Prenatal alcohol exposure selectively enhances young adult perceived pleasantness of alcohol odors

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HIGHLIGHTS

- Subjects from a prospective cohort with known prenatal alcohol exposure are studied.
- Hedonic responses to alcohol and other odors were assessed in young adults.
- Analyses controlled for other exposures and current drinking.
- Prenatal alcohol exposure increased perceived pleasantness of alcohol odors.

ABSTRACT

Prenatal alcohol exposure (PAE) can lead to life-long neurobehavioral and social problems that can include a greater likelihood of early use and/or abuse of alcohol compared to older teens and young adults without PAE. Basic research in animals demonstrates that PAE influences later postnatal responses to chemosensory cues (i.e., odor & taste) associated with alcohol. We hypothesized that PAE would be related to poorer abilities to identify odors of alcohol-containing beverages, and would alter perceived alcohol odor intensity and pleasantness. To address this hypothesis we examined responses to alcohol and other odors in a small sample of young adults with detailed prenatal histories of exposure to alcohol and other drugs. The key finding from our controlled analyses is that higher levels of PAE were related to higher relative ratings of pleasantness for alcohol odors. As far as we are aware, this is the first published study to report the influence of PAE on responses to alcohol beverage odors in young adults. These findings are consistent with the hypothesis that positive associations (i.e., “pleasantness”) to the chemosensory properties of alcohol (i.e., odor) are acquired prenatally and are retained for many years despite myriad interceding postnatal experiences. Alternate hypotheses may also be supported by the results. There are potential implications of altered alcohol odor responses for understanding individual differences in initiation of drinking, and alcohol seeking and high-risk alcohol-related behaviors in young adults.

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1. Introduction

Prenatal alcohol exposure (PAE) can lead to life-long neurobehavioral, cognitive and social problems that comprise the fetal alcohol spectrum disorders (FASD; [46]). Behavioral expressions of FASD include a greater likelihood of early use and/or abuse of alcohol and other substances compared to non-exposed adolescents and young adults. Early alcohol/substance use has been characterized as a “secondary disability” associated with fetal alcohol syndrome (FAS) in teens [68]. PAE was related to early initiation of alcohol use as well as to drinking-related problems at 14 and 21 years of age [8,9,67]. These results were independent of maternal demographics, smoking or drug use during pregnancy, and familial postpartum alcohol problems.

Several factors may explain the origins of this increased risk for early alcohol use/abuse after PAE. These factors include teratogenic influences of alcohol on physiological and/or neural processes relevant to...
alcohol metabolism, sensitivity or reward properties [3], as well as post-
natal parental drinking and/or smoking during a person’s childhood or
adolescence [61]. In fact, it has been argued on the basis of an asso-
ciation between PAE and subsequent alcohol use disorders and/or de-
pendence that an additional factor is some non-teratogenic “biological
origin of adult alcohol disorders” [4,5], although the nature of this factor
has not been identified.

Extensive basic research in animal models demonstrates that prena-
tal or early neonatal alcohol exposure alters a variety of later behavioral
[2,12,20,45,50], consummatory [21,28,52,60,73], pharmacological [28,
55], biochemical [50], and physiological [69, 71] responses to alcohol.
Possible means by which PAE influences postnatal responses to and
ingestion of alcohol include altered chemosensory experiences of alcohol
and/or learning about the rewarding (or aversive) properties of alcohol
cues in utero (e.g., [7,20,22,23,45,55,73]); ideas articulated well in the
theoretical review by N. Spear and Molina [66]. PAE leads reliably to
altered biobehavioral responses to sensory cues associated with alcohol
[29,66], including altered learned responses to paired alcohol odors and
tastes after brief PAE [1,7,23,55]. In rats, even low-dose alcohol exposure
during fetal development is associated with later increases in alcohol
ingestion [2,20,24,73].

While animal studies have shown that PAE alters various re-
sponses to alcohol odors [20,66], PAE also impairs olfactory function
for other odors. For example, PAE mice had more difficulty than non-
exposed mice in discriminating similar odors (spermincaraway) pin learning and memory [75]. Akers et al., also reported that
largest reductions in brain area size by high-resolution MRI in
these mice was found in the olfactory bulb. Although Barron and
Riley [10] also reported that PAE was associated with decreased vol-
ume of the olfactory bulb in rats, they found no evidence that PAE
impaired the ability of pre-weanling rats to detect a novel odor mea-
sured by a change in respiration.

There is evidence suggesting that human infants of mothers who
drank alcohol during pregnancy also appear to respond to or recognize
alcohol odors differently than infants of mothers who abstained while
pregnant. Of the few studies that examined how PAE may affect alcohol
tolerance and alcohol-seeking behavior in infants, teens or adults [4,5,
8,35,72], some included covariate controls (e.g., [8,9]). Each study
reported increased alcohol-associated problems related to PAE;
none addressed specific olfactory or gustatory responses to alcohol.
A study of 5- to 10-year-old children reported that 15 of 44 children
with some kind of “FASD” had a “definite difference” in “taste/smell
sensitivity,” but there was no comparison group [76]. One prior
report using the San Diego Smell Identification Test suggested that
PAE altered olfactory sensitivity in children [13]. We are aware of
no published studies assessing differences in hedonic responses to, or
ratings of pleasantness of alcohol odors by people who had been
exposed prenatally to alcohol compared to those who were not alcohol
exposed.

We hypothesized that increasing levels of PAE would alter responses
to alcohol odors in young adult men and women. Consistent with prior
human studies, we hypothesized that increasing levels of PAE would
alter responses to alcohol odors and be related to poorer abilities of
young adults to identify and rate odors, especially the odors of
alcohol-containing beverages. Specifically, we hypothesized that PAE
would be associated significantly with: 1) impaired recognition of
odors; and altered ratings of perceived alcohol odor 2) intensity and
3) pleasantness. We examined simple responses to chemosensory
properties (odor) of alcohol (ethanol) and other odorants in a
small sample of young adults from a large established prospective
longitudinal cohort with detailed prenatal and current histories of
experiences with alcohol and other drugs. We also considered other
select prenatal and current environmental factors thought to mediate
or moderate relations among PAE and ratings of alcohol pleasantness,
including proximity to other individuals who drink, especially current
caregivers.

2. Methods

The Wayne State University IRB approved all study procedures and
signed informed consent was obtained from all participants prior to in-
terviews and testing.

2.1. Participants

Participants (n = 75) were selected from our large, previously
established prospective cohort of 18- to 19-year-old male and female
urban African-Americans from the longitudinal “SCHOO-BE” study
described previously in detail (e.g., [25,27]). Recruitment for this
study began with the oldest teen who participated in the age 18- to
19-year follow-up assessment and moved forward until a sample of
75 was obtained for this report. The SCHOO-BE sample was identified
initially from a pregnancy sample recruited in 1988–1991 of the bio-
logic mothers of current study participants (cf., [25,27]). Exclusions in
the original pregnancy study included known HIV-positive
mothers, repeated pregnancies from the same mother, or major con-
genital malformations of the offspring identified at birth.

All female young adult participants were pre-screened for their
current pregnancy status during a pre-enrollment telephone recruit-
ment call. Those who indicated that they were pregnant were asked
to delay participation until after giving birth. Female participants
who were eligible for testing were asked to submit to an hCG urine
pregnancy test prior to participation since the long-term effects
of the selected odors on a fetus are unknown. Upon arrival to the
lab for testing, two female participants tested pregnant and thus
did not complete the odor assessment; they did complete the interview.

2.2. Prenatal alcohol assessment

In the original prospective cohort, women in the antenatal clinic
reporting peri-conceptional alcohol consumption averaging at least
1.0 oz of absolute alcohol per day (AAD) – the equivalent of about two
standard drinks per day – were recruited. A random sample of approxi-
mately 8% of lower level drinkers and abstainers was also invited to
participate. In addition, all pregnant women reporting any cocaine use
were recruited. At every antenatal clinic visit, semi-structured timeline
follow-back interviews [65] solicited information about each mother’s
alcohol consumption and drug use for the previous two weeks. Mothers
were asked to recall what they drank, both at the time of the first visit,
which on average occurred at the 23rd week of gestation (range: 6 to
38 weeks), and their drinking around the time of conception. Most
women (90.2%) were not interviewed until after the first trimester.
Detailed information regarding beverage type, specific drinking
habits, binge drinking, alcohol consumption (as number of standard
drinks) at particular times of the day and days of the week was
obtained. Drinking volume was noted for each day. Based on self-
reported drinking, we calculated several alcohol consumption mea-
sures: average ounces of absolute alcohol per day at: 1) conception
(AADD0), 2) at the first prenatal visit (AAD1) and 3) across pregnancy
(AADXP); as well as average ounces of absolute alcohol per drinking
day at 4) conception (AAD0), 5) at the first prenatal visit (AADD1),
and 6) across pregnancy (AADDXP). We, and others, have effectively
used these measures of alcohol use to examine prenatal alcohol-
related outcomes (e.g., [11,14,41,43,44,54]). In addition, at the first
antenatal visit we assessed problems associated with drinking
with the 25-item Michigan Alcoholism Screening Test (MASC;
[59]), the CAGE screen [36], and the 4-item T-ACE (or TACER-3) screen
[16,64]. The T-ACE/TACER-3 screen includes a question about
“tolerance” – the “T” in “T-ACE/TACER-3” – asking how many drinks it
takes to feel high.
2.3. At-risk alcohol metric

From all these individual alcohol assessment measures and instruments, a metric of prenatal “at-risk alcohol exposure” (ARAE) was calculated (cf. [19]). The ARAE metric dichotomized participants into those “at risk” or not. The ARAE metric defined a person “at risk” if any of one of the component prenatal drinking measures met the following criteria (see [19]): AADD0 ≥ 1.0 oz; AADD1 ≥ 0.5 oz; AADXP ≥ 0.5 oz; AADD0 ≥ 2.5 oz; AADD1 ≥ 2.5 oz; AADDXP ≥ 2.5 oz; MAST ≥ 5; CAGE ≥ 2; T-ACE ≥ 3 (i.e., the TACER-3 cut-point; [16]).

With the exception of the T-ACE, all cut-points are based on standard definitions of “at-risk drinking” (cf. [6,42,57]). The American College of Obstetrics & Gynecology [6] currently recommends a cut-point of 2 for the total T-ACE score which maximizes sensitivity in identifying women drinking at any level [63]. We had demonstrated previously that a total score cut-point of 3 or more rather than 2 or more on the T-ACE (i.e., the “TACER-3” screen), improved prediction of which pregnant women were consuming higher levels of alcohol, reduced “false positives” in detecting at-risk drinking, and improved prediction of alcohol-related neurobehavioral outcomes in children [16,17,19].

2.4. Caregiver alcohol use

At the age 14-year visit, caregivers were also queried about their own current alcohol consumption. For all women reporting any drinking, information about the type and pattern of drinking on each day during a typical week was also obtained. Measures of average amount of absolute alcohol consumed during a week (AAD) and average amount of absolute alcohol per drinking day (AADD) were also constructed.

2.5. Young adult risk alcohol use

To assess the young adults’ own current risk alcohol use, participants also completed the TACER-3 screen. The TACER-3 is the modification of the original T-ACE noted above using a total score cut-point of 3 which increases specificity while maintaining sensitivity equivalent to the original report [64] for identifying risk drinking.

2.6. Control variables

At the age 14-year visit, the primary caregiver, usually the biological mother (96%), was interviewed on many control variables for use in statistical analyses. These included assessments of the home environment, parenting quality, maternal age at the time of the first prenatal visit, primary caregiver SES, IQ, and education, and prenatal exposure to cigarettes, marijuana, and cocaine. A modified Home Observation for Measurement of the Environment (the “HOME”; [15]) was used to evaluate parenting quality and home environment. Socio-economic status (SES) was estimated using Hollingshead’s 4-factor index [40]. For a detailed discussion, see [26].

2.7. Odor function testing

Prior to testing, all participants rinsed their mouth with water and were told to refrain from chewing gum or mints, eating or drinking, and smoking or using chewing tobacco until testing was completed. A research assistant conducted confidential participant interviews about demographic characteristics and past and current alcohol and drug use.

2.7.1. Smell identification test

To assess basic olfactory function, all young adults completed the University of Pennsylvania Smell Identification Test (UP-SIT, [33,34]). The UP-SIT is a 40-item self-administered “scratch-and-sniff”-type test with high test–retest reliability (r = 0.94; [34]) and the ability to predict a variety of developmental or progressive neural disorders and psychopathologies (e.g., [30,32,47,70]). Performance on the UP-SIT reveals olfactory dysfunction as anosmia or mild, moderate, or severe smell loss [33]. UP-SIT results are sex-influenced, so males and females are considered separately.

2.7.2. Alcohol odor assessment via the “bottle test”

The alcohol odor assessment was based on work by Schmidt and Beauchamp [58] and Mennella and Garcia [49]. Odor stimuli were prepared and presented via 140-ml plastic (HDPE) squeeze bottles with flip-up caps. Each odorant solution (3 ml per bottle) was prepared in isolation and in a manner preventing cross-contamination of odors (see Table 1).

The translucent squeeze bottles were covered in foil and kept out of sight at least 2 ft from the participants. Odor presentation order was random. One at the time, the top of each opened bottle was positioned 3 cm from the participants’ nose. For each odor, “puffs” were delivered from the squeeze bottle to each nostril. Each young adult was given three attempts to identify the odor, if needed, with a 30-sec interval between each puff. The literal response was recorded and later coded as ‘correct’ or ‘incorrect’. Participants also rated, on a 5-point Likert scale, the pleasantness of the odor (1 = very unpleasant; 2 = unpleasant; 3 = neutral; 4 = pleasant; 5 = very pleasant), and odor intensity (1 = no odor; 2 = faint odor; 3 = moderate odor; 4 = strong odor; 5 = extremely strong odor). A visible scale was available to aid participant ratings.

2.8. Statistical analyses

Prior to analyses, checks were performed for missing and out-of-range data and for deviations from normality. To evaluate the relations between PAE and odor variables, hierarchical regressions were utilized entering PAE and 14-year caregiver alcohol use in the first step and then all covariates simultaneously in the second step using forward entry (p < 0.05 to enter, p < 0.10 to remove). Subsequent direct comparisons and other follow up analyses were used to elaborate the nature of the impact of PAE.

3. Results

3.1. Participants

The mean participant age was 20.9 years (SD = 0.5, range = 19.0 to 21.7). There were more females (61.3%) than males (males = 38.7%; χ² = 3.85, p = 0.05). We found that 9.3% of young adult participants were positive on the TACER-3 screen administered (“young adult” TACER-3 in Table 2). Among the participants who reported any drinking, the mean number of drinks they needed to feel “high” was just over three (i.e., 1.7 oz of absolute alcohol); and 57.3% of them said they needed two or more drinks (see Table 2).

The mean age of the biologic mothers of the participants was 26.4 years old at their first prenatal visit. Among these women, 42.7% had used cocaine during the pregnancy and just over 25% reported using cocaine during the pregnancy and just over 25% reported

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**Table 1**

<table>
<thead>
<tr>
<th>Nominal Odor</th>
<th>Chemical</th>
<th>Diluent</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mint</td>
<td>Carvone</td>
<td>–</td>
<td>100%</td>
</tr>
<tr>
<td>Citrus</td>
<td>Citral</td>
<td>Mineral oil</td>
<td>10%</td>
</tr>
<tr>
<td>Floral</td>
<td>Propionaldehyde</td>
<td>–</td>
<td>100%</td>
</tr>
<tr>
<td>Bubble gum</td>
<td>Bubble gum</td>
<td>Distilled water</td>
<td>50%</td>
</tr>
<tr>
<td>Spoiled milk</td>
<td>Pyridine</td>
<td>Water</td>
<td>0.03%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>200-proof alcohol</td>
<td>–</td>
<td>100%</td>
</tr>
<tr>
<td>Gin</td>
<td>Beeleater gin</td>
<td>–</td>
<td>100%</td>
</tr>
<tr>
<td>Beer</td>
<td>Rolling Rock</td>
<td>–</td>
<td>100%</td>
</tr>
<tr>
<td>Whiskey</td>
<td>Seagram’s 7”</td>
<td>–</td>
<td>100%</td>
</tr>
<tr>
<td>Water</td>
<td>Water</td>
<td>–</td>
<td>100%</td>
</tr>
</tbody>
</table>
regular cocaine use. Cocaine, marijuana and cigarette use were each controlled statistically in all regression analyses. Maternal in-pregnancy alcohol use and caregiver alcohol use at the participant’s 14-year assessment are also shown in Table 2. Based on the “ARAE” alcohol use risk metric, ~30% of the mothers in this sample reported risk alcohol use during pregnancy; the TACER-3 screen identified 22% at risk for pregnancy alcohol use.

3.2. Olfactory function (UP-SIT test)

Consistent with population characteristics of olfactory performance on the UP-SIT [32], there was a significant difference between males and females in identifying odors (t = -3.09, df = 58, p = 0.003). The mean UP-SIT score for males was 31.9 (SD = 4.5) and for females was 34.8 (SD = 2.8). Among males, 30% scored below the task-defined “cut-off” score of 31 indicating olfactory dysfunction, while 20% of females scored below their “cut-off” score of 33 indicating olfactory dysfunction. Participants with higher risk PAE as indicated by the ARAE metric significantly fewer odors on the UP-SIT. The UP-SIT score was included in regressions evaluating the influence of PAE.

3.3. Odor identification, intensity, and pleasantness (the “bottle test”)

Descriptive statistics for participant report of odor identification and ratings of intensity and pleasantness in the “bottle test” are in Table 3. The odors of mint and 200-proof alcohol, as well as the lack of an odor for water, were most often identified correctly (89%, 73%, & 77%, respectively). In contrast, the odors of gin, flowers, and spoiled milk were identified correctly least often (11%, 13%, & 20%, respectively). The rating of water as the least intense and of 200-proof alcohol as the most intense was interpreted as evidence of test validity. Overall, all the odors other than water were rated as intense.

Generally, the alcohol-related odors were rated as less pleasant (range of means = 1.96 to 2.79) than the non-alcohol odors (range of means = 3.03 for water to 3.88 for bubble gum), with the exception of “spoiled milk” which was rated most unpleasant (rating = 1.86). Since the most frequent response for water pleasantness was “there is no odor,” no value was entered for these 42 participants (56% of the sample). Among the other participants, 21 (28% of the sample) rated water pleasantness as “neutral.” Since only 14 non-neutral responses were made (18.6% of the sample), the effects of PAE on ratings of water pleasantness were not analyzed further.

### Table 2

<table>
<thead>
<tr>
<th>Sample characteristics (N = 75).</th>
<th>Mean or %</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Older teens/young adults</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>38.7%</td>
<td>–</td>
</tr>
<tr>
<td>Age (years)</td>
<td>20.9</td>
<td>0.5</td>
</tr>
<tr>
<td>TACER-3 mean score</td>
<td>0.7</td>
<td>1.1</td>
</tr>
<tr>
<td>TACER-3 (% positive — total score ≥ 3)</td>
<td>9.3</td>
<td>–</td>
</tr>
<tr>
<td>Tolerance (number of drinks to feel “high”)</td>
<td>1.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Tolerance (% ≥ 2 drinks on “T” question)</td>
<td>57.3%</td>
<td>–</td>
</tr>
<tr>
<td><strong>Mothers during pregnancy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first prenatal visit (years)</td>
<td>26.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Cocaine use (% positive)</td>
<td>42.7%</td>
<td>–</td>
</tr>
<tr>
<td>Heavy/persistent* cocaine use</td>
<td>26.7%</td>
<td>–</td>
</tr>
<tr>
<td>Marijuana use (% positive)</td>
<td>33.3%</td>
<td>–</td>
</tr>
<tr>
<td>Smoking (# of cigarettes/day)</td>
<td>10.0</td>
<td>11.6</td>
</tr>
<tr>
<td>ARAE (% positive)</td>
<td>29.3%</td>
<td>–</td>
</tr>
<tr>
<td>TACER-3 (% positive)</td>
<td>22.2%</td>
<td>–</td>
</tr>
<tr>
<td>Caregivers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drinking AA/day at 14-year visitb</td>
<td>0.4</td>
<td>1.1</td>
</tr>
<tr>
<td>SESc</td>
<td>27.7</td>
<td>11.3</td>
</tr>
<tr>
<td>HOME</td>
<td>51.4</td>
<td>9.2</td>
</tr>
<tr>
<td>Education (# of years completed)</td>
<td>12.0</td>
<td>1.8</td>
</tr>
</tbody>
</table>

* oz of absolute alcohol/day.
** Socio-economic status; [40].
* At least twice/week during pregnancy or positive lab for mother or infant at birth.

### Table 3

<table>
<thead>
<tr>
<th>N = 75 unless indicated otherwise</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Odor identity (proportion correct)</strong></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>0.77</td>
</tr>
<tr>
<td>Floral</td>
<td>0.13</td>
</tr>
<tr>
<td>Mint</td>
<td>0.89</td>
</tr>
<tr>
<td>Bubble gum</td>
<td>0.52</td>
</tr>
<tr>
<td>Spoiled milk</td>
<td>0.20</td>
</tr>
<tr>
<td>Citrus</td>
<td>0.63</td>
</tr>
<tr>
<td>200-proof alcohol</td>
<td>0.73</td>
</tr>
<tr>
<td>Beer</td>
<td>0.24</td>
</tr>
<tr>
<td>Gin</td>
<td>0.11</td>
</tr>
<tr>
<td>Whiskey</td>
<td>0.35</td>
</tr>
<tr>
<td>Overall alcohol</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Odor intensity (scale = 1 to 5, less to more)</strong></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>1.57</td>
</tr>
<tr>
<td>Floral</td>
<td>3.03</td>
</tr>
<tr>
<td>Mint</td>
<td>3.63</td>
</tr>
<tr>
<td>Bubble gum</td>
<td>3.17</td>
</tr>
<tr>
<td>Spoiled milk</td>
<td>3.61</td>
</tr>
<tr>
<td>Citrus</td>
<td>3.59</td>
</tr>
<tr>
<td>200-proof alcohol</td>
<td>4.29</td>
</tr>
<tr>
<td>Beer</td>
<td>3.41</td>
</tr>
<tr>
<td>Gin</td>
<td>3.31</td>
</tr>
<tr>
<td>Whiskey</td>
<td>3.81</td>
</tr>
<tr>
<td>Overall Alcohol</td>
<td>3.71</td>
</tr>
<tr>
<td><strong>Odor pleasantness (scale = 1 to 5, less to more)</strong></td>
<td></td>
</tr>
<tr>
<td>Water (n = 33)</td>
<td>3.03</td>
</tr>
<tr>
<td>Floral (n = 73)</td>
<td>3.52</td>
</tr>
<tr>
<td>Mint (n = 74)</td>
<td>3.82</td>
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<tr>
<td>Bubble gum (n = 73)</td>
<td>3.88</td>
</tr>
<tr>
<td>Spoiled milk (n = 73)</td>
<td>1.86</td>
</tr>
<tr>
<td>Citrus</td>
<td>3.79</td>
</tr>
<tr>
<td>200-proof alcohol</td>
<td>1.96</td>
</tr>
<tr>
<td>Beer</td>
<td>2.79</td>
</tr>
<tr>
<td>Gin (n = 73)</td>
<td>2.77</td>
</tr>
<tr>
<td>Whiskey</td>
<td>2.47</td>
</tr>
<tr>
<td>Overall alcohol</td>
<td>2.49</td>
</tr>
</tbody>
</table>

3.4. Relations between prenatal alcohol exposure and odor responses

3.4.1. Identification and intensity

The only effect of PAE on ratings of odor identity in the “Bottle Test” was a significantly lower identification of “bubble gum” odor, as a function of an increasing Maternal TACER-3 score (p < 0.05; Table 4). There was also a significant positive relation (p < 0.05) between being Maternal TACER-3-positive (when controlling for young adult tolerance) and incorrectly identifying the 200-proof alcohol odor (Table 4). There was no effect of PAE (Maternal ARAE or TACER-3) on ratings of odor intensity in the “bottle test” (Table 4).

3.4.2. Pleasantness

There were significant positive relations between PAE for both the ARAE metric and TACER-3 score and ratings of pleasantness for the odor of gin (p < 0.05) and mean alcohol odors overall (p < 0.01). The higher the maternal prenatal alcohol risk, the relatively higher were the young adult participants’ ratings of alcohol odor pleasantness (Table 4). This relation was seen even when controlling for young adult alcohol tolerance suggesting that the result is not influenced by more frequent alcohol use. There was also a marginally significant positive relation between the ARAE metric and the pleasantness rating of the spoiled milk odor (p < 0.10; Table 4). Participants whose mothers were positive for at-risk alcohol use during pregnancy (ARAE-positive) reported spoiled milk as more pleasant (or less unpleasant) than ARAE-negative young adults not exposed to at risk alcohol during pregnancy (p < 0.10) (Table 4). Further, direct comparisons of the mean pleasantness ratings of alcohol by young adults relative to their ARAE scores (Table 5) also reveal significant relatively higher ratings of
The implications of altered alcohol odor responses were demonstrated here. The findings for alcohol odors are consistent with the hypothesis that positive associations to the chemosensory properties of alcohol are acquired prenatally [20,66]. It is remarkable that the relatively greater alcohol odor pleasantness ratings associated with PAE were found many years later, after myriad interceding postnatal experiences. It is important to acknowledge that life-long post-natal and current experiential factors may have more proximal influences on ratings of alcohol odors, but this does not diminish the relation to PAE demonstrated here. The implications of altered alcohol odor responses for understanding the initiation of drinking and differences among teens in alcohol preference, alcohol-seeking, and high-risk alcohol-related behaviors, all remain to be examined.

The PAE-associated relative differences in alcohol odor pleasantness ratings we found occurred in the absence of either significant differences in the ability to identify alcohol odors, or in the ratings of alcohol odor intensity. Thus the general olfactory dysfunction in these older teens/young adults with PAE suggested by differences in the UP-SIT test results is not the source of PAE influences on pleasantness ratings of alcohol odors. It is important to note also, that the mean differences in alcohol odor pleasantness ratings between young adults with and without PAE were relative differences. Differences in alcohol odor ratings after PAE are as validly considered to indicate “less pleasant” as “more pleasant” ratings. The mean alcohol odor pleasantness ratings for the young adults with PAE were still below or near “neutral” (range = 2.14 to 3.18), although higher than in those without PAE (range = 1.89 to 2.74). Yet the effect of PAE is not only to reduce ratings of unpleasantness, since 31.8% of PAE participants, based on Maternal TACER-3 scores, also rated the odor of gin as “pleasant” or “very pleasant” compared to only 13.7% of teens without-at-risk PAE. Also, young adults with PAE were more than twice as likely to rate mean alcohol odors overall as “pleasant” compared to those without PAE (13.6% versus 5.6%).

The finding that PAE was associated with compromised general olfactory function in young adults in the UP-SIT test with 40 non-alcohol odors is consistent with the results of a prior study of 22 younger boys and girls (11 to 12 years old) reporting that PAE was associated with poorer performance on the 8-item San Diego Odor Identification Test [13]. It is important to recognize that the generally specific ratings of relatively greater alcohol odor pleasantness in the older participants with PAE in the present study occurred even in the presence of this apparent olfactory dysfunction. The UP-SIT focuses on odor identification but poor performance on the UP-SIT has been shown to indicate a broader olfactory dysfunction. It is also possible that PAE may be associated with a reduction in the relative perceived unpleasantness of odors, whether or not they are alcohol-related odors.

There are potentially substantial clinical implications of PAE-associated greater perceived relative pleasantness of alcohol beverage odors. It is possible that PAE may mediate increased risk for early initiating of drinking [62,74] or a greater likelihood of alcohol use problems in older teens/young adults with FASDs [38] by enhancing the relative hedonic value of alcohol odors. This is consistent with a model of developmental and trans-generational risk for alcohol abuse and alcoholism.

### 4. Discussion

The key finding from our controlled analyses is that higher levels of prenatal alcohol exposure (PAE) are related to higher relative ratings of pleasantness of alcohol odors in this small sample of young adults from our prospective longitudinal cohort. As far as we are aware, other than our own earlier abstract [18], this is the first published study to assess the influence of PAE on older teen/young adult responses to the odors of alcohol and alcohol beverages. The one previous study reporting differences in olfactory function after PAE at 11- to 12-years of age did not test alcohol odors [13]. Our findings for alcohol odors are consistent with the hypothesis that positive associations to the chemosensory properties of alcohol are acquired prenatally [20,66]. It is remarkable that the relatively greater alcohol odor pleasantness ratings associated with PAE were found many years later, after myriad interceding postnatal experiences. It is important to acknowledge that life-long post-natal and current experiential factors may have more proximal influences on ratings of alcohol odors, but this does not diminish the relation to PAE demonstrated here. The implications of altered alcohol odor responses

### Table 4

<table>
<thead>
<tr>
<th>Odor identity</th>
<th>Water</th>
<th>Floral</th>
<th>Mint</th>
<th>Bubble gum</th>
<th>Spoiled milk</th>
<th>Citrus</th>
<th>200-proof alcohol</th>
<th>Beer</th>
<th>Gin</th>
<th>Whiskey</th>
<th>Overall alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal ARAE</td>
<td>0.08</td>
<td>0.00</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
<td>0.06</td>
<td>0.04</td>
<td>0.04</td>
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<tr>
<td>Maternal TACER-3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>N = 75</td>
<td>N = 60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>j&lt;sup&gt;b&lt;/sup&gt;</td>
<td>j&lt;sup&gt;b&lt;/sup&gt;</td>
<td>j&lt;sup&gt;b&lt;/sup&gt;</td>
<td>j&lt;sup&gt;b&lt;/sup&gt;</td>
<td>j&lt;sup&gt;b&lt;/sup&gt;</td>
<td>j&lt;sup&gt;b&lt;/sup&gt;</td>
<td>j&lt;sup&gt;b&lt;/sup&gt;</td>
<td>j&lt;sup&gt;b&lt;/sup&gt;</td>
<td>j&lt;sup&gt;b&lt;/sup&gt;</td>
<td>j&lt;sup&gt;b&lt;/sup&gt;</td>
<td>j&lt;sup&gt;b&lt;/sup&gt;</td>
<td>j&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Table 5

<table>
<thead>
<tr>
<th>Mean odor pleasantness.</th>
<th>ARAE</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>t</th>
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<tr>
<td>Floral</td>
<td>Not at risk</td>
<td>52</td>
<td>3.54</td>
<td>0.92</td>
<td>0.23</td>
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<td></td>
<td>At risk</td>
<td>21</td>
<td>3.48</td>
<td>1.36</td>
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<tr>
<td>Mint</td>
<td>Not at risk</td>
<td>53</td>
<td>3.85</td>
<td>0.84</td>
<td>0.43</td>
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<tr>
<td></td>
<td>At risk</td>
<td>21</td>
<td>3.76</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Bubble gum</td>
<td>Not at risk</td>
<td>51</td>
<td>3.94</td>
<td>0.88</td>
<td>0.97</td>
</tr>
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<td></td>
<td>At Risk</td>
<td>22</td>
<td>3.73</td>
<td>0.83</td>
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<tr>
<td>Spoiled milk</td>
<td>Not at risk</td>
<td>53</td>
<td>1.74</td>
<td>0.96</td>
<td>1.74</td>
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<tr>
<td></td>
<td>At Risk</td>
<td>20</td>
<td>2.20</td>
<td>1.15</td>
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<tr>
<td>Citrus</td>
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<td>53</td>
<td>3.83</td>
<td>1.05</td>
<td>0.55</td>
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<tr>
<td></td>
<td>At Risk</td>
<td>22</td>
<td>3.68</td>
<td>1.09</td>
<td></td>
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<tr>
<td>200-proof alcohol</td>
<td>Not at risk</td>
<td>53</td>
<td>1.89</td>
<td>0.91</td>
<td>0.99</td>
</tr>
<tr>
<td></td>
<td>At Risk</td>
<td>22</td>
<td>2.14</td>
<td>1.17</td>
<td></td>
</tr>
<tr>
<td>Beer</td>
<td>Not at risk</td>
<td>53</td>
<td>2.74</td>
<td>1.15</td>
<td>0.59</td>
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<tr>
<td></td>
<td>At Risk</td>
<td>22</td>
<td>2.91</td>
<td>1.19</td>
<td></td>
</tr>
<tr>
<td>Gin</td>
<td>Not at risk</td>
<td>51</td>
<td>2.59</td>
<td>1.00</td>
<td>2.35</td>
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<tr>
<td></td>
<td>At Risk</td>
<td>22</td>
<td>3.18</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td>Whiskey</td>
<td>Not at risk</td>
<td>53</td>
<td>2.34</td>
<td>0.96</td>
<td>1.75</td>
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<tr>
<td></td>
<td>At Risk</td>
<td>22</td>
<td>2.77</td>
<td>1.02</td>
<td></td>
</tr>
<tr>
<td>Overall alcohol</td>
<td>Not at risk</td>
<td>53</td>
<td>2.38</td>
<td>0.62</td>
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<tr>
<td></td>
<td>At Risk</td>
<td>22</td>
<td>2.75</td>
<td>0.70</td>
<td></td>
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</table>

<sup>a</sup> SIT total and maternal alcohol use at 14-year visit included as covariate.
<sup>b</sup> Young adult tolerance from TACER-3 added as a covariate.
<sup>c</sup> p ≤ 0.10.
<sup>d</sup> p ≤ 0.05.
<sup>e</sup> p ≤ 0.01.
<sup>f</sup> p ≤ 0.001.

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such as effects on ethanol metabolism, nursing, or infant feeding. Discerning the mechanisms by which PAE may affect odor responses is important to this current research. Dr. Spear’s research on the persistent influence of early learning – whether from the perspective of infantile amnesia or psychopathology or substance use – emphasizes that early experience has a lifelong impact on our perceptions and thinking and behavior and health, even when we are unaware of that experience. More specific to the present paper, the research by Dr. Spear and his colleagues and students since 1984 has demonstrated convincingly, primarily in animal models, that early experiences with alcohol have potent and persistent effects. The fact that many researchers and clinicians are appreciating the important implications of early alcohol experiences for understanding problems ranging from fetal alcohol spectrum disorders (FASDs) to increased risk for early alcohol use, and problems associated with alcohol use across a lifetime, is due in large measure to Spear’s research and his legacy of “academic progeny” who authored other papers in this volume.

Conflicts of interest

The authors have no conflicts of interest to declare regarding this work.

Acknowledgments

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References
