved measurements of exposure and puberty events. Similar studies on prepubertal males would also be beneficial to determine whether 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 identi-
fying modifiable behaviors that could be targeted at early ages to protect reproductive health.

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