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# The Association Between Adverse and Positive Childhood Experiences and Marijuana Use During Lactation

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#### **Abstract**

**Background:** Adverse childhood experiences (ACEs) are associated with substance use later in life, including marijuana use. It is unknown whether these behaviors extend to lactating women. Our objective was to examine the association between childhood ACE and marijuana use in lactating individuals and determine whether positive childhood experiences (PCEs) modified this association.

*Methods:* This study included 617 lactating individuals from the UC San Diego Human Milk Research Biorepository enrolled from 2015 to 2020. ACE and PCE histories were assessed by the Positive and Adverse Childhood Experiences questionnaire. Past 2-week marijuana use was self-reported at enrollment. Multivariable log-linear regressions were used to calculate adjusted risk ratios (aRRs) and 95% confidence intervals (CIs) for ACE history and marijuana use, and to assess modification by PCE.

**Results:** Marijuana use during lactation was higher among individuals who reported three or more ACEs (aRR = 2.58, 95% CI = 1.23–5.44), household dysfunction (aRR = 3.08, 95% CI = 1.17–8.10), sexual abuse (aRR = 2.25, 95% CI = 1.08–4.68), or physical abuse (aRR = 2.10, 95% CI = 1.02–4.13). There was no association between emotional abuse and marijuana use during lactation. There was no effect modification by PCEs. **Conclusion:** Higher ACE frequency, and specifically history of household dysfunction, physical abuse, or sexual abuse increased risk for marijuana use during lactation. Because of marijuana's potential adverse effects on the infant through human milk, postpartum ACE screening is warranted.

**Keywords:** adverse childhood experiences, marijuana, lactation, human milk

#### Introduction

A DVERSE CHILDHOOD EXPERIENCES (ACEs) are defined as traumatic experiences before age 18 and include, but are not limited to, experiencing or witnessing violence, abuse, or neglect at home. ACEs have become increasingly recognized as an important public health problem. In the U.S. population, more than 60% have experienced at least one ACE, and over 20% have experienced three or more ACEs, illustrating the significant burden of ACEs within the United States. Studies have identified increased rates of a variety of acute and chronic diseases among adults who reported adverse experiences in childhood, including chronic

obstructive pulmonary disorder, heart disease, depression, posttraumatic stress disorder, neurological deficit, and preterm delivery. <sup>5–9</sup>

Felitti reported that along with other substances, the use of marijuana was highly prevalent and showed a dose–response relationship between amount consumed and the number of ACEs reported in a sample from the general population. In addition, studies have found that marijuana use is more prevalent among women who experienced ACEs, I including use during pregnancy. Less often considered, positive childhood experiences (PCEs) may be important modifiers in the association of ACEs and substance use due to a protective psychological influence.

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There is a growing body of literature examining marijuana use in lactating individuals. Marijuana has been shown to transfer into human milk,  $^{14-17}$  indicating a potential route of exposure for nursing infants. Recently, Bertrand et al reported that the primary psychoactive ingredient in marijuana,  $\Delta$ -9-tetrahydrocannabinol, was measurable in breast milk of 63% of individuals who reported regular marijuana consumption. To our knowledge, no information is currently available about whether the observed association between ACEs and substance use extends to lactating individuals, and whether this association is modified by exposure to PCEs.

The objectives of this study were to (1) report the prevalence of ACEs and PCEs among a sample of lactating individuals; (2) determine if ACEs were associated with self-reported use of marijuana in the past 2 weeks of lactation; and (3) evaluate whether the relation of ACEs and marijuana use during lactation was modified by PCEs.

#### **Methods**

## Study participants

The UC San Diego Human Milk Research Biorepository (HMB) is a cross-sectional study with longitudinal follow-up of the offspring established in 2014 with over 2,100 breast milk samples from over 1,700 women residing in the United States and Canada. Further details of the HMB, its participants, and enrollment have been described in detail elsewhere. This repository of human milk samples also includes data on recent exposures, and behavioral, sociodemographic, and postnatal characteristics of participants.

Data for this analysis come from an addendum study to HMB, where previous and current participants enrolled in HMB between 2015 and 2020, whose child was still age 5 or younger, were asked to complete the Positive and Adverse Childhood Experiences (PACE) questionnaire (n=666). The PACE questionnaire was completed online, and provided information on ACE and PCE history. After excluding women who declined participation in the addendum questionnaire (n=13) and those who did not complete at least 16 of the 18 items on the PACE questionnaire (n=36), 617 participants remained whose data were included in the final analytic sample for this study.

This study was approved by the University of California San Diego Human Research Protections Program. All participants in the HMB and the addendum provided consent before participation.

#### Measures

PCEs and ACEs were assessed using the PACE questionnaire that consists of 7 questions about positive experiences and 11 questions about adverse experiences in childhood. The Positive Childhood Experiences Questionnaire (PCEs-Q), a 7item assessment tool, is used to capture the positive experiences that a person feels when supported by family and society.<sup>19</sup> PCEs-Q adapts questions from validated subscales, including the Child and Youth Resilience Measure-28, the Psychological Caregiving subscale, the Education subscale, the Culture subscale, and the Peer Support subscale.<sup>19,20</sup> Its validity has been described in detail elsewhere.<sup>21</sup>

Positive experiences included questions such as "How often did you feel your family stood by you in difficult times?" and "How often did you feel supported by your friends?" Response choices for each item were never, rarely, sometimes, often, or very often. Respondents who answered "often" or "very often" were coded as endorsing positive experience; those who responded "sometimes," "rarely" or "never" were coded as not endorsing the question. <sup>19</sup> Following individual question coding, PCE response frequency was summed (0–7) and categorized as 0, 1–2, 3–4, and 5+ to examine the distribution of PCE exposure.

Adverse experiences were queried with a series of 11 yes/no questions that included, "Did you live with anyone who was depressed, mentally ill, or suicidal" and "Did you live with anyone who was a problem drinker or alcoholic?"19,22 Responses were coded as 1 if the participant answered "yes," and 0 if they answered "no." The remaining questions, which asked about physical abuse (for which we combined participants reporting witnessing physical abuse of a parent or experiencing physical abuse themselves because the modeled outcome risks did not vary between the two "physical abuse" questions), emotional abuse, and sexual abuse, had the following response choices: never, once, or more than once. Questions asking about physical and emotional abuse (Q13–15) were coded as absent if the participant responded never or once, and present if they responded "more than once," consistent with previous literature.

Questions asking about sexual abuse history (Q16–18) were coded as 0 if the participant responded as "never" and 1 if they responded "once" or "more than once." 8.23 Finally, response scores for all adverse experience questions were summed (0–11) and categorized as 0, 1–2, 3–4, and 5+. Due to low frequency of outcomes, ACE and PCE frequency were collapsed to a dichotomous variable of 0–2 and 3+ for ACEs and 0–4 and 5+ for PCE in regression models. In addition, we categorized ACEs by type into categories of "household dysfunction," "physical abuse," "emotional abuse," and "sexual abuse."

Twenty-one participants had missing responses to at least one PACE question, which included six with missing responses for two PACE questions. To err on the side of being conservative, zeros were assigned for these missing values. No additional imputation was required due to exclusion of participants with three or more missing responses. It is important to note that the cut points chosen for PCEs and ACEs in our study were different than those used in other publications. However, we did not find any consistently established cut point across articles, making comparisons across studies difficult.

Marijuana use during lactation was self-reported by HMB participants through interviews conducted by trained study staff around the time of human milk collection. Participants were asked frequency, duration, and quantity of marijuana consumption (in any form) in the last 2 weeks. Marijuana use was categorized as "yes" for any consumption or "no" for none

Covariates for our analysis were selected based on the principles of confounding and biological/etiological relevance, which include demographic information such as maternal age (18–25, 26–30, 31–35, and 36+ years); race (White, Asian, Black, Native American/Alaskan Native, and Pacific Islander); ethnicity (Hispanic and non-Hispanic); and education level (high school graduate/general education development, some college or specialization, college graduate,

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and graduate/professional degree), similar to other studies. <sup>24,25</sup> Other variables used to describe the population included maternal body mass index (BMI) (<24.9, 25.0–29.9, and 30+ kg/m²), anxiety, stress, and depression status.

Current anxiety status was assessed with the State-Trait Anxiety Inventory index<sup>26</sup> and dichotomized as 0–44 (no) and 45+ (yes).<sup>27</sup> Stress status was assessed with the Perceived Stress Scale<sup>28</sup> dichotomized at the 75th percentile, into 0–16 (low) versus 17+ (high).<sup>27</sup> Depressive symptoms were assessed with the Edinburgh Postnatal Depression Scale<sup>29</sup> index and dichotomized as 0–9 versus 10+,<sup>27,29,30</sup> while current antidepressant medication use was dichotomized as yes/no.

#### Statistical analysis

Response rates for each of the 18 PACE questions as well as demographic and sample characteristics were calculated to describe our study population. Log-linear regression analyses were used to estimate crude and adjusted risk ratios (aRRs) for frequency and type of ACEs with dichotomized marijuana use. In addition, we assessed each type of ACE (household dysfunction, physical, emotional, and sexual abuse) with marijuana use. All models were adjusted for maternal age, race/ethnicity, and education. Effect measure modification between ACEs and marijuana use by experiencing positive childhood events was tested by assessment of interaction term and stratification by PCE frequency. Significance level for multiplicative interaction of PCEs and ACEs was set at p < 0.10. Strata-specific estimates were also evaluated to determine if they differed from each other (i.e., point estimates and confidence interval [CI] overlap).

In a sensitivity analysis, we excluded the 21 participants with 1–2 missing PACE responses, which were imputed as 0's in the main analysis, and repeated models.

All analyses were completed using SAS Studio Version 3.8 (SAS Institute, Cary, NC).

## Results

Participants were 26–49 years of age (mean=33.7), and the majority self-identified as White and non-Hispanic, reported having a college degree or above, and reported normal BMI (Table 1). In addition, 31.4% reported no ACE, 33.9% reported 1 or 2 ACEs, 20.1% reported 3 or 4 ACEs, and 14.6% reported 5 or more ACEs. The most common ACE category reported was household dysfunction (55.8%), followed by emotional abuse (38.7%) and physical abuse (21.5%), while the least frequent category reported was sexual abuse (18.0%).

Prevalence of reporting any ACE (Table 1) was higher in those who were younger, Black, Hispanic, and who had less education. These differences increased as frequency of reported ACEs increased. Overall, 12% of participants reported taking antidepressants and 15% reported clinical depressive symptoms, both of which increased with the number of ACEs reported. Also, 26% met screening criteria for anxiety and 27% met screening criteria for high levels of stress, both increasing as ACE frequency increased. Most participants (67%) reported at least 5 PCEs, while 13.8% reported 2 or less. Endorsing more frequent ACEs was inversely associated with PCE frequency.

The number of ACE endorsement ranged from 0 to 11 and PCEs ranged from 0 to 7 (Table 2). The least endorsed PCE

question was how often the participant feels able to talk to family about their feelings (56.1%), whereas the most frequently endorsed question was reporting an adult made them feel safe and protected (86.4%). Rates of endorsement for individual ACE questions varied from 2.8% to 38.8%. The most frequently endorsed ACE question asked if a parent or adult swears, insults, or puts down the participant (38.8%), followed by reporting someone in the household who was depressed, mentally ill, or suicidal (37.3%) and having parents separated or divorced (31.0%).

One in six (15.8%) reported witnessing parental physical abuse, 8.4% reported parental physical abuse on multiple occasions, and 12.3% reported their own physical abuse. Sexual abuse items were the least frequent ACE category reported, varying from 2.8% to 16.6%; 16.6% reported someone touching them sexually, with 9.7% endorsing more than once. In addition, forcing the participant to touch someone sexually was reported in 11.6%, with nearly half of these (6.8%) endorsing more than once.

Of the 617 participants, 30 (4.8%) endorsed marijuana use (Table 3). Marijuana use was higher among those with three or more ACEs (8.9%) compared to those with two or fewer (2.7%). After adjusting for maternal age, race, ethnicity, and education, participants who reported three or more ACEs were 2.58 (95% CI: 1.23–5.44) times more likely to report marijuana use in the past 2 weeks compared to those reporting 2 or fewer ACE. By category of ACE, marijuana use increased in those reporting household dysfunction, physical abuse, and sexual abuse (aRR 3.08 [95% CI: 1.17–8.10], aRR 2.10 [95% CI: 1.02–4.13], and aRR 2.25 [95% CI: 1.08–4.68], respectively). Emotional abuse was not associated with marijuana use during lactation.

There was no evidence through either interaction terms or stratified analyses to suggest effect measure modification between ACE frequency and marijuana use by PCE (data not shown). Finally, in the sensitivity analysis, excluding the 21 participants with 1–2 imputed responses to the PACE questionnaire, results attenuated slightly, although interpretations were unchanged (Supplementary Table S1).

#### **Discussion**

In this study, higher ACE frequency, as well as exposure to household dysfunction, and physical or sexual abuse in childhood, was associated with increased risk for marijuana use during lactation. Our findings were not modified by exposure to PCEs. To our knowledge, this is the first study to examine the association between ACEs and marijuana use in lactating individuals.

The risk of marijuana use during lactation in those reporting more frequent ACEs in this sample was similar to that reported by other studies (not specific to lactation) in a recent meta-analysis<sup>2</sup> exploring ACEs and substance use, with pooled odds ratio of 2.20 for smoking, alcohol use, and drug use. Considering the recent changes in ease of access to marijuana due to legalization in many states, an increasing prevalence of ACEs in the United States is concerning for lactation outcomes. Due to marijuana's potential adverse effects on lactating individuals and their infants, these results have important public health implications.

To date, emotional abuse has been less studied than physical or sexual abuse, and it is unclear whether that is due

Table 1. Characteristics of Lactating Individuals by Adverse Childhood Experience; University of California San Diego Human Milk Research Biorepository, 2015–2020, *n*=617

	Total (Col %) N=617	No. of ACE (Col %)			
Characteristic		0 n=194	1-2 n=209	3–4 n = 124	5+ n=90
Age, years					
18–25	24 (3.9)	6 (3.1)	6 (2.9)	4 (3.2)	8 (8.9)
26–30	121 (19.6)	35 (18.4)	37 (17.7)	23 (18.6)	26 (28.9)
31–35 36–49	245 (39.7)	85 (43.8)	85 (40.7)	47 (37.9)	28 (31.1)
	227 (36.8)	68 (35.1)	81 (38.8)	50 (40.3)	28 (31.1)
Race	5.45 (00.2)	170 (01.7)	107 (00.5)	105 (04.7)	75 (92.2)
White	545 (88.3)	178 (91.7)	187 (89.5)	105 (84.7)	75 (83.3)
Asian	40 (6.5)	10 (5.2)	17 (8.1)	9 (7.3)	4 (4.4)
Black Native American	13 (2.1) 13 (2.1)	1 (0.5) 4 (2.1)	1 (0.5) 1 (0.5)	5 (4.0) 4 (3.2)	6 (6.7) 4 (4.4)
Pacific Islander/Alaskan Native	6 (1.0)	1 (0.5)	3 (1.4)	1 (0.8)	1 (1.1)
	` '	13 (6.7)	` ′	` '	` '
Ethnicity (% Hispanic) Education	54 (8.8)	13 (0.7)	19 (9.1)	8 (6.5)	14 (15.6)
High school graduate or GED	12 (1.9)	1 (0.5)	1 (0.5)	2 (1.6)	7 (7.8)
Some college or specialization	54 (8.8)	7 (3.6)	18 (8.5)	11 (8.9)	18 (20.0)
College graduate	191 (31.0)	58 (29.9)	62 (29.4)	38 (30.7)	33 (36.7)
Graduate/professional degree	360 (58.4)	128 (67.0)	130 (61.6)	73 (58.9)	31 (34.3)
Body mass index					
Underweight—normal (<24.9)	341 (55.5)	121 (62.4)	122 (58.4)	59 (48.4)	39 (43.3)
Overweight (25.0–29.9)	169 (27.4)	46 (23.7)	53 (25.4)	41 (33.6)	29 (32.2)
Obese (>30)	105 (17.1)	27 (13.9)	34 (16.3)	22 (18.0)	22 (24.5)
Current antidepressant medication	79 (12.7)	14 (7.1)	25 (11.6)	23 (18.6)	17 (18.9)
Current depressive symptoms (% reporting)	85 (14.9)	20 (10.9)	24 (12.6)	19 (17.0)	22 (25.6)
Missing	45 (7.2)				
Current anxiety symptoms (% reporting high)	151 (26.3)	33 (18.0)	46 (24.0)	37 (33.0)	35 (40.2)
Missing	43 (6.9)			()	( ,
Current stress symptoms (% reporting)	152 (26.5)	40 (20.6)	43 (20.6)	38 (30.7)	31 (34.4)
Missing	44 (7.1)	.0 (20.0)	.5 (2010)	20 (2017)	01 (0)
ACE category <sup>a</sup>	` ′				
Household dysfunction	344 (55.8)		141 (67.5)	113 (91.1)	90 (100)
Physical abuse	133 (21.5)		18 (8.5)	51 (41.1)	64 (71.1)
Emotional abuse	238 (38.7)		75 (36.1)	85 (68.6)	78 (86.7)
Sexual abuse	111 (18.0)		22 (10.5)	36 (29.03)	53 (58.9)
PCE no.					
0	21 (3.4)	0 (0.0)	2 (1.0)	6 (4.8)	13 (14.4)
1–2	64 (10.4)	3 (1.6)	13 (6.2)	27 (21.8)	21 (23.3)
3–4	118 (19.1)	17 (8.8)	41 (19.6)	32 (25.8)	28 (31.1)
5+	414 (67.0)	174 (89.7)	153 (73.2)	59 (47.6)	28 (31.1)

<sup>&</sup>lt;sup>a</sup>Percentages reporting the given category of ACE.

ACE, adverse childhood experience; GED, general education development; PCE, positive childhood experience.

to a lag in recognition of the negative effects of emotional abuse, <sup>31</sup> or whether emotional abuse may have smaller effect estimates relative to physical and sexual abuse and be omitted from findings, resulting in publication bias. Emotional abuse was the highest reported category in our sample of lactating women (39%). This observed prevalence was not without precedence; emotional abuse was the most prevalent ACE among women in a sample from South Carolina (36%)<sup>32</sup> and in a study of over 200,000 adults in 34 states in the United States (32%).<sup>4</sup> Despite the high prevalence, the distribution of reported emotional abuse was similarly high across marijuana use/abstinence categories, and none of our models examining the risk of marijuana use in relation to emotional was significant.

As expected, PCEs and ACEs co-occurred in our participants, similar to previous research by Bethell et al. <sup>19</sup> However, their study participants represented a statewide survey in Wisconsin that included 6,188 men and women, while ours included lactating individuals from a variety of U.S. states and Canada. Since our participants reported more frequent PCE endorsement across categories of ACE, this could indicate geographic variation of PCEs or could be related to different sociodemographic characteristics. There was no significant modification by PCE for marijuana use, as all models had large, overlapping CIs.

Most participants reported very high PCE frequency, resulting in insufficient heterogeneity in our sample to test for modification by PCE level. Also, most participants were well

Table 2. Participant Responses for the Positive and Adverse Childhood Experience Questionnaire; University of California San Diego Human Milk Research Biorepository Study, 2015–2020, N=617

	Ever n (%)	More than once n (%)	Missing n (%)
PCE			
1. How often did you feel your family stood by you during difficult times?	488 (79.0)	NA	1 (0.2)
2. How often did you feel that you were able to talk to your family about your feelings?	347 (56.1)	NA	0 (0)
3. For how much of your childhood was there an adult in your household who made you feel safe and protected?	533 (86.4)	NA	0 (0)
4. How often did you enjoy participating in your community's traditions?	452 (73.3)	NA	1 (0.2)
5. How often did you feel supported by your friends?	477 (77.3)	NA	0 (0)
6. How often did you feel that you belonged at your high school?	353 (57.2)	NA	4 (0.7)
7. How often were there at least two adults, other than your parents, who took a genuine interest in you?	465 (75.4)	NA	1 (0.2)
ACE			
Household dysfunction			
8. Did you live with anyone who was depressed, mentally ill, or suicidal?	230 (37.3)	NA	7 (1.1)
9. Did you live with anyone who was a problem drinker or alcoholic?	130 (21.1)	NA	3 (0.5)
10. Did you live with anyone who used illegal street drugs, or who abused prescription medications?	83 (13.5)	NA	3 (0.5)
11. Did you live with anyone who served time or was sentenced to serve time in a prison, jail, or other correctional facility?	40 (6.5)	NA	0 (0)
12. Were your parents separated or divorced? Physical abuse	191 (31.0)	NA	2 (0.3)
13. How often did your parents or adults in your home ever slap, hit, kick, punch, or beat each other up?	98 (15.8)	52 (8.4)	0 (0)
14. Before age 18, how often did a parent or adult in your home ever hit, beat, kick, or physically hurt you in any way? Do not include spanking	76 (12.3)	48 (7.8)	1 (0.2)
Emotional abuse 15. How often did a parent or adult in your home ever swear at you, insult you, or put you down?	239 (38.8)	NA	3 (0.3)
Sexual Abuse	100 (166)	60 (0 <b>=</b> )	6 (4 B)
16. How often did anyone at least 5 years older than you, or an adult, touch you sexually?	102 (16.6)	60 (9.7)	6 (1.0)
17. How often did anyone at least 5 years older than you, or an adult, try to make you touch them sexually?	71 (11.6)	42 (6.8)	8 (1.3)
18. How often did anyone at least 5 years older than you, or an adult, force you to have sex?	17 (2.8)	6 (1.0)	3 (0.5)

NA not applicable indicates questions that were asked as yes/no.

ACE, adverse childhood experience; PCE, positive childhood experience.

TABLE 3. UNADJUSTED AND ADJUSTED RISK RATIOS FOR ADVERSE CHILDHOOD EXPERIENCE AND MARIJUANA USE IN LACTATING INDIVIDUALS, N=617

Frequency and categories of ACE	n (%)	Unadjusted risk ratio (95% CI)	Adjusted risk ratio <sup>a</sup> (95% CI)
ACE frequency <sup>b</sup> None to two	11 (2.7)	Ref.	Ref.
Three or more ACE category	19 (8.9)	3.26 (1.58–6.71)	2.58 (1.23–5.44)
Household dysfunction Physical abuse Emotional abuse	24 (7.0) 12 (9.0) 15 (6.3)	3.17 (1.32–7.65) 2.42 (1.19–4.89) 1.58 (0.79–3.18)	3.08 (1.17–8.10) 2.10 (1.02–4.13) 1.46 (0.70–3.04)
Sexual abuse	11 (9.9)	2.63 (1.29–5.37)	2.25 (1.08–4.68)

<sup>&</sup>lt;sup>a</sup>Adjusted for maternal age, race, ethnicity, and education. <sup>b</sup>ACE frequency categorized as 0–2 (reference) and 3 or more.

ACE, adverse childhood experience; CI, confidence interval.

educated and may have had many other resources available, which influence substance use. However, our findings of no modification by PCE suggest that interventions aimed at reducing marijuana use in lactating individuals would have greater benefit by addressing harm linked to previous ACE. Future studies are needed in other populations to confirm these findings.

Our study had several strengths. As previously stated, this is the first study to examine the association of ACEs and marijuana use in a group of lactating individuals. Given the steady increase of marijuana use among reproductive-aged women<sup>33</sup> and the plausible concerns<sup>34,35</sup> with regard to impacting offspring neurodevelopment from exposure in utero or through human milk, this work is adding to a sparse, but increasingly urgent literature. In addition, this sample had a large proportion (93%) who consented to, and completed the PACE questionnaire, reducing possible selection bias, and allowed capture of a broad change of exposures from our participants. Finally, many studies that examine ACEs do not have access to PCEs within the same participant population. Our participants reported both PCEs and ACEs, enabling an examination of the modification by PCE within the same cohort.

Our study also had several limitations. First, the homogeneity of participants limits the generalizability of these results to a broader range of lactating individuals. Furthermore, those who volunteered for study participation were a selected group who may not have the same distribution of PACE or substance use as the general population. Second, due to the low prevalence of those reporting marijuana use, we were not able to look at dose, frequency, or modes of use with ACEs or ACE categories.

### Conclusion

PCEs and ACEs are important factors that shape physical, behavioral, and health risks for years. While many studies report that ACEs increase risk for substance use, our study is the first to our knowledge to examine the association of ACE history and current marijuana use in lactating individuals. ACE frequency and reported history of household dysfunction, physical abuse, or sexual abuse were each associated with increased marijuana use in lactating individuals. These results support recommendations for ACE screening in lactating individuals, regardless of demographic characteristics, to identify those who may benefit from discussing substance use during lactation.

#### **Authors' Contributions**

D.C.: formal analysis, article original draft, review and editing, and visualization. C.C.: resources, article review and editing, and funding acquisition. K.B.: data curation, article review and editing, and project administration. G.B.: conceptualization, article review and editing, supervision, and project administration.

## **Disclosure Statement**

No potential conflict of interests was reported by the authors.

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## **Supplementary Material**

Supplementary Table S1

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