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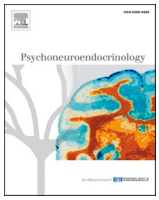

Exposure to diesel-related particulate matter, cortisol stress responsivity, and depressive symptoms in adolescents

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ABSTRACT

Exposure to air pollution is associated with higher risk for psychopathology; however, the mechanisms underlying this association are not clear. Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in response to stress has been implicated in depression. Here, we estimated annual exposure to particulate matter (PM) from diesel emissions in 170 9- to 15-year-old adolescents (56 % female) using their residential addresses and data from nearby monitoring sites. We obtained salivary cortisol samples from participants while they completed a social stress task and calculated area under the curve with respect to ground (AUCg) and with respect to increase (AUCi) in order to assess cortisol responsivity during stress. Participants also reported on their depressive symptoms and sleep disturbances. Greater exposure to diesel PM was associated with lower cortisol output (AUCg) during stress, which was associated with higher depressive symptoms, particularly for adolescents with more sleep disturbances. Importantly, these effects were independent of household and neighborhood socioeconomic disadvantage and exposure to early adversity. Thus, HPA-axis dysfunction may be one mechanism through which environmental pollutants affect adolescents' mental health.

1. Introduction

Air pollution is one of the leading threats to human health (World Health Organization, 2021). According to reports from the United States Environmental Protection Agency and other sources, anthropogenic sources of air pollution such as vehicle and diesel exhaust emissions contribute to more than half of the toxic substances released into the atmosphere each year (United States Environmental Protection Agency, 2024, 2020; Xue et al., 2013). These substances include elemental or black carbon, exposure to which has been associated with respiratory symptoms and airway inflammation in youth (Patel et al., 2013; Spira-Cohen et al., 2011), and ultrafine particles (i.e., particles with aerodynamic diameter less than 0.1 micrometers), which can be inhaled deep into the lungs, enter the bloodstream, and translocate into multiple organs, including the brain (Pryor et al., 2022). Indeed, in California, while particulate matter (PM) from diesel emissions sources comprises about 8 % of outdoor particulate matter less than 2.5 microns in diameter (PM2.5), more than 90 % of diesel PM consists of ultrafine particles (California Air Resources Board, n.d.). Although a majority of personal exposure to diesel PM occurs during travel on roadways, elevated levels of diesel PM are also present in and around ports and railyards where ships, trains, and trucks operate (California Air Resources Board, n.d.). Thus, individuals who live or work near these areas are likely to experience high levels of diesel PM exposure. Whereas ambient PM2.5 includes pollutants from anthropogenic and natural (e.g., wildfires) sources, diesel emissions are uniquely anthropogenic and thus have targeted implications for policy. For example, since the California Air Resources Board implemented policies to limit diesel emissions in the 1990s, diesel emissions have been reduced by 78 % from 1990 to 2014, resulting in a 50 % reduction in diesel-related cardiopulmonary deaths (Schwarzman et al., 2021).

Emerging evidence suggests that exposure to air pollution, including those from vehicle and diesel exhaust emissions, especially during early development, is associated with an increased risk for developing mental disorders across the lifespan (Bhui et al., 2023; Newbury et al., 2019; Salvi and Salim, 2019). Not surprisingly, therefore, investigating the

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mechanisms through which such exposures increases the likelihood that adolescents will develop psychopathology is of growing interest to researchers. Although inhaled pollutants can affect extrapulmonary organs via multiple pathways (e.g., absorption into the circulatory system, lung inflammation-related cytokine release, and activation of autonomic and neuroendocrine system through interactions with pulmonary nerves and receptors), evidence suggests that the neuroendocrine system is a necessary mediator of the systemic (e.g., neural, metabolic) effects of exposure to air pollution (Miller et al., 2016; Pan et al., 2021; Snow et al., 2018).

In this context, exposure to air pollution has been associated with dysregulation of hypothalamic pituitary adrenal (HPA) axis functioning both in non-human animals (Liu et al., 2024; Snow et al., 2018; Thomson, 2019) and in human adults (Mallach et al., 2023; Thomson et al., 2021). For example, experimental studies indicate that acute exposure to diesel exhaust (compared to filtered air) is associated with greater increases in salivary and plasma cortisol levels in adults, providing causal support linking diesel exposure to heightened cortisol reactivity (Mallach et al., 2023; Thomson et al., 2021). In contrast to these brief laboratory exposures, however, individuals living in neighborhoods with high levels of diesel PM are likely to experience chronic exposure to such HPA-axis-triggering pollutants and, therefore, may exhibit functioning that reflects chronic activation of the HPA axis. More specifically, although acute activation of the HPA axis and the resulting release of glucocorticoids is an essential and adaptive response to stress, prolonged or chronic activation of the HPA axis can trigger down-regulation processes that suppress the HPA axis and lead to blunted glucocorticoid reactivity (Fries et al., 2005). While it is not clear precisely how the transition from HPA hyper- to hypo-reactivity occurs, research with rodents suggests that increased sensitivity of the HPA axis to the negative feedback of glucocorticoids contributes to chronic stress-related HPA hypo-reactivity (Houshyar et al., 2001). Studies of pollution exposure and HPA-axis functioning in youth have focused mostly on basal levels of cortisol, and have found that adolescents exposed to higher levels of ambient air pollutants (e.g., nitrogen dioxide) exhibit a flatter diurnal slope in cortisol (Wing et al., 2018), higher concentrations of hair cortisol (Verheyen et al., 2021), and lower levels of morning serum cortisol (Toledo-Corral et al., 2021). These patterns of HPA-axis dysregulation are similar to those reported in children and adolescents who have experienced chronic and severe stress (Koss and Gunnar, 2018), suggesting that prolonged exposure to pollutants can lead to alterations in HPA-axis functioning similar to those found in response to exposure to psychosocial adversity.

Few studies have examined the role of pollution exposure on cortisol reactivity to acute psychosocial stress, which, although related to basal cortisol levels (Dienes et al., 2019; Sandner et al., 2020), has been found to have distinct associations with specific biological and behavioral outcomes (Alink et al., 2008; Henckens et al., 2016; Jiang et al., 2019). Importantly, altered (typically blunted) cortisol reactivity to acute psychosocial stress has been found in individuals diagnosed with depression compared to healthy controls (Cunningham et al., 2021; Mazurka et al., 2018; Zorn et al., 2017); it has also been shown to predict a diagnosis of depression in adolescent girls (Colich et al., 2015) and to be associated with internalizing problems in maltreated children (Perry et al., 2020). While the mechanisms linking stress-related HPA hypo-reactivity (and HPA axis dysfunction in general) and depressive symptoms are unclear, it is possible that alterations in HPA axis responding are associated with disrupted functioning of other systems that are sensitive to and/or dependent on optimal cortisol levels and that are also implicated in the etiology and pathophysiology of depression, including neurobiological (prefrontal, amygdala, and hippocampal) and immune functioning (McEwen, 2007; Miller and Raison, 2016). Only one study to date has examined the association between air pollution exposure and cortisol responsivity to stress in adolescents: Miller et al. (2020) found that greater exposure to fine particulate matter (PM2.5) was associated with heightened total cortisol output (as opposed to differences in amplitude of change) in response to psychosocial stress in anxious adolescent girls. However, it is not known whether exposure to diesel PM is associated with altered cortisol responsivity to psychosocial stress or whether such alterations in cortisol responsivity are related to depressive symptoms in a community sample of adolescents.

The associations among diesel PM exposure, cortisol stress responsivity, and depressive symptoms may also depend on a number of factors, including adolescents' pubertal status and sex (e.g., (Colich et al., 2015; Shirtcliff and Essex, 2008)) and adversity exposure (e.g., (Koss and Gunnar, 2018; Miller et al., 2020; Wade et al., 2024)). For example, lower/blunted cortisol responsivity to stress was found to be associated with risk for depression during early (but not late) puberty (Colich et al., 2015; Shirtcliff and Essex, 2008), particularly in girls (Colich et al., 2015) and those who experienced early adversity (Wade et al., 2024). Another factor that may also be important in moderating these associations, but has been relatively understudied, is sleep. In addition to its role in stress responsivity and regulation, the HPA axis also plays a critical role in sleep regulation and underlies the bidirectional relation between stress reactivity and sleep disturbances, both of which are strongly associated with depressive symptoms (Asarnow, 2020; McEwen and Karatsoreos, 2015; Simon and Admon, 2023). Studies have shown that sleep disturbances are associated with heightened HPA reactivity to stress and cortisol awakening response in adolescents and adults (Kater et al., 2022; Kuhlman et al., 2020; Minkel et al., 2014; Mrug et al., 2016; Murack et al., 2021), which in turn have been associated with greater depressive symptoms in adolescents (Kuhlman et al., 2020). Poor sleep has also been found to moderate associations between daily family stress and HPA-axis functioning such that family stress was associated with lower cortisol awakening response only among adolescents with poor sleep (Chiang et al., 2016), consistent with the allostatic load (McEwen, 1998) and diathesis-stress (Monroe and Simons, 1991) models. Thus, it is possible that the associations among diesel PM exposure, cortisol responsivity to stress, and depressive symptoms during adolescence are strengthened by sleep disturbances.

In the current study, we investigated whether exposure to diesel PM is associated with depressive symptoms in a community sample of adolescents (ages 9–15 years), and whether cortisol reactivity to stress mediates this association. We also explored whether associations were moderated by sex, pubertal stage, early adversity, and sleep disturbances. Based on previous research, we hypothesized that greater diesel PM exposure will be associated with blunted cortisol responsivity to psychosocial stress, which, in turn, will be associated with elevated levels of depressive symptoms in adolescents. Further, we hypothesized that these associations will be stronger among females, those earlier in pubertal development, and those who experienced greater early adversity and/or sleep disturbances.

2. Methods

2.1. Participants

Participants were 170 adolescents (96 female; 9–15 years, M=12.26 years, SD=1.39) who were part of a larger longitudinal study (N=225) examining the effects of early life stress on neurodevelopment and risk for psychopathology across puberty. Participants in the current study were recruited from the San Francisco Bay Area in California between 2013 and 2017 using a combination of online advertisements and locally distributed flyers. Participants were excluded if they had a history of major medical illness (e.g., epilepsy/seizures, cardiovascular or thyroid conditions) and severe learning disabilities (e.g., attention, reading, visual or auditory processing problems) that would make it challenging for them to comprehend study tasks. Because the parent study involved a magnetic resonance imaging (MRI) scan, exclusion criteria also included those that would preclude an MRI scan (e.g., metal implants, braces). The study was approved by the Stanford University Institutional Review Board. Participants provided informed assent, and parents/legal

guardians provided informed consent in accordance with the Declaration of Helsinki. In the parent study, we randomly split the sample in half: one half of the participants completed the modified Trier Social Stress Task (TSST) at early puberty and the other half completed the TSST at later puberty to allow us to compare cortisol output to acute stress as a function of puberty in youth using only one exposure to the TSST. The current study includes all participants who completed the TSST regardless of pubertal stage. Participants who completed the TSST did not differ from those who did not complete the TSST on distribution of sex (p=.31), distribution of race (p=.083), age (p=.24), pubertal stage (p=.59), parental education (p=.30), household income (p=.98), indicators of neighborhood socioeconomic disadvantage (ps>.44), diesel PM percentile (p=.43), and depressive symptoms (p=.15) at baseline (Table S1).

2.2. Measures

2.2.1. Diesel Particulate Matter (PM)

We estimated participants' exposure to diesel PM emission from on-road and off-road sources using the CalEnviroScreen, a tool created by the California Office of Environmental Health Hazard Assessment that provides estimates of various environmental indicators across California neighborhoods at the census tract level. The CalEnviroScreen 3.0 (updated June 2018; https://oehha.ca.gov/media/downloads/calenviroscreen/report/ces3report.pdf) estimates annual diesel PM emissions (in kg/day) for 2012 based on a day in July 2012 (M=19.59 kg/day, SD=11.83) while the CalEnviroScreen 4.0 (updated October 2021; https://oehha.ca.gov/media/downloads/calenviroscreen/report/calenviroscreen40reportf2021.pdf) estimates annual diesel PM emissions (in tons/year) for 2016 based on a typical week in July 2016 (M=0.1979 tons/year, SD=0.1699) (See Supplement for a detailed description of how diesel PM emissions were calculated). CalEnviroScreen also provides percentile rankings of diesel PM exposure for each census tract across the entire state, which we used in the current study because of the difference in units reported in both reports and the non-normal distribution of the raw values. Because data collection for the current study occurred during the time between CalEnviroScreen's releases/measurements of diesel PM (i.e., from October 2013 to September 2018), we used data from both reports to estimate participants' annual diesel PM exposure. We calculated a standardized average of the percentile scores across the CalEnviroScreen versions, which provides an estimate of participants' relative exposure to diesel PM. Higher scores indicate greater exposure to diesel PM.

2.2.2. Particulate matter 2.5 (PM 2.5)

Annual mean concentrations of PM 2.5 were extracted from the California Air Resources Board's air monitoring network database for each census tract for the years 2012–2014 (for CalEnviroScreen 3.0) and 2015–2017 (CalEnviroScreen 4.0) and converted to percentiles across all Californina census tracts. Participants' relative average annual exposure to PM 2.5 was estimated using a standardized average of the percentile scores of PM 2.5 exposure across the CalEnviroScreen versions.

2.2.3. Depressive symptoms

Participants completed the 10-item short form of the Child Depression Inventory (CDI-S; (Kovacs, 1992, 1985), a self-report measure of depressive symptoms for youth ages 8–17 years. Participants reported the severity of symptoms of depression they were experiencing over the past two weeks on a three-point scale from 0 (no symptoms) to 2 (definite symptoms). We calculated a summed score representing the cumulative severity of depressive symptoms, with higher scores indicating more symptoms. Studies have reported high validity and reliability of this measure (Kovacs, 1992). In the current sample, internal reliability of the CDI-S was 0.75 (95 % CI: [0.70, 0.80]).

2.2.4. Anxiety symptoms

Youth's self-reported anxiety symptoms were assessed using the Multidimensional Anxiety Scale for Children (MASC; March et al., 1997), which included 39 items rated on a 4-point scale (0="never true about me" to 3="often true about me"). Responses to items were summed, with higher scores indicating greater severity of anxiety symptoms.

2.2.5. Externalizing Symptoms

Participants completed the Youth Self Report (YSR; Achenbach and Rescorla, 2001), a self-report measure assessing emotional and behavioral problems. Participants rated 112 items on a 3-point scale (0=not true, 1=somewhat or sometimes, 2=very true or often true). We used the externalizing problems total score, which comprises the aggressive behavior and rule-breaking behavior syndrome scales.

2.2.6. Neighborhood socioeconomic disadvantage

We used data from the socioeconomic indicators on CalEnviroScreen 3.0 to create a composite measure of neighborhood socioeconomic disadvantage at the census-tract level by averaging standardized percentiles of poverty, educational attainment, unemployment, and housing burden indicators. Higher scores on this composite indicate greater neighborhood socioeconomic disadvantage.

The CalEnviroScreen 3.0 uses data from the 2011–2015 American Community Survey (ACS) to estimate for each census tract: 1) the proportion of the population with less than a high school education (educational attainment); 2) the proportion of individuals in each tract living below 200 percent of the federal poverty line (poverty); and 3) the proportion of the population over the age of 16 that is unemployed and eligible for the labor force (unemployment). For housing-burdened low-income households, data from the 2009–2013 Housing and Urban Development Comprehensive Housing Affordability Strategy were used to estimate the proportion of households per tract with household incomes less than 80 % of the county median and renter or homeowner costs that exceed 50 % of household income.

2.2.7. Household socioeconomic disadvantage

Household socioeconomic disadvantage was computed as an average standardized composite of parent education and income. The parent who accompanied the child to the laboratory session reported their highest level of completed education (1=No GED/High School Diploma, 2=GED/High School Diploma, 3=Some College, 4=Two-Year College Degree, 5=Four-Year College Degree, 6=Master's Degree, 7=Professional Degree (e.g., MD/JD/DDS, 8=Doctorate) and total household income over the past 12 months on a 10-point scale (1=< $5,000; 2=$5,001-$10,000; 3=$10,001-$15,000; 4=$15,001-$25,000; 5=$25,001-$35,000; 6=$35,001-$50,000; 7=$50,001-$75000; 8= $75,001- $100,000; 9=$100,001-$150,000; 10=>$150,0000).

2.2.8. Pubertal stage

Pubertal stage was determined using Tanner Staging (Marshall and Tanner, 1968). Participants are shown schematic drawings of two secondary sex characteristics (pubic hair and breast/testes development) on a scale of 1–5 and are asked to select the drawings that most accurately reflect their own development. We determined pubertal stage by averaging the pubic hair and breast/testes scores (Kircanski et al., 2019).

2.2.9. Sleep disturbances

We determined participants' level of sleep disturbance by calculating a sleep problems composite from three items assessing sleep quality on the YSR: "I sleep less than most kids," "I have trouble sleeping," and "I feel overtired." Each item is rated on a 3-point scale (0=not true, 1=somewhat or sometimes, 2=very true or often true). Scores were summed across items (range=0–6), with higher scores indicating more sleep problems. This sleep disturbances composite has been used in prior work (Uy and Gotlib, 2024) and has internal reliability consistent with

those of the validated Child Sleep Habits Questionnaire (Owens et al., 2000).

2.2.10. Early life adversity

We assessed early life stress using a modified version of the Traumatic Events Screening Inventory for Children (TESI-C; (Ford et al., 2002)), where we interviewed participants about their experiences of more than 30 types of stressful events (e.g., direct exposure to or witnessing of severe accidents, illness or disaster, and family or community conflict or violence) (see (Uy and Gotlib, 2024) for a detailed description of interview procedures). After the interviews, a panel of three trained coders who, blind to the participants' subjective severity ratings of each event, used a modified version of the UCLA Life Stress Coding System (Adrian and Hammen, 1993; Rudolph and Hammen, 1999) to rate the objective severity of each event on a scale ranging from 0 (not impactful) to 4 (extremely severe and impactful), with half-point increments (inter-rater ICC=0.99). Cumulative adversity severity scores were computed by summing the maximum objective severity scores for each type of stressor endorsed (King et al., 2020).

2.3. Trier social stress task

Participants completed a modified version of the Trier Social Stress Task (TSST; Kirschbaum et al., 1993), during which saliva samples were collected repeatedly. This modified version of the TSST – the TSST for Children – was adapted for children and adolescents and has been shown to elicit a robust cortisol response (Allen et al., 2017; Seddon et al., 2020). Shortly after arriving at the laboratory, participants provided a saliva sample (Sample 1) and participated in an MRI scan as part of the parent study. After the scanning session, participants were brought into a quiet room and the experimenter placed electrodes on participants to measure electrocardiogram and skin conductance activity. The experimenter instructed participants to relax for 5 minutes and a saliva sample was obtained after this first period (Sample 2); average duration between Samples 1 and 2 was 156 minutes (SD=50.20). After this baseline period, the experimenter told the beginning of a story to participants and instructed them to create an exciting ending to this story within the next 5 minutes. Participants were told that a judge would be videotaping them and would evaluate their ending based on content and memorization. After the 5-minute speech preparation period, participants delivered their story ending to an impartial judge (young adult male or female), who maintained a neutral expression and appeared to take notes on the presentation with the video camera next to them (purportedly, but not actually, recording). After the 5 minutes had passed, the judge instructed participants to complete a serial subtraction task aloud for another 5 minutes. The judge interrupted the participants if they made a mistake and instructed participants to start over. At the end of this 15-minute interval, we obtained another saliva sample (Sample 3, 15 minutes from the baseline or stressor onset; average duration between Samples 2 and 3 was 22.98 minutes [SD=3.13]). Participants then watched a 30-minute neutral video clip, during which two saliva samples were collected (Samples 4 and 5, 15 and 30 minutes after stressor offset). The average durations between Samples 3 and 4 and between Samples 3 and 5 were 18 (SD=2.49) and 36 minutes (SD=3.43). Participants were seated during the TSST.

2.4. Sample assays

All saliva samples were collected using SalivaBio Children's Swabs (Salimetrics, LLC) and stored in a −20°C freezer in the Stanford University Department of Psychology after the conclusion of the TSST. Samples were assayed using a high-sensitivity (0.004 μg/dL) immunoassay kit from Immuno-Biological Laboratories Inc. (Hamburg, Germany; intra- and inter-assay coefficients of variation range between 3 % and 5 %). Samples were assayed in three batches; we included batch number as a covariate in analyses.

2.5. Cortisol reactivity to stress

Consistent with field recommendations (Stalder et al., 2016) and our prior work (Kircanski et al., 2019), cortisol values for each sample that were >2 standard deviations (SD) above the mean value were winsorized. A total of 28 (4.12 %) cortisol values were winsorized. We calculated the area under the curve with respect to ground (AUCg) and area under the curve with respect to increase (AUCi) across the TSST (i.e., Samples 2 through 5) in order to assess total cortisol production and change in cortisol production, respectively (Pruessner et al., 2003). In addition, based on our previous work (Kircanski et al., 2019) and descriptive data (Table 1) showing that peak cortisol levels were observed 30 minutes from stressor onset (i.e., Sample 4) in the current sample, we also calculated AUCg and AUCi values for baseline-to-peak stress reactivity (i.e., from Samples 2–4) and post-peak stress recovery, during which cortisol levels returned to baseline (i.e., from Samples 4–5).

2.6. Statistical analyses

All analyses were conducted in R Studio (R Core Team, 2017). First, using the *lme4* and *stats* package, we conducted a multivariate analysis of covariance (MANCOVA) testing whether diesel PM was associated with cortisol production (i.e., AUCg) and/or with cortisol change (i.e., AUCi), and whether associations were moderated by sex, pubertal stage, early adversity, or sleep problems (path a). Significant effects were followed up with linear regressions to determine the nature of the effect on the cortisol variable(s). All variables and interactions were mean-centered and entered in one model, with significance evaluated at alpha=.05. Second, based on our finding that diesel PM was associated with total cortisol production (AUCg) and not with cortisol change (AUCi) (see below), we then tested whether AUCg was associated with depressive symptoms and whether the association was moderated by

Table 1
Sample characteristics and descriptive statistics.

Variables (Range)	N (%) or Mean (SD)
Sex	74 males/96 females (43.5 %/ 56.5 %)
Age (9–15 years)	12.26 (1.39)
Tanner (1−5)	2.70 (1.10)
Race/Ethnicity	
African-American	12 (7.1 %)
Asian	20 (11.8 %)
Biracial	40 (23.5 %)
Hispanic	15 (8.8 %)
Other	7 (4.1 %)
White	76 (44.7 %)
Diesel PM Percentile (2.93–99.0)	52.4 (25.0)
Parent Education (1−8)	4.87 (1.34)
Neighborhood Socioeconomic Disadvantage	
Education Percentile (0.18–84.57)	29.05 (20.19)
Poverty Percentile (0.03–86.66)	23.73 (20.84)
Unemployment Percentile (0.22–95.77)	29.63 (22.80)
Housing Burden Percentile (0.13–90.72)	32.36 (23.48)
Household Income (1−10)	8.51 (1.93)
Depressive Symptoms (0−11)	2.21 (2.53)
Sleep Disturbances (0−6)	1.53 (1.55)
Early Life Adversity (0−24)	6.74 (5.17)
Cortisol Concentrations	
Baseline (Sample 1) (0.016–4.26 μg/dL)	0.18 (0.33)
Baseline (Sample 2) (0.015–0.88 μg/dL)	0.15 (0.11)
15 minutes after stressor onset (Sample 3) (0.006–0.83 μg/dL)	0.18 (0.13)
15 minutes after stressor offset (Sample 4) (0.003–1.43 μg/dL)	0.23 (0.19)
30 minutes after stressor offset (Sample 5) (0.022–0.88 μg/dL)	0.16 (0.12)
AUCg (0.54–28.53)	10.80 (6.17)
AUCi (−10.11–15.34)	2.37 (4.87)

sex, pubertal stage, early adversity, or sleep problems, over and above exposure to diesel PM (path b). Finally, based on our results showing a significant interaction between AUCg and sleep problems on depressive symptoms (see below), we conducted a moderated mediation analysis testing whether the association between diesel PM and depressive symptoms was mediated by AUCg and whether the mediation was moderated by sleep problems. We conducted mediation analysis using Hayes' PROCESS macro in R and evaluated the index of mediation for significance based on bootstrapped 95 % confidence intervals with 5000 bootstraps. Furthermore, given previous research reporting differential effects of cortisol reactivity and cortisol recovery, we explored whether our findings were driven by cortisol reactivity or recovery by entering both variables as mediators in a parallel mediation model, allowing us to determine the unique effects of reactivity and recovery while controlling for the other variable and reducing the number of analyses conducted. We controlled for age, neighborhood socioeconomic disadvantage, household socioeconomic disadvantage, PM2.5 exposure, batch number, and time of day of TSST assessment in all analyses.

We also conducted supplemental analyses to determine whether cortisol levels at specific sample time points were driving the effects of diesel PM on AUCg. We conducted four linear regressions, regressing cortisol concentrations at baseline (Sample 2), 15 minutes after stressor onset (Sample 3), 15 minutes after stressor offset (Sample 4), and 30 minutes after stressor offset (Sample 5), on diesel PM exposure and controlling for covariates. We also tested whether cortisol concentration upon arrival to the lab (Sample 1) differed by diesel PM, controlling for covariates.

2.7. Specificity and sensitivity analyses

We conducted an additional set of analyses to determine the specificity of our findings. First, we tested the specificity of AUCg to the TSST as the mediator by conducting a moderated mediation analysis testing whether depressive symptoms mediated the association between diesel PM and AUCg (moderated by sleep disturbances). Second, we tested whether the effects of diesel PM and AUCg to the TSST were specific to depressive symptoms or to general affective/behavioral problems by examining participants' self-reported anxiety symptoms and externalizing symptoms as outcomes. Finally, we tested whether effects were specific to PM exposure from diesel sources or to air pollution more broadly by examining the effects of ambient PM2.5 exposure on cortisol reactivity to stress and depressive symptoms.

3. Results

Participant characteristics are reported in Table 1. Bivariate correlations among study variables are reported in Table 2. Greater diesel PM exposure was associated with greater household and neighborhood socioeconomic disadvantage, which were positively correlated with each other. Greater diesel PM exposure was also associated with lower cortisol output (AUCg) during the TSST, which was positively associated with cortisol reactivity (AUCi) during the TSST.

After accounting for covariates, the MANCOVA yielded significant effects of diesel PM ($F(2,134)=4.42$, $p=.014$), sex ($F(2,134)=3.08$, $p=.049$), age ($F(2,134)=4.55$, $p=.012$), and time of day ($F(2,134)=6.82$, $p=.0015$) on cortisol responsivity to stress (Table S2). Follow-up regressions indicated that greater diesel PM exposure was associated with lower cortisol output (AUCg), but not with cortisol reactivity (AUCi), during the TSST (AUCg: $b=-1.23$, $SE=0.57$, $t(135)=-2.17$, $p=.032$, Table S3; AUCi: $b=-0.02$, $SE=0.49$, $t(135)=-0.04$, $p=.97$, Table S4). The association between diesel PM exposure and AUCg did not differ by sex ($p=.51$), pubertal stage ($p=.54$), early adversity ($p=.41$), or sleep problems ($p=.30$) (Table S3). For AUCi, females ($p=.002$) and older adolescents ($p=.007$) had significant greater AUCi to the TSST (Table S4).

After controlling for diesel PM and covariates, there was a significant interaction between AUCg and sleep disturbances on depressive symptoms ($b=-0.06$, $SE=0.03$, $t(134)=-2.30$, $p=.023$) such that lower AUCg during the TSST was associated with higher levels of depressive symptoms among adolescents with high (+1 SD) levels of sleep disturbances ($b=-0.14$, $SE=0.05$, $t(134)=-2.51$, $p=.01$) but not among adolescents with low (-1SD; $p=.48$) or average ($p=.17$) levels of sleep disturbances. The association between AUCg during the TSST and depressive symptoms was not moderated by sex ($p=.86$), pubertal stage ($p=.59$), or early adversity ($p=.70$), though there was also a main effect of early adversity on depressive symptoms ($p=.043$; Table S5).

Moderated mediation analysis indicated that AUCg during the TSST mediated the association between diesel PM and depressive symptoms for adolescents with high (+1 SD) sleep disturbances (indirect effect = 0.18, $SE=0.10$, 95 % CI: [0.0058, 0.407]) but not for adolescents with low (-1SD) sleep disturbances (indirect effect = −0.054, $SE=0.0598$ 95 % CI: [-0.19, 0.04]; index of moderated mediation=0.076, $SE=0.045$, 95 % CI: [0.0041, 0.174]; Fig. 1). Including AUCg during the TSST, sleep problems, and its interaction explained 41.15 % of the variance in the association between diesel PM and depressive symptoms (total effect=0.53, $SE=0.24$, $t(142)=2.18$, $p=.031$; direct effect=0.34, $SE=0.22$, $t(139)=1.15$, $p=.13$).

We conducted exploratory analyses to examine whether the mediation of diesel PM and depressive symptoms by AUCg during the TSST was driven by cortisol output during reactivity or during recovery. Parallel moderated mediation analyses with AUCg both during reactivity and during recovery entered as mediators indicated that the mediation of diesel PM and depressive symptom through AUCg for adolescents with greater sleep disturbances was driven by AUCg during reactivity (index of moderated mediation = 0.14, $SE=0.08$, 95 % CI: 0.015, 0.32]), not by AUCg during recovery (index of moderated

Table 2
Bivariate correlations among study variables. *p<.05, **p<.01, ***p<.001.

	2	3	4	5	6	7	8	9	10	11	12	13
1. Age	.65***	−0.14	−0.14	−0.05	−0.11	0.08	−0.08	−0.06	−0.07	−0.07	−0.15	−0.09
2. Tanner Score		0	0.04	−0.06	−0.09	0.04	−0.01	0.03	−0.05	0	0.02	0.07
3. Household Socioeconomic Disadvantage			0.37***	0.21**	−0.12	−0.09	0.05	0.22**	−0.03	0.09	−0.06	0.28***
4. Neighborhood Socioeconomic Disadvantage				0.40***	−0.17*	0.01	0.03	0.32***	−0.15	0.05	0	0.15*
5. Diesel PM Percentile					−0.20*	−0.04	0.15	0.32***	0.01	0.15	0.08	0.04
6. AUCg						0.49***	−0.08	−0.12	0.03	0.06	0.08	−0.15
7. AUCi							−0.02	−0.10	0.11	0.02	0.09	−0.11
8. Depressive Symptoms								0.04	0.49***	0.49**	0.51***	0.28***
9. PM 2.5 Percentile									−0.04	−0.13	0	0.13
10. Anxiety Symptoms										0.47***	0.49***	0.17*
11. Externalizing Problems											0.44***	0.26**
12. Sleep Disturbances												0.27***
13. Early Life Adversity												

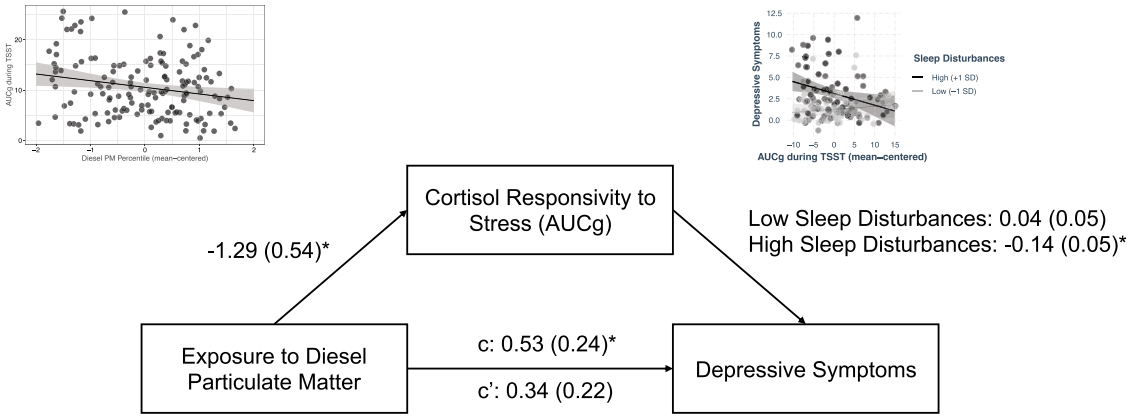

Fig. 1. Visualization of mediation model. Greater exposure to diesel particulate matter was associated with lower cortisol output during the TSST (a path: b=-1.29, SE=0.54, p=.019), which in turn was associated with elevated levels of depressive symptoms for adolescents with greater sleep disturbances (b path: b=-0.14, SE=0.05, p=.01). Covariates were age, sex, pubertal stage, household socioeconomic disadvantage, neighborhood socioeconomic disadvantage, assay batch, PM2.5, early adversity, and time of TSST assessment. *p<.05. AUCg = area under the curve with respect to ground.

mediation =-0.035, SE=0.051, 95 % CI: −0.17, 0.03]). That is, over and above the effects of coritsol output during stress recovery, greater exposure to diesel PM was uniquely associated with lower cortisol output during stress reactivity, which in turn was associated with elevated levels of depressive symptoms in adolescents who reported experiencing more sleep disturbances (indirect effect=0.30, SE=0.18, 95 % CI: 0.02, 0.72]) and not in adolescents with low sleep disturbances (indirect effect=0.11, SE=0.12, 95 % CI: [-0.39, 0.09] (Fig. 2).

Supplemental analyses indicated that greater diesel PM was associated with lower cortisol concentration at baseline (i.e., Sample 2; b=-0.02, SE=0.008, t(137)=-2.074, p=.04) and 15 minutes after stressor onset (i.e., Sample 3; b=-0.024, SE=0.01, t(137)=-2.34, p=.021), but not with cortisol concentration at any other time points (Table S6; Fig. 3). Diesel PM was also not associated with cortisol concentration for Sample 1 (study arrival; b=-0.008, SE=0.010, t(138)=-0.78, p=.44) (Figure S1).

We conducted an additional set of analyses examining the specificity of our findings. In these analyses we found, first, that depressive symptoms did not mediate the association between diesel PM and lower cortisol output to stress (indirect effect=-0.09, SE=0.10, 95 % CI: [-0.313 0.06]) nor was the mediation moderated by sleep disturbances (index of moderated mediation = 0.24, SE=0.22, 95 % CI: [-0.068, 0.77]), indicating specificity of the direction of effects. Second, we found that diesel PM and total cortisol output to stress were not related to self-reported anxiety symptoms (indirect effect=-0.012, SE=0.25, 95 % CI: [-0.54, 0.50]; index of moderated mediation = 0.24, SE=0.22, 95 % CI: [-0.068, 0.77]) or externalizing problems (indirect effect=-0.03, SE=0.14, 95 % CI: [-0.32, 0.24]; index of moderated mediation = 0.16, SE=0.14, 95 % CI: [-0.088, 0.47]), indicating specificity of effects to depressive symptoms. Finally, ambient PM2.5 exposure was not associated with AUCg across the TSST (b=-0.35, SE=0.77, t(140)=-0.46, p=.65), indicating specificity of the effects of PM from diesel emission on total cortisol output during the TSST.

4. Discussion

In the current study, we examined in a community sample of adolescents whether exposure to PM from diesel exhaust emissions is associated with alterations in HPA-axis functioning, operationalized as cortisol responsivity to a lab stressor, and whether differences in cortisol responsivity to stress is related to levels of depressive symptoms in a community sample of adolescents. We also explored whether associations among diesel PM exposure, cortisol responsivity, and depressive symptoms differed as a function of sex, pubertal stage, experiences of early adversity, or sleep disturbances. We found that greater diesel PM exposure was associated with lower cortisol output (AUCg) during the TSST, and that this effect did not differ by participant sex, pubertal stage, early adversity exposure, or sleep problems, and held even after controlling for these variables. Lower coritsol output during the TSST, in turn, was associated with elevated levels of depressive symptoms,

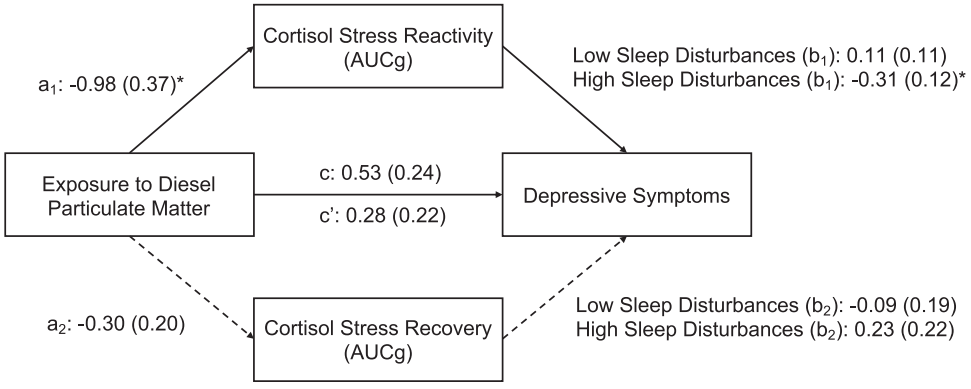

Fig. 2. Parallel moderated mediation analysis indicated that, over and above the effects of cortisol output during stress recovery, greater exposure to diesel particulate matter was associated with lower cortisol output during stress reactivity (a path: b=-0.98, SE=0.37, p=.009), which in turn was associated with elevated levels of depressive symptoms for adolescents with greater sleep disturbances (b path: b=-0.31, SE=0.12, p=.009). Covariates were age, sex, pubertal stage, household socioeconomic disadvantage, neighborhood socioeconomic disadvantage, assay batch, PM2.5, early adversity, and time of TSST assessment. *p<.05. AUCg = area under the curve with respect to ground.

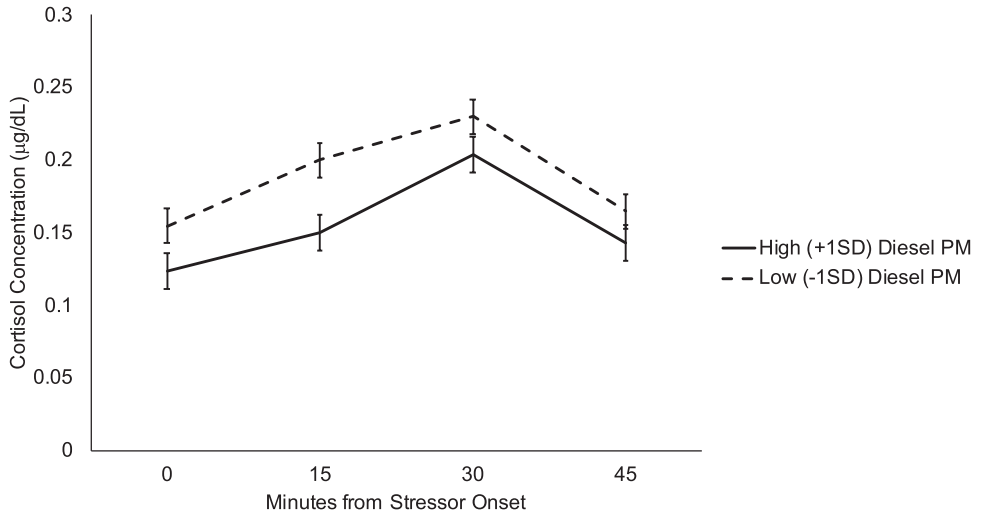

Fig. 3. Cortisol response to stress at high and low levels of diesel PM. Error bars represent standard errors. PM=particulate matter. SD=standard deviation.

particularly for adolescents with greater sleep disturbances. Diesel PM exposure was not associated with differences in changes in cortisol (i.e., AUCi) to the TSST; this dissociation of pollution exposure with AUCg and AUCi was also found in prior work examining the relation between PM2.5 exposure and cortisol responsitivity to the TSST in adolescent girls with anxiety (Miller et al., 2020). Lower cortisol production in response to acute stress has been found in adolescents who experienced chronic and severe stress, including those with a history of maltreatment (Trickett et al., 2014) and those from socioeconomically disadvantaged backgrounds (Desantis et al., 2015; Ursache et al., 2015). The allostatic load model (McEwen, 1998) posits that chronic exposure to stressors and consequent chronic activation of the HPA axis (and other stress-related physiological systems) engage allostatic processes that work to stabilize the body's response to stress. While adaptive in the short term, cumulative allostatic responses to chronic stressors eventually strain the body (i.e., increased allostatic load), increasing both vulnerability to future stressors and risk for adverse health outcomes. Thus, blunted cortisol responsivity to acute stress may reflect the result of allostatic adaptation to chronic activation of the HPA axis. Considered together with studies that have documented associations between pollution exposure and altered basal cortisol levels in adolescents, our findings suggest that residing in neighborhoods with higher levels of diesel PM is associated with general dysregulation of the HPA axis rather than with sensitivity of the HPA axis to stress.

We found that, of the moderators that we examined, sleep disturbances moderated the association between AUCg during the TSST and depressive symptoms such that lower total cortisol output during the TSST was associated with higher levels of depressive symptoms for adolescents who also have higher levels of sleep disturbances. AUCg was not related to depressive symptoms for adolescents with lower levels of sleep disturbances. These findings are consistent with allostatic load and diathesis-stress models of health and disease whereby a proximal stressor (sleep disturbances in this context) appears to exacerbate existing vulnerabilities (altered HPA-axis functioning) to depressive symptoms. Sleep disturbances are also strongly associated with – and perhaps even precede – depressive symptoms in adolescents (Goldstone et al., 2020; Lovato and Gradisar, 2014; Uy and Gotlib, 2024). Given the circadian pattern of cortisol and the bidirectional relationship between HPA axis functioning and sleep, it is perhaps not surprising that the combination of disrupted HPA-axis functioning and greater sleep disturbances contributes to elevated risk for depressive symptoms. However, studies examining the associations among sleep disturbances, HPA axis functioning, and depression during adolescence are rare. Furthermore, there are numerous ways in which HPA-axis functioning can be assessed: cortisol can be measured in blood, urine, saliva, and hair, and a number of parameters can be derived from salivary cortisol, including indices of reactivity, recovery, and total cortisol output in response to a laboratory stressor, as well as diurnal indices such as the cortisol awakening response, diurnal slope, and total output derived from multiple daily samples collected across multiple days (Koss and Gunnar, 2018). Our findings support the need for future research that incorporates diverse measures of sleep disturbances and HPA-axis functioning to understand their roles in the etiology and pathophysiology of depression during adolescence.

Our exploratory analyses indicated that exposure to diesel PM was associated with lower cortisol output during the reactivity, but not during the recovery, portion of the TSST. This effect may be driven primarily by baseline differences in cortisol levels as a function of diesel PM, given our finding that greater diesel PM was associated with lower cortisol levels at baseline and 15 minutes after stressor onset, but not 15 or 30 minutes later; however, cortisol levels upon arrival to the lab (i.e., Sample 1) were not associated with diesel PM exposure. Given that most participants completed an MRI scan after giving Sample 1 but before performing the TSST, combined with a relatively short (i.e., 5-minute) rest period between the scan and the onset of the TSST, it is possible that this baseline difference at the onset of the TSST stressor reflects residual reactivity to, and/or recovery from, the MRI scan and/or the laboratory context. This possibility is consistent with the hypothesis that an allostatic adaptation to a chronically activated HPA axis is blunted reactivity of the HPA axis to acute stress, perhaps through alterations in glucocorticoid receptor functioning, as have been documented in individuals with post-traumatic stress disorder and depression (Shishkina and Dygalo, 2017; Somvanshi et al., 2020). Future studies should include a longer accommodation period prior to the TSST to ensure that reactivity to the TSST is not confounded by variation in reactivity and recovery to the novel lab context and other lab activities.

Our specificity analyses indicated that residing in neighborhoods with relatively greater levels of ambient PM2.5 was not associated with cortisol responsivity in adolescents, and, further, that diesel PM was uniquely associated with AUCg, independent of ambient PM2.5. In contrast to PM2.5, PM from diesel sources is composed mostly of ultrafine (i.e., aerodynamic diameter less than 0.1 micrometers) particles (California Air Resources Board), which have the potential to infiltrate multiple organs and have more immediate effects on HPA-axis functioning, even in otherwise healthy individuals (Betha and Balasubramanian, 2013). Indeed, experimental studies in adults have shown that, while exposure to higher levels of PM2.5 and to ultrafine particles is associated with immediate alterations in heart rate variability, a

measure of autonomic nervous system function, only exposure to higher levels of ultrafine particles is associated with increased cortisol levels within the first hour of exposure in women (Mallach et al., 2023). It is also noteworthy that in that same study, higher levels of both ultrafine particles and PM2.5 exposure were associated with lower cortisol levels in men, suggesting that pollution exposure has sex-differentiated effects on HPA-axis reactivity. These findings are consistent with those of Miller et al. (2019), (2020), who found a main effect of residential PM2.5 exposure on autonomic reactivity to stress but not on HPA-axis reactivity in adolescents. Further, Miller et al. (2020) found that exposure to PM2.5 was associated with HPA-axis responsivity to stress only in adolescent girls with high levels of anxiety, and Miller et al. (2019) found that the association of PM2.5 exposure on autonomic reactivity to stress was exacerbated in adolescents with high levels of internalizing symptoms, suggesting that difficutlies in mental health interact with greater pollution exposure to exacerbate effects on adolescents' physiological responses to stress. In addition to PM size, different compounds are likely to have varying effects on HPA-axis functioning. Future studies examining a range of pollutants and measures of autonomic and HPA-axis functioning across development are needed to gain a more comprehensive understanding of their unique and combined effects of polllutants.

Our specificity analyses also indicated that the effects of diesel PM and blunted cortisol reactivity to stress were specific to depressive (as opposed to anxiety) symptoms, despite the fact that depressive symptoms were moderately correlated with both anxiety and externalizing symptoms in our study. Thus, diesel PM and blunted cortisol reactivity to stress may have specific effects on characteristics that are unique to depression, altering such symptoms as anhedonia and/or blunted neural and behavioral reward processing (Fischer et al., 2019; Forbes and Dahl, 2012; Kasparek et al., 2023; Nelson et al., 2016). Indeed, researchers have reported that blunted cortisol responsivitiy on the TSST is associated with an attenuated response bias to reward in depressed adults who have higher levels of anhedonia (Cunningham et al., 2021). Although no studies to date have examined the effects of pollution exposure on reward processing, there is now evidence that childhood pollution exposure is associated with alterations in reward-related brain structures in youth (Fowler et al., 2023). Future studies are needed that examine the role of reward processing in the context of pollution exposure and depression in adolescents in order to test these formulations more explicitly and systematically.

We should note three limitations of this study. First, although our results indicate statistical mediation between diesel PM exposure and depressive symptoms through cortisol responsivity to stress, the cortisol and depression data are cross-sectional – that is, participants reported their depressive symptoms and completed the TSST concurrently. Therefore, we cannot make strong claims regarding causality, although we did find that depressive symptoms did not mediate the association between diesel PM and cortisol responsivity. Second, we estimated participants' exposure to diesel PM based on their residential proximity to nearby monitoring sites; we did not measure participants' direct exposure, which can vary based on the amount of time spent outdoors vs. indoors at their residences, amount of time windows/doors are open, and/or the presence and quality of indoor air filtration devices. It is noteworthy, however, that, studies have found that pollutant concentrations from personal exposures are moderately correlated with concentrations measured from residential monitoring sites, especially at longer time scales (Gruzieva et al., 2024; Lin et al., 2020), suggesting that estimates obtained from monitoring sites may reflect long-term exposure to pollutants. As a related point, it is possible that there are variables related to diesel emissions exposure and/or HPA-axis functioning (e.g., noise exposure, exposure to indoor pollutants, daily stressors) that were not captured by the covariates in our study. For instance, air pollutant density may correlate with other features of the neighborhood environment, such as access to outdoor activities and green space, that could influence stress regulation. Controlling for neighborhood-level sociodemographic variables may partially mitigate this concern, although more research is needed. Future studies that use personal monitoring devices and/or collect information on participants' daily activities and locations are needed to provide a more comprehensive examination of these associations. Finally, our community sample of adolescents had, on average, relatively low levels of depressive symptoms; thus, our findings are explaining variation in symptoms within the general adolescent population. It is not clear whether these findings generalize to clinical samples and other populations. Further research is needed to test the replicability and generalizability of our findings.

In conclusion, we found that in a community sample of otherwise healthy adolescents, youth exposed to relatively greater PM from diesel emissions had blunted cortisol output in response to an acute psychosocial stressor, indexing possible alterations in their HPA-axis functioning. Blunted cortisol reactivity to stress, in turn, was associated with elevated levels of self-reported depressive symptoms, particularly for adolescents with more sleep problems. These findings contribute to a growing body of research examining mechanisms through which environmental pollutants might affect mental health outcomes in adolescents and support the need for further study of HPA-axis functioning as a potential contributor to these effects.

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CRediT authorship contribution statement

Jessica P. Uy: Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Formal analysis, Conceptualization. **Katy Shin:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Anne E. Berens:** Writing – review & editing, Investigation, Data curation. **Ian H. Gotlib:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Katharina Kircanski:** Writing – review & editing, Investigation, Data curation. **Joelle LeMoult:** Writing – review & editing, Investigation, Data curation. **Jessica L. Buthmann:** Writing – review & editing, Methodology, Conceptualization.

Declaration of Competing Interest

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2024.107214.

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