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Sex differences in the roles of nicotine use and puberty on youth C-reactive protein levels: Effects above and beyond adversity

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ABSTRACT

Inflammation likely mediates associations between nicotine use and negative health outcomes. Sex differences have been observed in nicotine use–inflammation links, and physiological processes during puberty might allow for these differences to arise. In this cross-sectional study of 498 youth (ages 8–13, 52% girls, 77% with history of child maltreatment (CM) investigation), sex-differentiated associations between self-reported nicotine use and high-sensitivity C-reactive protein (hs-CRP) were explored. Additionally, self-reported pubertal stage was investigated as a moderator of such nicotine use–hs-CRP links. Hierarchical generalized estimating equation models were adjusted for a wide range of adversity effects: CM investigation history derived from state records, self- and caregiver-report of traumatic life events, adversity-related demographic risk factors (i.e., identification with historically marginalized racial and ethnic groups, household income), and other characteristics that may influence the variables of interest (e.g., medication use, age, body mass index). Nicotine use had a negative main effect on hs-CRP among boys ($\beta = -0.50$, $p = 0.02$), and pubertal stage did not moderate this association ($\beta = 0.06$, $p = 0.71$). In contrast, pubertal stage moderated the association between nicotine use and hs-CRP among girls ($\beta = 0.48$, $p = 0.02$) such that a positive association between nicotine use and hs-CRP levels was stronger at more advanced pubertal stages ($\beta = 0.45$, SE = 0.21, 95% CI [0.03, 0.87]). Findings suggest that puberty may influence the effect of nicotine on inflammation in sex-differentiated ways and have implications for timing of prevention and treatment efforts geared toward reducing nicotine use and subsequent inflammation-related health risk among youth.

1. Introduction

Smoking is a leading cause of preventable death in the United States, with over 5 million youth expected to die prematurely due to a smoking-related illness (U.S. Department of Health and Human Services, 2014). Additionally, early nicotine use places individuals at greater risk for negative outcomes (e.g., nicotine dependence, suicide-related behavior (Kendler et al., 2013; Korhonen et al., 2018)).

One mechanism likely linking nicotine exposure to worse health outcomes is inflammation. Inflammation is believed to mediate the link between nicotine and numerous negative health outcomes (e.g., cardiovascular disease, chronic obstructive pulmonary disease, cancer (McCarty, 1999; Sinden and Stockley, 2010; Singh et al., 2019)). Associations between nicotine exposure and inflammation have been detected as early as adolescence, with smoking associated with greater systemic inflammation at age 16 (Pirkola et al., 2010).

1.1. Sex differences in the nicotine–inflammation link

Though men generally start using nicotine earlier and engage in nicotine use more than women, women tend to develop nicotine dependence faster and have more difficulty with smoking cessation

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(Ashare and Wetherill, 2018). This may be due to sex-linked physiological responses to nicotine first observed during early development, including higher reward effects of nicotine via greater dopamine release in the brain among females versus males (Beltz et al., 2015; Lynch, 2009; O'Dell and Torres, 2014; Wetherill et al., 2014).

Levels of inflammation also differ by sex. Among adults, levels of systemic inflammation are consistently greater among women than men (Ashare and Wetherill, 2018; Chen et al., 2020). This difference is already apparent during adolescence; among a sample of over 600 adolescents, girls had higher circulating levels of C-reactive protein (CRP) and interleukin-6 than boys (Mac Giollabhui et al., 2021).

The impact of nicotine on inflammation may vary by sex, with potential implications for individual differences in risk for nicotine-related health outcomes (Ashare and Wetherill, 2018). Studies linking nicotine and inflammation have found that women can be more susceptible to increased inflammation following exposure to nicotine than men (Faner et al., 2014). It is still unclear, however, what causes these sex differences in the relation between nicotine exposure and inflammation and when such differences are most likely to occur.

1.2. The potential role of puberty in nicotine–inflammation sex differences

Physiological changes propelled by puberty (e.g., increases in adrenal and gonadal hormone levels (Mendle et al., 2019)) are theorized to underlie sex differences in nicotine–inflammation associations that emerge during adolescence. Moreover, puberty itself is associated with both nicotine exposure and inflammation.

The relation of puberty to nicotine has been demonstrated in animals. Adolescent female rats become more likely to self-administer nicotine than male rats as the adolescent period progresses (Lynch, 2009). Rates of nicotine self-administration are also associated with gonadal hormone levels, suggesting that shifts in hormone levels brought about by the pubertal transition may underlie sex differentiation in nicotine sensitivity (Lynch, 2009). Nicotine seems to have the greatest impact on gene expression among female rats during early and mid-adolescence (puberty) compared to adulthood (post-puberty) (Polesskaya et al., 2007). Translation of these animal models to human ones has led to the theory that increases in pubertal hormone levels drive sex-differentiated neuroplasticity to substances during adolescence, thereby contributing to downstream differential risk pathways for substance use and abuse (Heitzeg et al., 2018).

Pubertal development is also associated with inflammation but may vary by sex. In a cross-sectional study of adolescents, more advanced pubertal stage was associated with higher high-sensitivity CRP (hs-CRP) levels among girls (Stumper et al., 2020). In contrast, pubertal stage was not significantly associated with hs-CRP among boys.

Thus, a potential mechanism linking puberty to the nicotine–inflammation association is as follows: As gonadal hormone levels increase during puberty, sexual differentiation of the brain occurs along with puberty-dependent immune system development. These neural and physiological changes could culminate in increased sensitivity to the acute rewarding effects of nicotine, resulting in further neural and physiological changes (Cross et al., 2017). This process could be more pronounced in girls than in boys.

1.3. Disentangling adversity effects from nicotine exposure and puberty effects on inflammation

Though there is compelling evidence for the biological impact of nicotine on inflammation (particularly for girls during early and mid-adolescence), it is also necessary to consider that nicotine use alone may not have a strong effect on inflammation. Adverse experiences, including child maltreatment (CM), racial discrimination, and poverty-related stress are associated with inflammation (Cuevas et al., 2020; Fraga et al., 2020; Iob et al., 2022). Early adversity (e.g., abuse, neglect, witnessing domestic/community violence) in particular is theorized to increase inflammation through alterations in neural development of the amygdala, hippocampus, and prefrontal cortex (Chiang et al., 2015). Nicotine exposure has also been shown to impact the functional development of these neural structures (Goriounova and Mansvelder, 2012; Mihov and Hurlemann, 2012; Zeid et al., 2018), making it imperative to parse how adversity and nicotine respectively influence inflammation.

Additionally, observed nicotine–inflammation linkages may be better conceptualized as proxies of psychosocial effects on physiology. Many studies have found that exposure to early adversity increases one's likelihood of using nicotine (Duffy et al., 2018). These associations between adversity and smoking and the role of nicotine use as a potential coping mechanism for stress management (Hiscock et al., 2012; Scales et al., 2009) might indicate adversity-driven sex differences in inflammation. Women have a greater likelihood of experiencing adversity (Östberg et al., 2015; Shih et al., 2006), which may result in women's more frequent nicotine use as a coping mechanism and explain their faster development of nicotine dependence compared to men.

Known early adversity influences on puberty make it even more important to consider adversity when investigating the link between nicotine use and inflammation in youth populations. Early adversity is related to pubertal development in sex-differentiated ways, with the strongest evidence for earlier pubertal timing among girls who have experienced trauma (Colich et al., 2020; Negriff et al., 2015; Noll et al., 2017). Thus, explorations into whether puberty opens a period of heightened sensitivity to nicotine must account for adversity as a potential higher-level driving force of puberty-linked inflammation.

Given known associations of adversity with inflammation, nicotine use, and puberty, the biological effects of nicotine may not be the strongest explanation for greater inflammation during adolescence. This is a concern as the extant literature supporting biological effects of nicotine does not consistently account for the possible effects of adversity on nicotine use, puberty, and inflammation. The potential overlap of adverse experiences, nicotine use, and puberty is particularly understudied among youth, whose experiences and behaviors likely set the stage for later life health.

1.4. Present study

Investigating nicotine use effects on CRP in youth at higher risk for disruptions in stress-mediated processes and pubertal development will help uncover whether adversity may better explain inflammation than nicotine use among youth and provide foundational knowledge on how observed sex differences among adults may develop. The present study is, to our knowledge, the first investigation into the roles of nicotine use and puberty on sex differences in inflammation (specifically, CRP) among youth that also accounts for adversity effects. We used cross-sectional data collected from a sample of youth recruited for a large, prospective study on mechanisms underlying risk and resilience to negative health outcomes in the context of CM reports (Schreier et al., 2021). The data obtained from this high-risk youth sample (based on high rates of CM investigation history (77%) and exposure to traumatic life events (average of six events reported) allowed us to investigate sex-differentiated associations between nicotine use, puberty, and CRP while accounting for variation explained by a wide range of adversity exposures (e.g., maltreatment, other traumatic experiences, racial and ethnic discrimination, economic disadvantage).

First, we hypothesized that nicotine use would be significantly associated with CRP levels above and beyond any significant adversity–CRP links found in this high-risk sample of youth given previously identified links between nicotine exposure and inflammation among youth (Pirkola et al., 2010). Second, and in line with prior research, we hypothesized that nicotine use would be positively associated with CRP levels among girls, whereas nicotine use would not be associated with CRP levels among boys based on sex-differentiated effects found among adult populations (Ashare and Wetherill, 2018). Third, informed by

work suggesting puberty as a potential mechanism through which sex-differentiated influences on physiology occur (Cross et al., 2017; Heitzeg et al., 2018; Stumper et al., 2020), we hypothesized that pubertal stage would moderate the nicotine use–CRP association for girls such that the link between nicotine use and CRP levels is stronger at more advanced pubertal stage.

2. Material and methods

2.1. Sample recruitment and study design

Participants were youth who participated in the Child Health Study (CHS) together with a caregiver. The CHS is an ongoing, prospective cohort study of 700 youth ages 8–13 with and without histories of recent child maltreatment (CM) investigation. Participant baseline data were available at the time of the present analysis.

Individuals with a recent (past 12-month) history of a CM (sexual abuse, physical abuse, or neglect) investigation were identified via a report to the child welfare system within the state of Pennsylvania. The eligibility criteria were 1) the youth was between the ages of 8–13, 2) the youth was within one year of their case dispensation, and 3) a non-maltreating, custodial caregiver provided informed consent. Youth in the comparison group were recruited across the state via local digital/electronic, broadcast, and print advertising. They were matched to the CM group on age, sex, historically marginalized racial/ethnic identity, income, and state region. They were eligible if they 1) were between the ages of 8–13, 2) had no record of child welfare involvement via screening through the statewide child welfare registry, and 3) had consent from their custodial caregiver. Individuals were excluded if they had a developmental delay, if the youth or caregiver did not speak/understand English, or if the youth had been residing with the participating caregiver for less than two months. Appropriate regulatory compliance was granted via the institutional review board (IRB). For full details, see Schreier et al. (2021).

2.2. Procedures

Participating families arrived at the research facility in the morning for a full-day assessment. Participants provided informed assent (youth) and consent (caregiver). Youth underwent a physical exam, followed by fasting whole blood collection via antecubital venipuncture by a trained phlebotomist. Following the blood draw, the families received breakfast and participated in the remaining study procedures, including youth and caregiver questionnaires. Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Penn State Health Milton S. Hershey Medical Center and Penn State College of Medicine (Harris et al., 2009). Multiple breaks and activities to educate and engage participants were interspersed throughout the approximately eight and a half-hour visit. Study procedures were designed with an emphasis on making youth feel comfortable and safe.

2.3. Measures

2.3.1. Nicotine use

Youth reported on whether they had ever smoked cigarettes or vaped (0 = Never to 4 = 10 times or more) on a substance use questionnaire based on items from the Monitoring the Future National Survey (Johnston et al., 2022). Though nicotine consumption method (e.g., combustion, vaping) may differentially impact inflammation (Glynos et al., 2018), low base rates of any nicotine use among youth ages 8 to 13 (about 11% of middle school students (Gentzke et al., 2022)) suggest that nicotine–inflammation signals might not be detected if separate smoking and vaping effects were examined in the present sample. Thus, cigarette and vape items were combined and dummy-coded to yield a dichotomous variable assessing whether youth had ever used nicotine (0 = no, 1 = yes).

Additional data were collected on recency and frequency of nicotine use, so we investigated potential group differences in the variables of interest. Recent users (i.e., within the past 12 months but not within the past 30 days) were more likely to identify as Hispanic compared to past (i.e., have used nicotine but not within the past 12 months) and current users (i.e., within the past 30 days); no other significant differences were found on the variables of interest (Supplemental Table 1). There were no significant associations among any of the variables of interest based on frequency of nicotine use in youth's lifetime (i.e., one to two times, three to five times, six to 10 times, 10 times or more) (Supplemental Table 2). Thus, we opted to not include nicotine use recency and frequency in our models.

2.3.2. hs-CRP

Peripheral whole blood was collected into an 8 ml serum separator tube (SST). After the blood draw, the SST sat at room temperature for 30 min and was then centrifuged for 15 min and refrigerated until same-day pick up by Quest Diagnostics. Serum was assayed for hs-CRP at the nearest Quest Diagnostics lab within 24 h of blood collection. hs-CRP data were winsorized due to the presence of outliers (values three standard deviations above or below the mean) and log transformed due to the data's positive skew (Huffhines et al., 2021). There are no established clinical CRP cut-offs for youth, but prior studies with youth samples (e.g., Oliveira-Santos et al., 2016; Schlenz et al., 2014) have followed established adult cut-offs of 0–3 mg/L (expected), 3–10 mg/L (subclinically elevated), and above 10 mg/L (clinically high). Clinically high levels of CRP may be indicative of acute illness.

2.3.3. Sex

Caregivers reported on youth gender using the following categories: female, male, trans female (male to female), trans male (female to male), and other. Most participants were identified as female or male. Two participants were identified as transgender male but neither had undergone any gender-affirming treatments at the time of data collection. Due to hypothesized sex-linked processes underlying nicotine use–inflammation associations (AlSharari et al., 2017; Faner et al., 2014; Moscovis et al., 2015; Shen et al., 2016), we utilized DNA methylation data to cross-validate and code the sex of these two participants as female (as in Etzel et al. (2022) and Hastings et al. (2022)).

2.3.4. Pubertal stage

Pubertal stage was assessed using youth report on the Tanner Staging Scale (Marshall and Tanner, 1969), which consists of two ordinal ratings of physical pubertal development based on secondary sex characteristics. Though the Tanner is typically conducted via nurse visual inspection, ratings made by youth trained by health care professionals to self-report on their current pubertal stage are generally reliable with nurse ratings (rs = 0.83–0.93) (Noll et al., 2017). Given the need for great sensitivity based on the past experiences of youth in this cohort, youth were shown standardized pictures depicting five stages of pubertal development (breast and pubic hair development for girls, testes and pubic hair development for boys). Stage 1 is considered to represent pre-puberty, stage 2 pubertal onset, stages 3 and 4 mid-puberty, and stage 5 post-puberty. The breast/testes and pubic hair ratings were highly correlated (rs = 0.69–0.78) and were averaged to yield an overall continuous pubertal stage score.

2.3.5. Constructs included as covariates

2.3.5.1. Steroid medication use. Caregivers reported whether youth were currently using any steroid medications. Because steroids are known to impact inflammation (Barnes, 2006), we ran our analyses first including participants who used steroid medications and adjusting for their medication use and then second excluding these participants. Because results did not change substantively between the two sets of

analyses, we ultimately retained these participants and adjusted for use of steroid medications in the final analyses to maximize sample size. Steroid medication use was dummy-coded (0 = no, 1 = yes).

2.3.5.2. Age. Youth age was adjusted for to help isolate the link between pubertal stage and inflammation (Chung et al., 2019).

2.3.5.3. Body mass index. Age- and sex-adjusted body mass index (BMI) was calculated using measurements of participant height and weight. BMI data were then converted to percentiles using Centers for Disease Control growth charts.

2.3.5.4. Child maltreatment investigation history. CM (e.g., sexual abuse, physical abuse, neglect) investigation (regardless of substantiation status) is associated with experiences of early adversity (Brown et al., 2019). CM investigation history status (0 = no history, 1 = history) was adjusted for in Models 2–5. See Schreier et al. (2021) for further information on CM investigation data collected for the parent study.

2.3.5.5. Traumatic life events. Traumatic life events (TLEs) were adjusted for in Models 2–5 because of their strong associations with nicotine use (Duffy et al., 2018; Krinner et al., 2020) and inflammation (Slopen et al., 2013). TLEs were assessed by caregiver and youth report on the Trauma History Profile of the UCLA Posttraumatic Stress Disorder Reaction Index (UCLA PTSD-RI) for DSM-5 (Pynoos and Steinberg, 2015). The UCLA PTSD-RI is a well-established measure of trauma exposure and subsequent PTSD symptoms in youth (Steinberg et al., 2013) and was administered as a structured interview in the CHS. In the Trauma History Profile section of the UCLA PTSD-RI, caregivers and youth were each asked whether youth were ever exposed to 23 different traumatic events (e.g., domestic violence, bullying). Interviewers were trained to assess for the presence of trauma exposure and reached excellent levels of reliability ($ks > 0.75$) before being cleared to conduct the interviews.

The sum of TLEs reported by caregiver and/or youth (i.e., an event was counted if either or both informants endorsed it) was calculated to yield a single measure that accounted for multiple informants and addressed trauma event reporting discrepancies between children and caregivers (Goodman et al., 2010; Lai et al., 2015). This either/both sum score served to maximize sensitivity to exposure to adversity, especially because youth may not have remembered or perceived having experienced some traumatic events that caregivers were aware of, particularly events that happened in early childhood. Additionally, the either/both sum score aimed to capture discrepancies where youth reported events that their caregivers did not. It has been suggested that children tend to report more traumatic events than their caregivers (particularly for youth-specific events (Kushner and Tackett, 2017)), which may be due to caregiver underestimation of their child's exposure to violence and the severity of events that children report to caregivers (Stover et al., 2010; Tingskull et al., 2015). In the present sample, agreement between caregiver and youth ranged from 0% to 100%, with an average of 83% (SD = 11%).

2.3.5.6. Adversity-related demographic risk factors. Race, ethnicity, and household income were chosen as adversity-related demographic risk factors for inflammation given their associations with adverse experiences and/or nicotine use. Youth identification with historically marginalized racial and ethnic groups (e.g., Black, Native American, Asian American, multiracial, Hispanic/Latine) was adjusted for due to the greater likelihood of experiencing discrimination and other TLEs that arise from the systemic racism and other structural inequities that these groups contend with in current society (Shonkoff et al., 2021). These adverse experiences likely contribute to race- and ethnicity-related differences in inflammation observed in extant work (Lam et al., 2021; Nazmi and Victora, 2007). Youth race was reported by caregivers and coded as American Indian/Alaskan Native, Asian/Pacific Islander, Black/African American, White/Caucasian, other, or multiracial. Though these terms were used in questionnaires administered to participants, to reduce bias in our language, we instead use the following terms to refer to racial groups represented in the analysis sample: Native American/Alaskan Native, Asian American/Pacific Islander, Black/-African American, White/European American, other, and multiracial. Historically marginalized racial group was dummy-coded (0 = non--marginalized, 1 = marginalized). Youth identification with Hispanic ethnicity was also reported by caregiver and dummy-coded (0 = non--Hispanic, 1 = Hispanic).

Lower household income is associated with adversity related to economic disadvantage (Cohen-Cline et al., 2019; Evans, 2004). Additionally, youth from low-income households have higher odds of recent (i.e., past month) nicotine use (Afifi et al., 2023). Caregivers reported their current total household family income before taxes on an ordinal scale in increments of $10,000 (0 = under $10,000 to 11 = over $120,000). Household income was used as a continuous measure in the main analyses.

2.3.5.7. Other substance use. The present study did not include alcohol and other substance use as variables of interest. But given existing links between nicotine use and use of alcohol and other substances (Richter, 2019), participant reports of alcohol and other substance (i.e., marijuana, prescription drugs, methamphetamine, ecstasy, cocaine, heroin, other illegal drugs) use on the same substance use questionnaire from which nicotine use was measured were both dummy-coded (0 = no, 1 = yes) and controlled for in sensitivity analyses to determine whether they influenced findings related to nicotine use.

2.4. Analytic strategy

Statistical analyses were performed in R. Mean differences in variables of interest between girls and boys were assessed via *t*-tests for continuous variables and Chi-Square tests for dichotomous variables. Correlations, *t*-tests, and Chi-Square tests were used to assess associations between the variables of interest by sex.

A hierarchical regression approach was used to examine associations of nicotine use, pubertal stage, adversity, and other covariates with hs-CRP. Analyses were performed separately by sex because of theorized sex-differential processes underlying the links between nicotine use, pubertal stage, and inflammation (Ashare and Wetherill, 2018; Cross et al., 2017). Nesting in families due to sibling participants in the sample was accounted for by modeling generalized estimating equations (GEEs) and estimating family-level robust standard errors with family ID as the repeated subject (Etzel et al., 2022).

Five hierarchical regression models were run separately within girls and within boys. Continuous predictors were centered for ease of interpretation. Model 1 included steroid medication use, age, and BMI as covariates. In Model 2, CM investigation history, TLEs, historically marginalized racial group identity, Hispanic ethnicity, and household income were added to establish significant adversity effects that may better explain inflammation than nicotine use. Nicotine use was then added in Model 3 to examine whether nicotine use was significantly associated with CRP above and beyond adversity effects. Next, pubertal stage was added in Model 4. Finally, the interaction between nicotine use and pubertal stage was included in Model 5.

Two sets of sensitivity analyses were performed. In the first set of sensitivity analyses, main effects of alcohol and substance use were added along with the main effect of nicotine use in Models 3–5 to control for their potential influences. In the second set of sensitivity analyses, participants with high hs-CRP levels (10 mg/L and above) were excluded to control for potential influences of acute illness.

3. Results

3.1. Sample characteristics

Youth demographic information is summarized in Table 1. The analytical sample of 498 participants (77% with a history of child maltreatment (CM) investigation) was approximately evenly split between girls and boys. On average, youth were 11.41 years old (*SD* = 1.55, range 6.89–13.99). Thirty percent of participants identified with a historically marginalized racial group, and 15% identified as Hispanic. About 42% of youth were from households with annual incomes of less than $30,000. There were no sex differences in youth demographic characteristics or main variables of interest.

Table 1
Descriptive statistics by sex for analytical sample.

Measure	Girls (*N* = 260)	Boys (*N* = 238)	Sex difference
	M (*SD*) or *N* (%)	*M* (*SD*) or *N* (%)	
Nicotine use			$X^2(1) = 0.93$
Yes	43 (17%)	32 (13%)	
No	217 (83%)	206 (87%)	
Pubertal stage (1–5)	2.54 (1.05)	2.58 (1.03)	$t(496) = 0.44$
hs-CRP (raw; 0.10–43.90)	1.74 (3.80)	1.50 (2.56)	$t(496) = -0.83$
CM investigation history			$X^2(1) = 0.05$
History	201 (77%)	182 (76%)	
No history	59 (23%)	56 (24%)	
TLEs (0–16)	6.27 (3.45)	5.92 (3.27)	$t(496) = -1.14$
Race			$X^2(5) = 10.01$
Native American/Alaskan Native	2 (1%)	0 (0%)	
Asian American/Pacific Islander	0 (0%)	1 (<1%)	
Black/African American	27 (10%)	33 (14%)	
White/European American	176 (68%)	173 (73%)	
Other	10 (4%)	8 (3%)	
Multiracial	45 (17%)	23 (9%)	
Ethnicity			$X^2(1) = 0.23$
Hispanic	40 (15%)	33 (14%)	
Non-Hispanic	220 (85%)	205 (86%)	
Household income			$X^2(11) = 13.39$
Under $10,000	24 (9%)	34 (14%)	
$10,000–19,999	36 (14%)	35 (15%)	
$20,000–29,999	45 (18%)	35 (15%)	
$30,000–39,999	26 (10%)	25 (11%)	
$40,000–49,999	24 (9%)	10 (4%)	
$50,000–59,999	21 (8%)	15 (6%)	
$60,000–69,999	24 (9%)	15 (6%)	
$70,000–79,999	11 (4%)	19 (8%)	
$80,000–89,999	12 (5%)	10 (4%)	
$90,000–99,999	6 (2%)	6 (3%)	
$109,000–119,999	13 (5%)	15 (6%)	
Over $120,000	18 (7%)	19 (8%)	
Age (years; 8.01–13.99)	11.53 (1.56)	11.29 (1.51)	$t(496) = -1.73$
BMI (percentile; 0.20–99.80)	73.61 (27.87)	68.94 (29.96)	$t(496) = -1.80$
Steroid medication use			$X^2(1) = 0.87$
Yes	21 (8%)	25 (11%)	
No	239 (92%)	213 (89%)	
Alcohol use			$X^2(1) = 0.17$
Yes	44 (17%)	37 (15%)	
No	216 (83%)	201 (85%)	
Other substance use			$X^2(1) = 1.41$
Yes	28 (11%)	34 (14%)	
No	232 (89%)	204 (86%)	

Note. Sex differences in continuous variables were assessed via *t*-tests and in dichotomous variables via Chi-Square tests. Sample ranges are provided. CM = child maltreatment, TLEs = traumatic life events, hs-CRP = high-sensitivity C-reactive protein, BMI = age- and sex-adjusted body mass index percentile.

Caregivers who participated in the study with youth were on average 40 years old (*SD* = 8.26, range 23.74–75.41). Eighty-eight percent of caregivers identified as women, 12% as men, and one caregiver identified as a transgender man. About 19% percent of caregivers identified with a historically marginalized racial group, and about 11% identified as Hispanic.

3.2. Missingness

Two hundred two youth who were missing data for the variables included in the hierarchical regression models were excluded from the analysis sample (Supplemental Table 3). Seventy-two percent of the excluded participants were missing hs-CRP data; 98 of these cases were due to refusal of the blood draw. Missingness for the other variables of interest were all less than 10% with the exception of nicotine use (12% missing). Participants who were missing data were less likely to have used nicotine, were less pubertally advanced, experienced fewer traumatic life events (TLEs), were more likely to identify as Black/African American and less likely to identify as multiracial, and were younger than participants included in analyses.

3.3. Bivariate associations

Many bivariate associations involving nicotine use, pubertal stage, or hs-CRP were significant for girls and not for boys (Table 2). Girls who used nicotine had greater hs-CRP levels ($M = 0.05$, $SD = 1.29$) than girls who were non-users ($M = -0.51$, $SD = 1.21$) ($t(258) = -2.78$, $p = 0.01$), but hs-CRP did not significantly differ as a function of nicotine use among boys. Additionally, nicotine use was associated with lower household income ($t(258) = 2.44$, $p = 0.02$) and BMI ($t(258) = -3.44$, $p < 0.001$) for girls but not boys, although Hispanic ethnicity was significantly correlated with nicotine use for boys but not girls. Boys who identified as Hispanic were over twice as likely to have used nicotine (27%) compared to boys who did not identify as Hispanic (11%) ($X^2(1, N = 238) = 6.29$, $p = 0.01$).

Pubertal stage was also significantly associated with measures of adversity for girls but not boys. Girls who were more advanced in pubertal development were more likely to have a history of CM investigation ($t(258) = -3.13$, $p = 0.002$) and to have more TLEs ($r(258) = 0.26$, $p < 0.001$) than girls at an earlier pubertal stage.

Some associations were significant in both girls and boys, however. Nicotine use was associated with pubertal stage such that users were more advanced in puberty (*M*s = 3.16–3.36, *SD*s = 0.97–1.00) than non-users (*M*s = 2.41–2.46, *SD*s = 0.99–1.01) (girls: $t(258) = -4.43$, $p < 0.001$; boys: $t(236) = -4.80$, $p < 0.001$). Nicotine use was also associated with CM investigation history (girls: $X^2(1, N = 260) = 1.18$, $p < 0.001$; boys: $X^2(1, N = 238) = 4.12$, $p = 0.04$) and exposure to more TLEs (girls: $t(258) = -5.49$, $p < 0.001$; boys: $t(236) = -4.44$, $p < 0.001$). Youth who reported having used nicotine were more likely to be older (girls: $t(258) = -4.73$, $p < 0.001$; boys: $t(236) = -3.45$, $p < 0.001$).

3.4. Hierarchical regressions

Results from the five hierarchical regression models run separately by sex are presented in Table 3. Model 1 results indicated that steroid medication use and age covariates were not significantly associated with hs-CRP in girls and that age was not significantly associated with hs-CRP in boys. The adversity-related measures were not significantly associated with hs-CRP levels among girls and boys (except for CM investigation among boys) when added to Model 2.

In Model 3, which included all covariates and adversity-related measures, nicotine use was associated with hs-CRP levels in opposite directions for girls and boys. Girls who used nicotine had greater hs-CRP levels compared to non-user girls ($\beta = 0.45$, $p = 0.045$) whereas boys who used nicotine had lower hs-CRP levels compared to non-user boys ($\beta = -0.41$, $p = 0.02$). These differential associations remained

Table 2
Bivariate associations (correlations, T-Tests, chi-square tests) between variables of interest, split by sex.

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Any nicotine use		-4.43***	-2.78**	12.18***	-5.49***	0.46	0.41	2.44*	-4.75***	-3.44***	0.10	49.00***	51.83***
2. Pubertal stage	-4.80***		.09	-3.13**	.26***	-1.24	-0.73	-.06	.76***	.36***	0.07	-3.27**	-2.89**
3. hs-CRP	1.83	-.02		-0.84	.05	-0.79	-0.47	-.09	.02	.27***	0.16	-2.13*	-1.28
4. Any CM investigation history	4.12*	-1.86	0.98		-6.50***	0.94	2.80	5.21***	-3.12**	-1.74	0.45	1.39	1.26
5. TLEs	-4.44***	.10	.03	-3.27**		0.97	-0.72	-.21***	.26***	.11	0.37	-5.03***	-2.55*
6. Historically marginalized racial group identity	0.10	-1.17	-0.72	0.06	-0.41		23.10***	2.97**	1.25	-1.04	2.45	0.18	0.17
7. Hispanic ethnicity	6.29*	-3.31**	-0.01	2.77	-0.90	2.82		1.51	0.01	-0.31	0.60	0.32	0.15
8. Household income	0.90	-.11	-.02	5.23***	-.26***	3.15**	1.96		-.03	-.15*	-0.20	2.17*	1.83
9. Age	-3.45***	.57***	-.14*	-1.47	.03	1.46	-1.63	.03		.24***	0.50	-3.28**	-2.20*
10. BMI	-0.42	.07	.51***	-1.88	.15*	-1.12	-0.61	-.15*	-.07		0.60	-1.42	-1.82
11. Any steroid medication use	1.03	-1.13	0.47	1.11	-1.56	0.31	7.69**	0.19	0.11	-1.77		0.77	4.04*
12. Any alcohol use	33.43***	-2.46*	1.07	0.52	-2.49*	0.71	12.65***	0.61	-2.00*	1.47	1.21		36.11***
13. Any other substance use	53.17***	-1.40	2.59*	0.19	-3.40***	0.01	0.02	0.69	-1.81	0.86	0.90	15.55***	

Note. Associations among girls are displayed above the diagonal and shaded in grey; associations among boys are displayed below the diagonal. Associations between two continuous variables were examined using correlations and are represented with *r*s. A Spearman correlation was used with household income as an ordinal variable. Associations between a continuous variable and a dichotomous variable were examined using *t*-tests and are represented with *t*s. Associations between two dichotomous variables were examined using Chi-Square tests and are represented with X^2s. Continuous variables of interest were pubertal stage, hs-CRP, TLEs, and age. Dichotomous variables of interest were nicotine use, CM investigation history, historically marginalized racial group identity, Hispanic ethnicity, and steroid medication use. Nicotine use, CM investigation history, historically marginalized racial group identity, Hispanic ethnicity, and steroid medication use were dummy-coded (nicotine use: 0 = no, 1 = yes; CM investigation history: 0 = no history, 1 = history; historically marginalized racial group identity: 0 = non-marginalized group, 1 = marginalized group; Hispanic ethnicity: 0 = non-Hispanic, 1 = Hispanic; steroid medication use: 0 = no, 1 = yes). hs-CRP values were winsorized and log transformed. hs-CRP = high-sensitivity C-reactive protein, CM = child maltreatment, TLEs = traumatic life events, BMI = age- and sex-adjusted body mass index percentile.
*$p < .05$. **$p < .01$. ***$p < .001$.

significant in Model 4 once pubertal stage was added as a predictor. Pubertal stage by itself was not significantly associated with hs-CRP.

When the interaction between nicotine use and pubertal stage was accounted for in Model 5, the main effect of nicotine use was no longer significant for girls. Instead, nicotine use and pubertal stage interacted to predict hs-CRP levels among girls ($\beta = 0.49$, $p = 0.02$). Probing this interaction in Model 5 demonstrated that, after adjusting for steroid medication use, age, adversity, and adversity-related demographic risk factors, the association between nicotine use and hs-CRP levels was stronger with more advanced pubertal stage for girls. Among girls who had used nicotine, hs-CRP levels were greater at more advanced pubertal stages ($\beta = 0.46$, SE = 0.22, 95% CI [0.03, 0.89]) (Fig. 1). Conversely, hs-CRP levels did not significantly differ across pubertal stages among girls who had never used nicotine ($\beta = -0.03$, SE = 0.12, 95% CI [−0.27, 0.22]). The addition of the nicotine use x pubertal stage interaction term for boys did not change the negative main effect of nicotine use on hs-CRP levels ($\beta = -0.50$, $p = 0.02$), and the interaction itself was not significant among boys.

In sensitivity analyses controlling for alcohol and other substance use (Supplemental Table 4), the nicotine use x pubertal stage interaction remained significant for girls ($\beta = 0.47$, $p = 0.03$) in Model 5. The main effect of nicotine use on hs-CRP levels among boys, however, was no longer significant; instead, other substance use significantly predicted hs-CRP in Model 5 ($\beta = -0.42$, $p = 0.03$). In sensitivity analyses excluding participants with hs-CRP levels of 10 mg/L or higher (Supplemental Table 5), previously statistically significant Model 5 effects were slightly attenuated (nicotine use x pubertal stage interaction for girls: ($\beta = 0.35$, $p = 0.05$); nicotine use main effect for boys: ($\beta = -0.62$, $p = 0.06$)).

4. Discussion

In the present study of a sample of youth at high risk for nicotine use (77% with a history of child maltreatment (CM) investigation), we examined whether nicotine use by itself was associated with hs-CRP levels after accounting for adversity, other adversity-related demographic risk factors, steroid medication use, age, and BMI. We also investigated whether pubertal stage moderated nicotine use–hs-CRP associations. In sex-stratified analyses, we found that nicotine use by itself predicted hs-CRP levels for both girls and boys but in opposite directions. Among girls, nicotine use was associated with greater hs-CRP levels. Among boys, nicotine use was associated with lower hs-CRP levels. This first finding supports prior findings that men demonstrate lower inflammation than women in response to nicotine exposure (Faner et al., 2014) and extends current knowledge by indicating that this sex difference may already be present during late childhood and early adolescence.

Table 3
Hierarchical regression models predicting high-sensitivity C-reactive protein, split by sex.

	Model 1		Model 2		Model 3		Model 4		Model 5	
	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys
Any steroid medication use	−0.00 (0.31)	−0.38* (0.19)	−0.00 (0.31)	−0.44* (0.19)	−0.03 (0.30)	−0.43* (0.18)	−0.03 (0.31)	−0.44* (0.18)	0.01 (0.30)	−0.44* (0.18)
Age	−0.06 (0.08)	−0.13 (0.07)	−0.07 (0.08)	−0.12 (0.07)	−0.10 (0.08)	−0.09 (0.07)	−0.15 (0.10)	−0.13 (0.09)	−0.13 (0.10)	−0.13 (0.09)
BMI	0.35*** (0.08)	0.67*** (0.07)	0.34*** (0.08)	0.69*** (0.07)	0.32*** (0.08)	0.69*** (0.07)	0.31*** (0.09)	0.69*** (0.07)	0.32*** (0.09)	0.69*** (0.07)
Any CM investigation history			0.02 (0.19)	−0.38* (0.17)	−0.01 (0.19)	−0.36* (0.17)	−0.01 (0.19)	−0.36* (0.17)	−0.00 (0.18)	−0.36* (0.17)
TLEs			0.03 (0.09)	−0.01 (0.08)	−0.01 (0.09)	0.03 (0.08)	−0.01 (0.09)	0.03 (0.08)	−0.03 (0.09)	0.03 (0.08)
Historically marginalized racial group identity			0.04 (0.18)	0.01 (0.17)	0.06 (0.17)	0.00 (0.17)	0.04 (0.18)	−0.01 (0.17)	0.01 (0.18)	−0.02 (0.17)
Hispanic ethnicity			0.04 (0.24)	0.09 (0.20)	0.03 (0.23)	0.14 (0.19)	0.03 (0.23)	0.12 (0.19)	0.04 (0.23)	0.11 (0.19)
Household income			−0.06 (0.07)	0.02 (0.08)	−0.05 (0.07)	0.03 (0.08)	−0.05 (0.07)	0.03 (0.08)	−0.07 (0.07)	0.03 (0.08)
Nicotine use					0.45* (0.23)	−0.41* (0.18)	0.45* (0.22)	−0.44* (0.18)	0.21 (0.21)	−0.49* (0.21)
Pubertal stage							0.06 (0.12)	0.07 (0.09)	−0.03 (0.12)	0.06 (0.10)
Nicotine use x pubertal stage									0.49* (0.21)	0.09 (0.16)

Note. Beta coefficients and robust standard errors are shown. Steroid medication use, CM investigation history, historically marginalized racial group identity, and Hispanic ethnicity were dummy-coded (steroid medication use: 0 = no, 1 = yes; CM investigation history: 0 = no history, 1 = history; historically marginalized racial group identity: 0 = non-marginalized group, 1 = marginalized group; Hispanic ethnicity: 0 = non-Hispanic, 1 = Hispanic)). hs-CRP values were winsorized and log transformed. BMI = age- and sex-adjusted body mass index percentile, CM = child maltreatment, TLEs = traumatic life events.
*$p < .05$. **$p < .01$. ***$p < .001$.

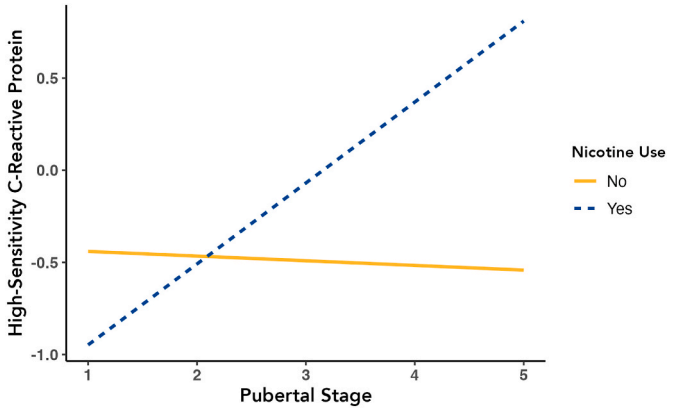

Fig. 1. Nicotine Use and Pubertal Stage Interact to Predict hs-CRP Levels Among Girls.
Note. High-sensitivity C-reactive protein was winsorized and log transformed.

4.1. Nicotine use and puberty interact to predict hs-CRP levels among girls

We also found sex differences in how puberty moderated the relation between nicotine use and hs-CRP levels. Among boys, pubertal stage did not alter the association between nicotine and hs-CRP. Among girls, however, the association between nicotine use and hs-CRP was stronger (more positive) at more advanced, rather than earlier, pubertal stages. Though the sample size of girls having used nicotine was small (n = 43), we investigated whether this effect could have been driven by more frequent nicotine use in more pubertally advanced girls. Nicotine frequency tended to be higher for girls at pubertal stage 3 and later, though this trend was not significant ($F(3, 39) = 1.230$, $p = 0.29$).

The directionality of this significant interaction among girls supports the notion that puberty can increase individuals' physiological plasticity (Fuhrmann et al., 2015). Puberty is believed to drive increased sensitivity to environmental influences; this puberty-linked plasticity is also theorized to be stronger for girls than it is for boys (Stumper et al., 2020). This theory is reflected in previous work on "pubertal recalibration", which posits that puberty opens a window of increased sensitivity to the environment. During this developmental window, previously dysregulated physiological systems have opportunities to recalibrate toward more typical functioning. One line of evidence shows that individuals who were institutionalized as infants and toddlers and then adopted by age 5 only demonstrate hypothalamic-pituitary-adrenal (HPA) recalibration once puberty commences (DePasquale et al., 2021; Gunnar et al., 2019).

Regarding the present findings, the hormonal and neural processes that underlie puberty might cause the individual to become more physiologically sensitive to substances such as nicotine. If this is true, then exposure to nicotine could more easily get under the skin and increase inflammation during puberty compared to during other developmental stages. Work on pubertal hormones indicates that estrogen especially may strengthen the effect of nicotine on inflammation in a sex-differentiated way during puberty (Ashare and Wetherill, 2018). Estrogen, linked to female differentiation, can be proinflammatory (compared to testosterone, an anti-inflammatory and male-linked hormone) (Bianchi, 2019) and is associated with higher levels of systemic inflammation (Straub, 2007). Estrogen has been demonstrated to interact with nicotine to impact enzymes related to lung functioning; this process is suggested to play a role in why women are more likely to have tobacco-linked inflammation than men (Tam et al., 2011).

4.2. Effects of nicotine on hs-CRP levels above and beyond adversity

We adjusted for history of CM investigation, traumatic life events (TLEs), identification with historically marginalized racial and ethnic groups, and household income to determine whether nicotine use may simply be a proxy for effects of psychosocial adversity on hs-CRP levels rather than having a more direct effect on hs-CRP. Nicotine use explained variation in hs-CRP levels for both girls and boys (as an interaction with pubertal stage and as a main effect, respectively) even after accounting for adversity and adversity-related demographic risk factors.

Though this finding provides support for the notion that nicotine is

associated with hs-CRP levels independently of adversity exposures, it is important to emphasize that it does not completely negate the idea that nicotine use may act on physiology as a proxy for adversity. Examination of bivariate associations in this sample indicated that, though none of the adversity-related measures were significantly associated with hs-CRP levels, the CM investigation history and TLE measures were significantly associated with nicotine use for both girls and boys. Additionally, nicotine use was associated with household income for girls and Hispanic identity for boys. These could be indications that youth might engage in nicotine use as a strategy to cope with adversity and that such nicotine use then more directly impacts hs-CRP levels as part of a mechanism linking adversity to health outcomes.

Relatedly, nicotine–hs-CRP links found in the present study may also underlie associations between other constructs of interest and inflammation, especially those that are strongly linked to adversity. For example, nicotine use may explain the influence of internalizing psychopathology on hs-CRP levels. Internalizing problems, which have been consistently linked to adversity (Taylor et al., 2011), have been demonstrated to predict higher CRP levels among youth (Flouri et al., 2020), and findings from the adult literature indicate that negative affect is related to greater inflammation (Sin et al., 2015). In turn, internalizing emotional and behavioral difficulties can predict tobacco use onset among youth (Green et al., 2018) and are associated with nicotine use currency among adults (Ganz et al., 2022). An increased tendency to use nicotine, whether to cope with adverse events themselves or with emotional/behavioral difficulties associated with exposure to adversity, may then be one explanation as to how psychosocial factors could impact physiology. It will be important for future investigations into associations between inflammation and adversity and adversity-related factors (e.g., demographic risk factors, psychopathology) to account for nicotine use as well as for studies of nicotine and inflammation-related outcomes to similarly control for psychosocial effects.

4.3. Strengths and limitations

The present study had multiple strengths. First, we were able to examine the nicotine use−hs-CRP association among relatively young participants (8–13 years old), which allowed us to capture youth at a time when substance use may start and long-term health implications of both nicotine use and inflammation across the lifespan may begin to form (Danese et al., 2011; Kendler et al., 2013; Korhonen et al., 2018). Second, we leveraged available hs-CRP data in a younger cohort to study nicotine use in the context of puberty which most other extant studies focusing on nicotine use and inflammation are unable to do. Third, the inclusion of youth both with and without a history of CM investigation, combined with other in-depth assessments of traumatic life events, allowed us to account for a wide range of adversity exposures. Fourth, the use of the Tanner Staging Scale to assess puberty in the present study is a strong measure of current pubertal stage compared to other self-report measures (Dorn and Biro, 2011; Mendle et al., 2019).

The present study was not without its limitations, however. We only had available data regarding hs-CRP and not other indicators of inflammation. Stumper et al. (2020) investigated inflammatory biomarkers among adolescents and found that, although CRP was positively associated with pubertal stage among girls, more advanced puberty was associated with lower inflammation when inflammation was measured via tumor necrosis factor-alpha and interleukin-8. Nonetheless, hs-CRP is a commonly used indicator of inflammation with established clinical cut-offs and relevance. Future studies should, however, include several markers of inflammation where possible as they may be differentially predicted by nicotine use and pubertal stage. Additionally, though many participants had hs-CRP levels within the expected range (<3 mg/L), there were 61 participants with subclinically elevated levels (3–10 mg/L) and 10 participants with clinically high levels (>10 mg/L). In the case of clinically high levels, this may be indicative of acute illness (Sproston and Ashworth, 2018), which may have influenced our results as seen through sensitivity analyses where participants with high hs-CRP levels were removed (Supplemental Table 5). It is important to note, however, that attenuated effects observed through these additional analyses may also simply be due to reduced power.

Relatively few participants reported any nicotine use (15%) but this was to be expected given the age range of the sample (Gentzke et al., 2022), and there is value in utilizing data from 8- to 13-year-old youth because it allows for investigation of the nicotine use−hs-CRP association as substance use first emerges and youth go through puberty. Furthermore, our nicotine use measure did not account for recency or frequency of use. Both factors may have implications for hs-CRP levels, with current and daily use placing youth at higher risk for increased hs-CRP levels than past and infrequent use. These mostly non-significant differences (Supplemental Tables 1 and 2) across uneven and small group sizes (e.g., 36 individuals who used nicotine once or twice compared to seven individuals who used six to 10 times) informed our decision to not account for nicotine use recency and frequency in our models.

The cross-sectional nature of the available data limited our ability to interpret observed effects as causal. Though we found associations between nicotine use, hs-CRP levels, and pubertal stage, it is unclear which mechanistically impacts which. Longitudinal data would allow for the examination of causal mechanisms and the potential effects of pubertal timing and tempo on nicotine use and hs-CRP levels. Additionally, longitudinal data would allow for a more explicit test of whether nicotine use mediates the association between adversity and hs-CRP levels.

We did not account for gender identity in the present study. Regardless of sex-linked biological processes that are assumed to be similar across transgender youth who have not undergone gender-affirming treatments and cisgender youth, adversity levels and nicotine use rates are likely higher in transgender youth populations due to social and health inequities resulting from systemic discrimination (Carmel and Erickson-Schroth, 2016). Thus, it is possible that the associations we investigated differ in transgender youth. The present sample included only two transgender youth, so there were not large enough groups to examine within-gender effects. Results did not differ meaningfully in analyses that did not include the two transgender participants in the sample, so their data were retained for the final analyses. We acknowledge this limitation and highlight the need for more studies explicitly examining transgender experiences and health (Ortiz-Martínez and Ríos-González, 2017; Reisner et al., 2016).

We also did not control for hormonal birth control due to partial data availability and low frequency of use. Assessment of birth control use began over halfway through baseline data collection with the full sample. Of the 85 girls who were asked about birth control, only two participants endorsed hormonal birth control.

Another limitation concerned the nature of the hierarchical regression models in the present study; there were multiple comparisons used to answer the research questions. The models built directly on each other, but the possibility of Type I error persists.

4.4. Conclusions

Youth nicotine use is associated with hs-CRP levels that may contribute to increased vulnerability for developing substance use disorders (Andersen, 2019; Lucerne et al., 2021) as well as increased risk for other physical and mental health issues (Furman et al., 2019; Renna et al., 2018). The present findings indicate that puberty may play a role in how nicotine exposure influences hs-CRP levels. This has meaningful implications for the strategic timing of prevention initiatives and interventions aimed at reducing rates of nicotine use and subsequent health risk among youth. Particularly for girls, it may be most effective to act on nicotine–inflammation links during early puberty.

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CRediT authorship contribution statement

Holly T. Pham: Conceptualization, Formal analysis, Methodology, Visualization, Writing – original draft. **Stephanie T. Lanza:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing. **Eric D. Claus:** Investigation, Writing – review & editing. **Christine M. Heim:** Investigation, Writing – review & editing. **Jennie G. Noll:** Funding acquisition, Investigation, Writing – review & editing. **Chad E. Shenk:** Investigation, Writing – review & editing. **Hannah M.C. Schreier:** Conceptualization, Funding acquisition, Investigation, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The dataset analyzed during the current study is available through agreement with the study investigators.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2024.100841.

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