Substance Use and Mental Health Symptoms in Adults with Prenatal Alcohol Exposure

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Abstract

Background: Substance use and mental health problems have been documented in individuals with prenatal alcohol exposure (PAE) in young adulthood, but little is known about how these patterns progress over time into midlife. The current study examined rates of substance use in a sample of adults with PAE in mid-life compared to a demographically similar contrast group. **Methods**: Participants (n=233) were drawn from two longitudinal cohorts of individuals recruited prenatally and followed into adulthood. Measures of cognition, substance use, and self-reported mental health functioning were obtained. **Results**: Differences among groups (PAE no dysmorphology, PAE with dysmorphology, contrast group) were examined on demographic variables of interest and substance use outcomes. Both PAE groups experienced higher levels of Adverse Childhood Experiences (ACEs) compared to the contrast group. We also observed higher rates of current tobacco use in those with PAE; those with PAE and no dysmorphology had almost twice the rate of current tobacco use as the nonexposed contrast group. Though a larger number of individuals with PAE demonstrated abstinence from alcohol compared to the contrast group, we observed similar rates of high risk drinking on the Alcohol Use Identification Test (AUDIT) in all groups. Individuals with PAE also showed high rates of cannabis use compared to national averages. Generalized linear regressions examining predictive effects of PAE on substance use outcomes did not show significant results, though female sex at birth was predictive of current cannabis use. Current alcohol use predicted depression and PTSD symptoms, and significant interactions were observed between PAE group and ACEs on depression, PTSD, anxiety, and psychotic symptoms. **Conclusion**: This is one of the only studies to examine rates of alcohol and other substance use among adults in mid-life with PAE. Results suggest that relationships between PAE, substance use, and mental health symptoms are

complex, and it will be important for future studies to examine factors associated with high-risk substance use among this vulnerable population.

Prenatal Alcohol Exposure (PAE) has been associated with an array of negative outcomes both during childhood and as individuals age. An increased risk of substance use problems (Lynch et al., 2017; Streissguth et al., 1996) has been a major concern for exposed individuals based on a frequently observed association between parental and offspring substance use (Meque et al., 2019; Ossola et al., 2021). Occurrence of substance use problems in those with PAE has been studied mostly in adolescence and young adulthood (Baer et al., 2003; Barr et al., 2006; Lynch et al., 2017) and has often been reported in clinical samples (Koponen et al., 2020; McLachlan et al., 2020). While we know that young adults in general report the highest rates of substance use (SAMHSA, 2022), and observed rates of substance use in young adults with PAE have also been high, whether patterns of substance use observed in young adults persist into midlife is largely unknown. If adults with PAE do demonstrate patterns of increased substance use in mid-life, this would be an important area for prevention and intervention.

Much of the data on substance use patterns in those with PAE has focused on young adults, demonstrating higher rates of alcohol and substance misuse in this age group, as well as a greater likelihood of meeting criteria for a substance use disorder (SUD) (Baer et al., 2003; Barr et al., 2006; O'Brien & Hill, 2015). Effects seem to be more robust in those who were exposed in utero to heavier maternal drinking episodes. Baer and colleagues (2003) reported that young adults exposed prenatally to heavy episodic drinking were three times more likely to meet criteria for mild alcohol dependence (using terminology at the time) and were more likely to report negative effects of alcohol use (e.g., passing out, blackouts). Young adults in Australia who were exposed to three or more servings of alcohol in utero demonstrated higher rates of alcohol use disorders particularly when exposed to alcohol in early pregnancy (Alati et al., 2006). In the Atlanta Longitudinal cohort, a slightly different pattern of results showed that

young adults with PAE but no cognitive or physical effects (compared to those with PAE and cognitive/physical effects) were more likely to experience substance-related problems including higher reported alcohol and cannabis use, and out of range gamma-glutamyl transferase (GGT) values, indicative of heavy alcohol consumption (Lynch et al., 2017). Young adult males with PAE but no cognitive/physical effects were at particularly high risk for such problems. Only one study to our knowledge has examined patterns of substance use in an older cohort of individuals with PAE. In a Canadian clinical sample that assessed various difficulties of daily living in adolescents (12 to 17 years), transition aged youth (18 to 24 years), and adults (aged 25 to 60 years), alcohol and substance misuse were observed across all three age groups, with age associated with worsened substance use in adults compared to adolescents and transition-aged youth (McLachlan et al., 2020).

Additional factors, including gender and psychiatric comorbidities, may also contribute to observed patterns of substance use in adults with PAE or with Fetal Alcohol Spectrum Disorders (FASD). Women with FASD have demonstrated higher rates of SUDs than the general population in some studies (e.g., Gelb & Rutman, 2011; McLachlan et al., 2020). Psychiatric problems have also been well documented in individuals with PAE, including increased likelihood of any mental health diagnosis (Dirks et al., 2019), higher rates of certain personality traits (Barr et al., 2006), greater likelihood of suicidal behavior (Streissguth et al., 1996) and depression (Coles et al., 2022; Streissguth et al., 1996), as well as higher rates of bipolar disorder and attention deficit hyperactivity disorder (Coles et al., 2022). Data demonstrating higher rates of anxiety in those with PAE in adulthood is more mixed, with some studies showing an increased likelihood of anxiety conditions in those with PAE (Coles et al., 2022; Streissguth et al., 1996), while other studies show insufficient evidence for these associations (Duko et al.,

2022). Because mental health and substance use problems are frequently comorbid (Kessler et al., 2005; Lai et al., 2015; SAMHSA, 2022), and substance use can exacerbate mental health problems (Abrams, 2024), examination of their relationship in those with PAE may be useful in informing prevention and treatment strategies.

Environmental factors are important to take into consideration. In the general population, exposure to maternal alcohol use disorder in childhood predicts higher levels of alcohol use (Ross et al., 2023) and alcohol use disorders (Meque et al., 2019; Ossola et al., 2021) in adulthood. Similarly, exposure to maternal drug use disorders during adolescence increases the risk for the development of a drug use disorder in emerging adulthood (Yule et al., 2013). Individuals with SUDs have also been found to have higher levels of Adverse Childhood Experiences (ACEs) than the general population (Leza et al., 2021), and ACEs have been shown to be higher in children whose mothers used alcohol in pregnancy (e.g., Kambeitz et al., 2019). Coles et al. (2022), for example, found that PAE predicted higher ACEs and lower socioeconomic status (SES), which in turn predicted higher mental health symptoms observed in adults with PAE in mid-life. Similarly, Koponen et al. (2020) examined these relationships in a sample of young adults, finding that although PAE was initially associated with mental and behavioral health variables, including ACEs in the model attenuated such relationships. The strongest relationships with mental health were seen not with PAE in this sample, but instead with other variables, such as out-of-home placement, low birth weight, and other maternal risk factors (e.g., the mother having a diagnosed mental, behavioral, or substance use disorder, or having a criminal record). A review of mental health outcomes associated with PAE similarly found that a range of factors, in addition to PAE, contributed to mental health and substance use problems, including SES, environmental stressors, and parent or caregiver mental health

difficulties (O'Connor, 2014). These data therefore collectively suggest that there are likely complex relationships among PAE, environmental factors, mental health, and substance use in adulthood. Taken together, results on substance use patterns in individuals with PAE suggest that there may be a unique vulnerability to substance-related problems in those with PAE, and that other environmental variables likely contribute to these outcomes.

The current study examined relationships between PAE and substance use in mid-life since this life stage has not been well explored. We hypothesized that adults with PAE would demonstrate higher levels of alcohol, tobacco, cannabis and illicit substance use, including greater likelihood of problem substance use behaviors and effects. We also hypothesized that these relationships would be partly explained by other social determinants including childhood adversity, SES and gender. Finally, we conducted exploratory analyses looking at mental health symptoms in these groups to understand the degree to which substance use contributed to mental health issues.

Methods

Subjects

Participants (n=233) were drawn from longitudinal cohorts in Atlanta (the Atlanta Longitudinal Alcohol Study) (Coles et al., 2022) and Seattle (Seattle Fetal Alcohol Follow-up Study; Streissguth, 2007) following individuals with PAE. The study methodology was approved by Institutional Review Boards at Emory University School of Medicine and the University of Washington. Data were collected between January 2017 and October 2021.

The sample included alcohol-exposed and contrast groups. Those in the PAE group (n=148) met either of the following criteria: 1) the individual had a documented diagnosis of FASD in childhood or adolescence, or 2) the individual had documented prenatal exposure to

alcohol based on maternal self-report during the prenatal period. The contrast group were individuals without PAE (n=85).

Participants in Atlanta were recruited from a cohort of 427 low-SES, predominantly African American individuals born from 1980 to 1986. Participants' mothers were identified prenatally, and prenatal exposure was determined based on a prenatal interview about alcohol use during pregnancy. Quantity and frequency of alcohol use during pregnancy was assessed by self-report, and participants whose mothers reported consuming at least 1 ounce of absolute alcohol per week (about two drinks) were included in the alcohol-exposed group, though of note, many reported consuming much larger amounts of alcohol, with an average of ~8 to 13oz of absolute alcohol per week. See Lynch et al. (2015) for more details on methodology. Participants in Seattle were recruited from a primarily White and Native American clinical sample of 475 individuals with 178 (37.4%) having a Fetal Alcohol Syndrome (FAS) diagnosis and 297 (62.7%) who were classified as having Fetal Alcohol Effects (FAE, using the diagnostic terminology at the time). Individuals with FAE did not have the dysmorphic features associated with FAS. A nonexposed contrast group was recruited from individuals participating in concurrent studies by the Seattle investigators.

For the sample included here, contact information was obtained from study records and from commercially available databases. Eligible participants were then informed via mail, phone, or email about the opportunity to participate. For those who could be located and who agreed to participate in follow-up, informed consent was obtained in person or remotely using REDCap (Research Electronic Data Capture), a secure, Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliant web application for online surveys and databases (Harris et al., 2019). Although the COVID-19 pandemic occurred during the study period, data collection was

completed in person, including blood tests and urine drug screens to identify current alcohol and drug use, NIH toolbox assessments, and self-report measures.

Measures

Demographics

A demographic form was used to obtain basic information about participants and their families, including participants' sex at birth, racial identification, marital and employment status, as well as information necessary to calculate the Hollingshead Social Status Index (Hollingshead, 2011), including educational achievement and occupation of participants and their spouses/partners if applicable.

PAE Levels. [since they are asking for this data I suppose we need to add a sentence here on how this was assessed in addition to adding to the results.]

Dysmorphology

Participants were divided into three groups based on determination of PAE during the original phases of the studies when they were children: those with PAE and no dysmorphic features, those with PAE and dysmorphic features, and those without PAE. In Atlanta, dysmorphic features were identified based on evaluation of growth characteristics and facial features using the Dysmorphia Checklist (Coles et al., 1997). Those classified as exposed but nondysmorphic had Dysmorphia Checklist scores less than one standard deviation above the mean of the full sample, and those in the dysmorphic group obtained a score on the Dysmorphia Checklist of one standard or more above the mean of the full sample. See Lynch et al. (2015) for additional detail about classifications. In Seattle, dysmorphology examination and diagnosis of FASD was carried out by a clinical team that included a pediatric dysmorphologist.

Adverse Childhood Experiences (ACEs)

ACEs (Felitti et al., 1998) were reported as part of a health survey based on the Behavioral Risk Factor Surveillance System (BRFSS) used by the Centers for Disease Control and Prevention (CDC; 2021).

Stressful Life Events

The Life Stressors and Social Resources Inventory (LISRES; Moos & Moos, 1994) evaluated current life stressors in eight areas: physical health, spouse/partner, finances, work, home/neighborhood, children, friends and social activities, and extended family. T-scores were calculated based on the test norms provided by the test developers (Mean of 50, Standard Deviation of 10) for negative and positive life events based on event counts occurring in the past year across these life contexts.

Cognitive Functioning

Results of cognitive functioning reported here have been published previously (Shapiro et al., 2023). Cognitive functioning was assessed using Fluid Cognition, or an individual's efficiency in learning and processing novel information. A composite score for Fluid cognitive (Akshoomoff et al., 2013) is derived from performance on a subset of tests from the National Institutes of Health (NIH) Toolbox Cognition Battery (Weintraub et al., 2013) that assess nonverbal intelligence. See Shapiro et al. (2023) for a full report of these subtests and results.

Current Psychiatric Symptoms

The Psychiatric Diagnostic Screening Questionnaire (PDSQ; Zimmerman & Mattia, 2001) is a self-report questionnaire completed by the participant at in person assessments, that assesses current symptoms of mental health diagnoses including major depressive disorder, bulimia, posttraumatic stress disorder, panic disorder, agoraphobia, social phobia, generalized

anxiety disorder, obsessive compulsive disorder, alcohol use disorder, drug use disorder, somatization, hypochondriasis, and psychosis.

Substance Use

Substance use and misuse was measured in several ways. The Alcohol Use Disorder Identification Test (AUDIT; Saunders et al., 1993) was used to measure self-reported symptoms of alcohol use disorder. We used World Health Organization (WHO) guidelines to also examine severity categories, in which harmful/hazardous drinking was defined as a score above an 8 and moderate-severe substance use disorder is defined as a score of 15 or more (Conigrave et al., 1995). We examined three severity ranges: none/abstinence (a score of zero), low risk alcohol use (score of 1-7), and harmful alcohol use (a score of 8 or higher).

The Drug Checklist (Coles et al., 1992) was used to assess current or past use of tobacco, alcohol, illicit drugs (including cannabis), and prescription medication. In addition, biological measures were used to obtain concurrent objective data about current substance use and its impact, including a urine drug screen assessing the presence of seven drugs: amphetamines, benzodiazepines, barbiturates, cocaine, opiates, cannabis, and phencyclidine. A blood draw assessed gamma-glutamyl transferase (GGT) as a biomarker for heavy drinking.

We defined current use of a substance as 1) endorsing current use on the drug checklist (yes/no) or 2) testing positive for the substance on the urine drug test. Any lifetime substance use was defined as having endorsed use of a substance at any point in life on the drug checklist or testing positive for that substance on the urine drug screen.

Data Analysis

We examined the primary hypothesis that prenatal exposure would be associated with increased substance use in two ways. We initially examined frequency of substance use

comparing the contrast group and all individuals with PAE. However, due to previous evidence of unique associations between variables of interest and those with and without facial dysmorphology, additional associations were tested examining differences among the three categorical groups (contrast group, PAE without dysmorphology, PAE with dysmorphology). Analyses were performed using SPSS 29 Software to test the associations between variables of interest in both two group (all individuals with PAE and the contrast group), and three group comparisons. Initial analyses included descriptive statistics, frequency of substance use and mental health status. Chi-square analyses were used to assess associations between categorical outcome variables among the three groups and ANOVA was used for interval data.

Following descriptive analyses, we used Generalized Linear Regression (GLR) to model the effect of PAE (contrast group, PAE without dysmorphology, PAE with dysmorphology) on substance use outcomes while controlling for potentially significant covariates. To identify appropriate covariates, bivariate correlations were computed between outcome variables and demographic variables, including site of data collection, as well as ACEs, the latter based on previous research with this cohort (Coles, et al. 2022). Variables with significant correlations at $p<.01$ were included in the regression analyses as covariates (see Tables 3 and 4 for covariates that were included in each model). GLR models were used to determine whether PAE group predicted outcomes for current tobacco use, alcohol use, cannabis use, stimulant use, or opioid use, as well as AUDIT severity ranges, AUDIT total scores, and GGT results (in or out of range). We also examined whether PAE predicted any lifetime tobacco, alcohol, cannabis, stimulant, or opioid use, or any illicit drug use (all drugs combined). Separate regression models were run examining the effects of PAE on each substance use outcome, entering covariates with significant correlations with that substance use variable as described above. For each regression

model, we also included the interaction of PAE and ACEs, based on previous research with this sample (Coles et al., 2022). All variables were included in the model with designated default convergence probabilities.

Finally, exploratory analyses evaluated the relationship between substance use and mental health symptoms. GLR was used to evaluate the predictive relationship between PAE, substance use variables and mental health diagnoses, entering as covariates variables with bivariate correlations $p<.01$.

Due to multiple comparisons, adjustment using the Benjamin-Hochberg procedure was done using a False Discovery Rate (FDR) of .10 to reduce the likelihood Type I error. Adjustments were made for chi-square and ANOVA examining differences in substance use among the three groups (Table 2), GLR modeling effects of PAE on substance use outcomes (Table 3), and GLR modeling effects of PAE and substance use variables on mental health outcomes (Table 4).

Results

Demographic characteristics

Differences in demographic variables between the groups (All individuals with PAE compared to the contrast group (two group comparisons), and those with PAE with dysmorphology and those with PAE without dysmorphology and the contrast group (3 group comparisons) are displayed in Table 1. Significant differences between the three groups were observed in several variables that were consistent with the literature, including significant differences in education levels, with fewer in the PAE groups compared to the contrast group graduating from college. There were also significant differences in employment status, where the PAE groups showed lower rates of full-time employment and higher rates of disabled status

compared to the contrast group. The groups with PAE showed lower income levels overall and had lower Hollingshead SES scores compared to the contrast group. As we have previously reported (Shapiro et al., 2023), both groups with PAE demonstrated significantly lower Fluid Cognition scores compared to the contrast group, and those in the PAE with dysmorphology group showed statistically lower Fluid Cognition compared to the PAE without dysmorphology group. We additionally saw higher reported ACEs in the PAE groups compared to the contrast group. When examining stressful life events in the last year, two group comparisons between PAE and the contrast group did not show significant differences; however, when examining differences among the three groups, we saw that those with PAE without dysmorphology had similar rates of negative stressful life events to the contrast group, and those with PAE and dysmorphology had lower rates of negative events. In addition, those with PAE and dysmorphology reported significantly fewer positive life events, compared to those with PAE without dysmorphology and the contrast group.

PAE by group [add results for prenatal exposure levels for each group]

Substance Use Patterns Among Groups

Chi-square analyses examining differences in substance use variables between all of those with PAE and the contrast group (two group comparisons) and those with PAE/no dysmorphology and PAE/with dysmorphology and the contrast group (three group comparisons) are summarized in Table 2. After Benjamin Hochberg adjustments for multiple comparisons, we saw significantly higher rates of tobacco use in all of those with PAE compared to the contrast group, and significantly lower rates of current alcohol use in the PAE group compared to the contrast group. We did not see significant differences in current or past substance use for any other substances, AUDIT totals or AUDIT severity ranges, or GGT levels (totals or in/out of

range). Of note, we saw comparable rates of individuals in both PAE groups and the contrast group who fell in the moderate-high risk range of alcohol use on the AUDIT, and current cannabis use in both PAE groups (46.2% of those with PAE/no dysmorphology and 50% in the PAE with dysmorphology group) was higher than national averages (SAMHSA, 2022).

Prediction of Substance Use Outcomes by Group

Generalized linear regressions (GLR) examined predictive relationships between PAE (No PAE (contrast group), PAE without dysmorphology, PAE with dysmorphology,) and each substance use outcome variable of interest. See Table 3 for results of GLR models as well as covariates included in each model. When looking at the predictive effects of PAE on alcohol use and its effects, including GGT levels (in/out of range), AUDIT total scores, and self-reported current alcohol use, we found that neither PAE group nor its interaction with ACEs predicted any of the alcohol use variables. Only SES significantly predicted current self-reported alcohol use, such that higher SES was associated with a greater likelihood of current use. Otherwise, no other alcohol-related outcomes were significant.

The effect of PAE on current tobacco use was modeled, using Sex, Age, SES, and ACEs as covariates, as well as the interaction of ACEs and PAE. Neither PAE nor its interaction with ACEs predicted current tobacco use, though SES significantly contributed to the model, such that lower SES was associated with greater likelihood of current tobacco use.

Current cannabis use, using Sex, Site, Age, SES and ACEs as covariates, and modeling the interaction of PAE and ACEs on cannabis use, was not predicted by PAE, though Sex contributed significantly to the model, such that being female was associated with greater likelihood of current cannabis use.

Current stimulant use, using SES and ACEs as covariates, was not predicted by PAE, SES or interaction of ACEs and PAE. Current opiate use could not be examined in the predictive models due to the very few individuals reporting current opioid use.

Mental Health Symptoms and Substance Use

Exploratory hypotheses examined differences in self-reported mental health symptoms by group (PAE with and without dysmorphology and contrast group), using ANOVA. Only social anxiety showed significance ($F(2,218)=3.75$, $p=.025$), where those with PAE and no dysmorphology reported higher levels of social anxiety symptoms.

GLR analyses (Table 4) further explored these relationships, examining the predictive effects of PAE and substance use variables on mental health outcomes. Significant relationships were seen between demographic variables, current alcohol and current tobacco use and Depression symptoms, whereby higher depression symptoms were predicted by lower SES, current use of alcohol, and not endorsing current tobacco use. A significant interaction was also observed between PAE group, ACEs, and Depression, in which the highest depression symptoms were seen for those in the PAE/no dysmorphology group at higher levels of ACEs.

Significant relationships were similarly seen between current tobacco and current alcohol use and PTSD symptoms, whereby higher PTSD symptoms were predicted by current use of alcohol, and currently not endorsing tobacco use. A significant interaction was observed between PAE group, ACEs, and PTSD symptoms, whereby greater symptoms of PTSD were observed in both PAE groups at higher levels of ACEs.

Significant relationships were also seen between demographic variables, current tobacco (but not current alcohol use), and anxiety symptoms (summed anxiety score on the PDSQ), whereby higher anxiety symptoms were predicted by lower SES, and currently not endorsing

tobacco use. A significant interaction was observed, as with Depression and PTSD, between PAE group, ACEs, and anxiety, in which the highest symptoms of anxiety were observed in the PAE/no dysmorphology group at higher levels of ACEs.

Finally, symptoms of psychosis were predicted by SES and current tobacco use, where lower SES and not using tobacco predicted greater symptoms of psychosis. A significant interaction was also observed between PAE group, ACEs, and psychotic symptoms, in which higher psychotic symptoms were observed in the PAE/no dysmorphology group at higher levels of ACEs. No other significant relationships were seen between other mental health variables on the PDSQ and PAE or substance use.

Discussion

Effects of PAE have been examined extensively in childhood, adolescence, and to some extent in young adulthood, with limited data on how and whether these effects progress into adulthood. This is one of few studies to examine substance use and mental health symptoms during mid-life in a sample of individuals with PAE, compared to rates of those in a nonexposed contrast group. Despite similarities when groups were initially recruited, our sample showed differences that were expected and consistent with the literature, including higher levels of disability, lower income and SES, and lower cognitive functioning in all individuals with PAE. Also consistent with some emerging literature, we saw that those with PAE but no dysmorphology reported levels of current negative/stressful life events comparable to the contrast group, whereas the group with PAE with dysmorphology showed lower levels of current stressful life events as well as lower levels of positive life events. Both groups with PAE demonstrated higher levels of ACEs compared to the contrast group, indicating that participants with PAE experienced higher levels of stress and trauma beginning during childhood.

When examining patterns of current substance use, our results were consistent with literature showing higher levels of substance use in those with PAE, however our results diverged from what would be expected based on the literature in other ways. We observed that a greater number of individuals with PAE reported current abstinence from alcohol use compared to the contrast group, who showed significantly higher rates of self-reported alcohol use. We explored this apparent contradiction by examining problematic alcohol use specifically on the AUDIT, observing similar rates of individuals reporting moderate – high risk alcohol consumption in both of the PAE groups and the contrast group. This may indicate that though many individuals with PAE abstain, those who do consume alcohol are doing so at problematic levels. Given that lifetime reported alcohol use was similar across groups, it is also possible that a subset of individuals with PAE have used alcohol problematically in their lifetimes but now are abstainers due to their alcohol use disorder history. Though we were unable to determine with the measures used in this study (e.g., AUDIT covers only past year use, and our measure of Lifetime alcohol use does not assess for lifetime use disorder, only lifetime use) whether individuals reporting some alcohol use in their past met criteria for AUD, future research could further explore these associations. An alternate explanation for the lower levels of current alcohol use observed in the PAE groups is the theory of social drift and lower incomes to consume substances (though the groups do report similar levels of cannabis use). Though both groups began the study at similar levels of SES, in mid-life, the two PAE groups both showed significantly lower SES than the contrast group. As individuals with disabilities age, [briefly describe theory of social drift], we see declines in income and means. This could potentially impact their current use of alcohol.

Based on the literature, we know that there are many factors that can contribute to substance use outside of PAE. For example, individuals with PAE typically are exposed to higher levels of ACEs (Kambeitz et al., 2019; Koponen et al., 2020), may be more likely to have a parent who is using substances problematically (Koponen et al., 2020), and show high rates of psychiatric comorbidity (O'Connor, 2014), all of which are associated with increased likelihood of substance use problems. Future research may be geared towards better understanding the contribution of such other factors and how they may contribute to higher risk substance use.

In examining rates of use of other substances, we observed higher levels of tobacco use in individuals with PAE, particularly in the group with PAE but no dysmorphology, who had almost twice the rate of tobacco use compared to the contrast group. All groups reported fairly high rates of cannabis use, and although both groups with PAE reported higher rates of use compared to the contrast group, these differences were not significant. Interestingly, rates of current cannabis use in all three groups (46% in the PAE/no dysmorphology,50% of those in the PAE/dysmorphology, and 38% of the contrast group) were higher than reported national averages. For example, rates of past month cannabis use in the National Survey on Drug Use and Health (NSDUH) reported in this age group are only 12.2% (SAMHSA, 2022). This lower rate may be explained by the fact that the NSDUH relies exclusively on self-report and does not obtain concurrent measures such as urine drug screens, as we did in our study. NSDUH rates therefore may be subject to underreporting common in surveys of substance use. In addition, recreational cannabis use is legal in Washington State (where one of our study sites is located) which may contribute to higher self-report rates in our study. With regard to other illicit substances (including heroin and prescription opiates, stimulants including methamphetamines and cocaine, ecstasy, hallucinogens, and inhalants), in general we observed low rates of use in

our study, at rates that are comparable to those reported in the general population (SAMHSA, 2022).

A final pattern of substance use of note was related to sex at birth, in that female sex at birth was predictive of increased likelihood of current cannabis use. With the increasing decriminalization and legalization of cannabis in the United States and Canada, its use is on the rise among many groups (SAMHSA, 2022), including women of reproductive age (Young-Wolff et al., 2019), as well as pregnant women (Corsi et al., 2019). Given some data showing higher rates of alcohol and substance misuse in women with PAE (McLachlan et al., 2020), as well as worsened outcomes associated with substance use in women more generally including more rapid progression to substance use disorder (Towers et al., 2023), it will be important for future research to take gender into account when examining substance use among individuals with PAE. From a prevention standpoint, problematic substance use in women may put them at risk for other negative outcomes including adverse health consequences, having alcohol or drug-affected pregnancies themselves, or being at greater risk for victimization and additional trauma. There is thus a need for gender-informed care in this high-risk group (Greenfield et al., 2014; McLachlan et al., 2020)

Finally, exploratory analyses were performed looking at rates of mental health symptoms by group, given consistent research showing higher levels of certain mental health conditions in individuals with PAE (Coles et al., 2022; O'Connor, 2014; Pei et al., 2011) as well as high rates of comorbidities of substance use and other mental health concerns more generally (Lai et al., 2015; SAMHSA, 2022). When looking at differences in mental health symptoms by group, only social anxiety was significant, with higher levels of social anxiety reported in those with PAE/no dysmorphology compared to those with PAE and dysmorphology and the contrast group.

However, further examination of predictive relationships among mental health variables and PAE groups yielded additional understanding about these associations. In general, we saw that current alcohol use predicted current Depression and PTSD symptoms. Additionally, interaction effects demonstrated a significant role of ACEs; specifically, the interaction effect in which the interaction of ACEs with PAE predicted higher levels of both depression and PTSD symptoms, and this effect was particularly robust in the PAE/no dysmorphology group. Though current alcohol use did not predict current anxiety or psychotic symptoms, we did also observe interaction effects of PAE on anxiety and psychotic symptoms, in which higher levels of psychiatric symptoms in both groups were observed at higher levels of ACEs, which again was notable in the PAE/no dysmorphology group. The possible hidden vulnerability of individuals with PAE but no dysmorphology has been discussed previously (Lynch et al., 2017; McLachlan et al., 2020); these individuals may be unidentified at a young age as a result of not experiencing visible, overt effects of PAE, and therefore may not receive services or supports that could help them to enhance their functioning or build on existing strengths. Another potential effect of being undiagnosed is that they (and their caregivers) may be more likely to experience the trauma and stress of "knowing something is wrong but not knowing what it is", having less environmental and social support, and having fewer coping resources.

A final comment on the potential impact of cognition and its relationship to substance use and mental health outcomes relates to differences in Fluid Cognition found between the PAE/no dysmorphology and PAE/with dysmorphology groups. Consistent with our results, extensive MRI data have confirmed that PAE affects brain structure and function from childhood through adolescence (Moore & Xia, 2022), with effects persisting through middle age (Pfefferbaum et al., 2023; Bischoff-Grethe et al., 2024). Impacts on brain structure and function, including those

that affect executive functioning and impulsivity (Nuñez et al., 2011), may also contribute to increased likelihood of substance use and other impulsive behaviors (Kim-Spoon et al., 2017). Reinforcing the complexity of these relationships, stressful life experiences, early initiation of substance use, and mental health problems, can also influence brain development and functioning later in life. Therefore, future studies may use MRI to investigate such trajectories, accounting for the complex factors that appear to affect functioning in individuals with PAE.

In this study, while the demonstrated relationships among substance use and mental health in those with PAE were exploratory in nature and warrant replication in other samples, our data point towards the complexity of these relationships and the importance of screening for mental health conditions, particularly in those that have PAE with no obvious dysmorphic features or overt physical effects.

Though this study has notable strengths, several limitations warrant acknowledgment. In general, our sample displayed relatively low levels of substance use and the use reported may not meet criteria for substance use disorders. We were also unable to determine with the measures used in this study whether individuals at some point in their lifetimes would have met criteria for an alcohol or substance use disorder. At the same time, subsets did demonstrate problematic alcohol use, and rates of cannabis use are notable in that they are higher than national rates of use, suggesting the importance of further investigation as to the potential for impairment secondary to cannabis use. Despite lower levels of reported use of illicit substances, our data adds to the scant literature on substance use patterns in mid-life among those with PAE. Our sample is likely representative of a typical community sample of individuals with PAE rather than a clinical sample. Some of our substance use data was obtained by self-report, but we used objective measures for current substance use (urine drug screens, GGT levels) which were

consistent with subjective reports. Analyses examining relationships between PAE and mental health symptoms were exploratory in nature and also based on self-report. Future studies could examine such relationships in clinical samples or use clinical interview to assess whether the symptoms reported would meet full diagnostic criteria. We additionally did not have psychiatric status data on parents of individuals in our sample; we were therefore unable to examine the potential genetic contribution of parental genetic load as a predictor of mental health status in our sample. Finally, our relatively small sample size did not allow for complex modeling into effects of interest. Future studies may further explore the complexities of the relationships identified here in mental health, substance use and trauma in those with PAE.

Future directions therefore also include better understanding the direction of relationships between psychiatric comorbidities and SUDs, exploring more fully how they interact, develop, and what other environmental or psychosocial factors drive these relationships. Co-occurring psychiatric and substance use disorders in the general population are associated with more severe course of illness, greater time to treatment, and more negative psychosocial and functional outcomes (SAMHSA, 2022), with even worse outcomes seen in those from underrepresented groups (Priester et al., 2016). Given existing data that indicates that early intervention generally leads to the most optimal outcomes for both SUDs and FASDs, understanding these complex relationships can guide areas of targeted prevention or intervention efforts.

Based on data from our study and others, we suggest that prevention and intervention efforts should include, if not focus on, high risk groups such as those with PAE/no dysmorphology and high levels of childhood trauma and should incorporate strategies that are gender informed. Because protective factors such as a caring childhood environment can also improve outcomes (Ossola et al., 2021), such prevention efforts should be focused on helping

families develop areas of strength and resilience to reduce negative outcomes for individuals with PAE.

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Table 1.

Demographic variables, Fluid Intelligence, and Stress variables in individuals with PAE (with and without dysmorphology) compared to a nonexposed contrast group (N=233).

		Alcohol Exposed				
	Nonexposed contrast (n= 85)	All PAE (n=148)	PAE/no Dys (n= 78)	PAE/with Dys (n=70)	Statistic and significance of two group comparisons (contrast vs. PAE)	Statistic and significance of three group comparisons (contrast vs. PAE without dysmorphology and PAE with dysmorphology)
Age (years) at assessment M(SD), range	38.38 (5.1) (range 32-60)	38.18 (6.16)	38.06 (6.8) (range 29-69)	38.2 (5.0) (range 29-60)	$F_{(1,231)}$=.10, p=.757, ns	$F_{(2,230)}$=0.06, p=.941, ns
Biological sex female F(%)	51 (60.0)	83 (56.5)	45 (57.7)	38 (55.1)	$X^2_{(1)}$=0.28, p=.599, ns	$X^2_{(2)}$=0.38, p=.827, ns
Racial group F(%)					$X^2_{(5)}$ =4.57, p=.471, ns	$X^2_{(10)}$ =10.99, p=.359, ns
American Indian/Alaska Native	3 (3.5)	9 (6.1)	4 (5.1)	5 (7.1)		
Black/African American	41 (48.2)	67 (45.3)	34 (43.6)	33 (47.1)		
More than one race	5 (5.9)	16 (10.8)	9 (11.5)	7 (10)		
Native Hawaiian/Other pacific islander	0 (0)	1 (0.7)	0 (0)	1 (1.4)		
White	36 (42.4)	53 (35.8)	31 (39.7)	22 (31.4)		
Non-Hispanic F(%)	81 (95.3)	139 (93.9)	75 (96.2)	64 (91.4)	$X^2_{(3)}$ =4.75, p=.191, ns	$X^2_{(6)}$ = 8.67, p=.193, ns
Marital Status					$X^2_{(6)}$ = 8.17, p=.226, ns	$X^2_{(12)}$ = 17.05, p=.148, ns
Married or living with partner	35 (41.1)	53 (36.1)	32 (41.0)	21 (30.0)		
Never married, divorced, widowed or separated	49 (57.7)	94 (63.9)	46 (59.0)	48 (69.6)		
Highest level of education F(%)					$X^2_{(8)}$=54.70, p<.001	$X^2_{(16)}$=65.55, p<.001
Middle school or less	2 (2.4)	8 (5.4)	5 (6.4)	3 (4.3)		
Partial high school	12 (14.1)	30 (20.3)	12 (15.4)	18 (25.7)		
High school graduate	8 (9.4)	41 (27.7)	18 (23.1)	23 (32.9)		
Some college	15 (17.6)	51 (34.5)	29 (37.2)	22 (31.4)		

College graduate	30 (35.3)	12 (8.1)	9 (11.5)	3 (4.3)		
Partial or graduate degree	17 (20.0)	5 (3.4)	5 (6.4)	0 (0)		
Employment status F(%)					$X^2_{(7)}$=21.08, p=.004	$X^2_{(14)}$=29.01, p=.010
Full time	64 (75.3)	82 (55.4)	47 (60.3)	35 (50.0)		
Part time	14 (16.5)	28 (18.9)	13 (16.7)	15 (21.4)		
Retired/Disability	2 (2.4)	27 (18.2)	11 (14.1)	16 (22.9)		
Student/other	2 (2.4)	1 (0.7)	1 (1.3)	0 (0)		
Unemployed	2 (2.4)	9 (6.1)	6 (7.7)	3 (4.3)		
Monthly household income M(SD)					$X^2_{(8)}$=54.24, p<.001	$X^2_{(16)}$=61.48, p<.001
< 500	1 (1.2)	9 (6.1)	5 (6.4)	4 (5.7)		
501 – 1000	3 (3.5)	26 (17.6)	11 (14.1)	15 (21.4)		
1001 – 2000	7 (8.2)	28 (18.9)	17 (21.8)	11 (15.7)		
2001 – 3000	16 (18.8)	19 (12.8)	9 (11.5)	10 (14.3)		
> 3001	50 (58.9)	43 (29.1)	27 (34.6)	16 (22.8)		
Unknown or refused	7 (8.3)	20 (13.6)	8 (10.2)	12 (17.2)		
Fluid IQ M(SD) (n=190)	98.7 (23.2)	81.8 (17.5)	85.5 (16.2)	77.2 (18.2)	$F_{(1,189)}$=32.17, p<.001	$F_{(2,188)}$=19.27, p<.001
Hollingshead SES M(SD)	40.0 (15.6)	28.7 (12.0)	31.1 (12.9)	25.8 (10.2)	$F_{(1,231)}$=41.59, p<.001	$F_{(2,230)}$=23.42, p<.001
ACES total M(SD)	2.0 (2.1)	3.7 (2.9)	4.0 (3.1)	3.4 (2.7)	$F_{(1,231)}$=22.79, p<.001	$F_{(2,230)}$=12.32, p<.001
LISRES Negative Life Events M (SD) (n=202)	57.0 (14.1)	54.6 (13.1)	58.5 (13.5)	50.2 (11.3)	$F_{(1,201)}$=1.54, p=.216	$F_{(2,200)}$=6.98, p=.001
LISRES Positive Life Events M (SD) (n=201)	66.3 (16.2)	62.0 (17.4)	64.9 (17.4)	58.8 (17.1)	$F_{(1,200)}$=3.01, p=.084	$F_{(2,199)}$=3.54, p=.031

Note: Significance values are reported Chi-square for categorical and ANOVA for continuous variables between groups.

Table 2.

Substance use in individuals with Prenatal Alcohol Exposure (with and without facial dysmorphology) compared to an unexposed contrast group (N=233)

		Alcohol Exposed (n=148)				
	Contrast group (n=85)	All PAE (n=148)	PAE/no Dys. (n=78)	PAE with Dys. (n=70)	Statistic and significance of two group comparisons (contrast vs. PAE)	Statistic and significance of three group comparisons (contrast vs. PAE without dysmorphology and PAE with dysmorphology)
GGT total level M(SD)	33.5 (62.3)	30.5 (33.5)	30.9 (31.8)	30 (35.7)	$F_{(1,189)}$=.20, p=.657, ns	$F_{(2,188)}$=.10, p=.901, ns
GGT out of range F(%)	3 (4.6)	10 (6.8)	6 (8.7)	4 (6.9)	$X^2_{(1)}$=0.72, p=.395, ns	$X^2_{(2)}$=0.89, p=.642, ns
AUDIT total M(SD)	3.4 (3.5)	3.3 (4.7)	3.7 (5.6)	2.7 (3.3)	$F_{(1,229)}$=.05, p=.820, ns	$F_{(2,228)}$=1.03, p=.359, ns
AUDIT severity ranges F(%)					$X^2_{(2)}$= 6.03, p=.049	$X^2_{(4)}$=6.82, p=.146, ns
None	11 (13.1)	38 (25.9)	18 (23.1)	20 (29.0)		
Low risk consumption	65 (77.4)	92 (62.6)	51 (65.4)	41 (59.4)		
Moderate – high risk consumption	8 (9.5)	17 (11.6)	9 (11.5)	8 (11.6)		
Current Substance Use F(%)						
Tobacco	19 (22.4)	59 (39.9)	34 (43.6)	25 (35.7)	$X^2_{(1)}$=7.44, p=**.006***	$X^2_{(2)}$=8.46, p=.015
Alcohol	70 (82.4)	95 (64.2)	50 (64.1)	45 (64.3)	$X^2_{(1)}$=8.62, p=**.003***	$X^2_{(2)}$=8.62, p=.013
Marijuana	32 (37.6)	71 (48.0)	36 (46.2)	35 (50.0)	$X^2_{(1)}$=2.33, p=.127, ns	$X^2_{(2)}$=2.57, p=.279, ns
Stimulants	10 (11.8)	27 (18.2)	12 (15.4)	15 (21.4)	$X^2_{(1)}$=1.70, p=.193, ns	$X^2_{(2)}$=2.71, p=.259, ns
Opiates/Prescription pain medication	3 (3.5)	7 (4.7)	4 (5.1)	3 (4.3)	$X^2_{(1)}$=0.00, p=.993, ns	$X^2_{(2)}$=0.58, p=.971, ns
Tranquilizers	1 (1.2)	0 (0)	0 (0)	0 (0)	$X^2_{(1)}$=1.75, p=.186, ns	$X^2_{(2)}$=1.75, p=.417, ns
Sedatives	6 (7.1)	3 (2.0)	2 (2.6)	1 (1.4)	$X^2_{(1)}$=3.68, p=.055	$X^2_{(2)}$=3.81, p=.149, ns
Hallucinogens	1 (1.2)	2 (1.4)	2 (2.6)	0 (0)	$X^2_{(1)}$=0.01, p=.909, ns	$X^2_{(2)}$=1.92, p=.383, ns
Ecstasy	2 (2.4)	1 (0.7)	1 (1.3)	0 (0)	$X^2_{(1)}$=1.20, p=.274, ns	$X^2_{(2)}$=1.67, p=.433, ns
Inhalants	1 (1.2)	2 (1.4)	2 (4.3)	0 (0)	$X^2_{(1)}$=0.05, p=.815	$X^2_{(2)}$=1.93, p=.380, ns

Any Lifetime Substance Use F(%)						
Tobacco	52 (61.2)	97 (65.5)	54 (69.2)	43 (61.4)	$X^2_{(1)}$=0.45, p=.504, ns	$X^2_{(2)}$=1.42, p=.492, ns
Alcohol	76 (89.4)	131 (88.5)	71 (91.0)	60 (85.7)	$X^2_{(1)}$=0.04, p=.834, ns	$X^2_{(2)}$=1.09, p=.579, ns
Marijuana	63 (74.1)	112 (75.7)	61 (78.2)	51 (72.9)	$X^2_{(1)}$=0.07, p=.791, ns	$X^2_{(2)}$=.634, p=.728, ns
Stimulants	20 (23.8)	53 (35.8)	30 (38.5)	23 (32.9)	$X^2_{(1)}$= 3.58, p=.059	$X^2_{(2)}$=4.12, p=.128, ns
Opiates/Prescription pain medication	17 (20.0)	43 (29.1)	20 (25.6)	14 (20.0)	$X^2_{(1)}$=0.87, p=.351, ns	$X^2_{(2)}$=0.97, p=.617, ns
Tranquilizers	11 (12.9)	12 (8.2)	9 (11.7)	3 (4.3)	$X^2_{(1)}$=1.38, p=.241, ns	$X^2_{(2)}$=3.63, p=.163, ns
Sedatives	6 (7.1)	8 (5.4)	4 (5.1)	4 (5.7)	$X^2_{(1)}$=0.26, p=.609, ns	$X^2_{(2)}$=0.28, p=.868, ns
Hallucinogens	19 (22.4)	27 (18.2)	18 (23.1)	9 (12.9)	$X^2_{(1)}$=0.12, p=.732, ns	$X^2_{(2)}$=2.77, p=.250, ns
Ecstasy	16 (18.8)	30 (20.3)	21 (26.9)	9 (12.9)	$X^2_{(1)}$=0.07, p=.789, ns	$X^2_{(2)}$=4.68, p=.096, ns
Inhalants	3 (5.3)	4 (4.7)	4 (8.5)	0 (0)	$X^2_{(1)}$=.03, p=.868, ns	$X^2_{(2)}$=3.34, p=.188, ns
Alcohol Use Disorder Symptoms (PDSQ)	0.52 (1.3)	0.55 (1.2)	0.49 (1.3)	0.6 (1.1)	$F_{(1,218)}$=0.01, p=.905, ns	$F_{(2,217)}$=0.14, p=.869, ns
Drug Use Disorder Symptoms (PDSQ)	0.14 (0.49)	0.37 (1.3)	0.31 (1.1)	0.42 (1.4)	$F_{(1,218)}$=2.40, p=.123, ns	$F_{(2,217)}$=1.40, p=.249, ns

Note: Significance values are reported for Chi-square analyses for categorical and ANOVA for continuous variables. Current substance use = an endorsement of "yes" on the Drug Checklist or having a positive urine drug test result for that substance; Any lifetime alcohol or illicit substance use includes any endorsement of past or current use (or positive urine drug screen result in the case of illicit substances); Stimulants = includes cocaine, crack cocaine, methamphetamine, or amphetamines; Opiates = prescription pain medications, methadone or heroin; Hallucinogens = LSD, PCP, mushrooms, mescaline, etc; Alcohol and Drug use disorder from the Psychiatric Diagnostic Screening Questionnaire (PDSQ).

*p values that remained significant after Benjamin Hochberg adjustment for multiple comparisons.

Table 3.

Predictive effects of PAE group (PAE without dysmorphia, PAE with dysmorphia, and contrast) on substances use variables

Outcome	B	Statistic	*P* value
GGT Value (in or out of range)			
PAE group			
Contrast	-.098	Wald $X^2_{(1)}$=2.04	.154, ns
PAE without dysmorphia	-.061	Wald $X^2_{(1)}$=.790	.374, ns
PAE with dysmorphia	--	--	--
Sex	.046	Wald $X^2_{(1)}$=1.51	.219, ns
Site	-.059	Wald $X^2_{(1)}$=2.09	.149, ns
Age	.001	Wald $X^2_{(1)}$=.043	.835, ns
SES	-.001	Wald $X^2_{(1)}$=.305	.581, ns
ACEs	.007	Wald $X^2_{(1)}$=.374	.541, ns
Interaction between PAE and ACEs	.043	Wald $X^2_{(1)}$=5.67	.017[a]
AUDIT total score			
PAE group			
Contrast	.007	Wald $X^2_{(1)}$=.000	.995, ns
PAE without dysmorphia	-1.211	Wald $X^2_{(1)}$=1.17	.279
PAE with dysmorphia	--	--	--
Sex	1.203	Wald $X^2_{(1)}$=4.53	.033
SES	-.002	Wald $X^2_{(1)}$=.008	.931, ns
ACEs	-.114	Wald $X^2_{(1)}$=.372	.542, ns
Interaction between PAE and ACEs	.585	Wald $X^2_{(1)}$=5.79	.016[b]
Current Alcohol Use			
PAE group			
Contrast	.043	Wald $X^2_{(1)}$=.151	.698, ns
PAE without dysmorphia	-.217	Wald $X^2_{(1)}$=3.48	.062, ns
PAE with dysmorphia	--	--	--
SES	.006	Wald $X^2_{(1)}$=8.83	**.003***
ACEs	-.034	Wald $X^2_{(1)}$=3.10	.078, ns
Interaction between PAE and ACEs	.051	4.180	.041
Current Tobacco Use			
PAE group			
Contrast	.065	Wald $X^2_{(1)}$=.352	.553, ns
PAE without dysmorphia	-.096	Wald $X^2_{(1)}$=.712	.399, ns
PAE with dysmorphia	--	--	--
Sex	.133	Wald $X^2_{(1)}$=5.20	.023
Age	-.010	Wald $X^2_{(1)}$=4.07	.044
SES	-.011	Wald $X^2_{(1)}$=24.68	**<.001***
ACEs	.001	Wald $X^2_{(1)}$=.004	.949
Interaction between PAE and ACEs	.056	Wald $X^2_{(1)}$=5.21	.023[b]
Current Marijuana Use			

PAE group			
Contrast	-.067	Wald $X^2_{(1)}$=.308	.579, ns
PAE without dysmorphia	-.107	Wald $X^2_{(1)}$=.720	.396, ns
PAE with dysmorphia	--	--	--
Sex	.248	Wald $X^2_{(1)}$=14.04	**<.001***
Site	-.181	Wald $X^2_{(1)}$=6.19	.013
Age	-.010	Wald $X^2_{(1)}$=3.163	.075, ns
SES	-.002	Wald $X^2_{(1)}$=.660	.417, ns
ACEs	.004	Wald $X^2_{(1)}$=.044	.835, ns
Interaction between PAE and ACEs	.025	Wald $X^2_{(1)}$=.856	.355, ns[b]
Current Stimulant Use			
PAE group			
Contrast	-.046	Wald $X^2_{(1)}$=.251	.616, ns
PAE without dysmorphia	-.151	Wald $X^2_{(1)}$=2.44	.118, ns
PAE with dysmorphia	--	--	--
SES	-.003	Wald $X^2_{(1)}$=2.99	.084, ns
ACEs	-.003	Wald $X^2_{(1)}$=.034	.853, ns
Interaction between PAE and ACEs	.027	Wald $X^2_{(1)}$=1.65	.199, ns[b]
Current Opiate Use	--	--	--

[a]Interaction reported for group 1 (contrast), interaction for group 2 was ns and group 3 was set to zero because parameter was redundant

[b]Interaction reported for group 2 (PAE without dysmorphia), interaction for group 1 was ns and group 3 was set to zero because parameter was redundant

Regressions examining current opiate use could not be completed due to the low number of cases of current use

*p values that remained significant after Benjamin Hochberg adjustment for multiple comparisons.

Table 4.

Predictive effects of current substance use and PAE (PAE without dysmorphia, PAE with dysmorphia, and contrast group) on mental health symptoms

Outcome: Depression	**B**	**Statistic**	***p** value**
Predictors			
SES	-.043	Wald $X^2_{(1)}$=4.36	**.037***
Current alcohol use	1.31	Wald $X^2_{(1)}$=4.94	**.026***
Current tobacco use	-1.16	Wald $X^2_{(1)}$=3.79	**.052***
Interaction between PAE and ACEs			
Contrast Group	.723	Wald $X^2_{(1)}$=16.61	**<.001***
PAE without dysmorphia	.295	Wald $X^2_{(1)}$=7.11	**.008***
PAE with dysmorphia	.256	Wald $X^2_{(1)}$=3.76	**.052***
Outcome: PTSD			
Predictors			
SES	-.027	Wald $X^2_{(1)}$=1.87	.172, ns
Current alcohol use	1.17	Wald $X^2_{(1)}$=4.18	**.041***
Current tobacco use	-1.25	Wald $X^2_{(1)}$=4.56	**.033***
Interaction between PAE and ACEs			
Contrast Group	.627	Wald $X^2_{(1)}$=13.10	**<.001***
PAE without dysmorphia	.334	Wald $X^2_{(1)}$=9.56	**.002***
PAE with dysmorphia	.396	Wald $X^2_{(1)}$=9.45	**.002***
Outcome: Anxiety			
Predictors			
SES	-.106	Wald $X^2_{(1)}$=8.31	**.004***
Current alcohol use	1.75	Wald $X^2_{(1)}$=2.78	.095, ns
Current tobacco use	-2.12	Wald $X^2_{(1)}$=3.94	**.047***
Interaction between PAE and ACEs			
Contrast Group	1.22	Wald $X^2_{(1)}$=14.90	**<.001***
PAE without dysmorphia	.833	Wald $X^2_{(1)}$=17.72	**<.001***
PAE with dysmorphia	.534	Wald $X^2_{(1)}$=5.10	**.024***
Outcome: Psychosis			
Predictors			
SES	-.010	Wald $X^2_{(1)}$=4.68	**.031***
Current alcohol use	-.132	Wald $X^2_{(1)}$=.924	.336, ns
Current tobacco use	-.544	Wald $X^2_{(1)}$=15.19	**<.001***
Interaction between PAE and ACEs			
Contrast Group	.037	Wald $X^2_{(1)}$=.815	.367, ns
PAE without dysmorphia	.052	Wald $X^2_{(1)}$=4.04	**.045***
PAE with dysmorphia	.015	Wald $X^2_{(1)}$=.236	.627, ns

Note: Anxiety as an outcome was examined using the sum of anxiety subscales on the Psychiatric Diagnostic Screening Questionnaire.

*p values that remained significant after Benjamin Hochberg adjustment for multiple comparisons.