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Externalizing trajectories predict elevated inflammation among adolescents exposed to early institutional rearing: A randomized clinical trial

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ABSTRACT

Background: There has been mounting interest in the pathophysiological relation between inflammation and psychopathology. In this paper, we examined associations between internalizing and externalizing psychopathology and inflammation in adolescents with a history of severe psychosocial deprivation and children reared in typical family contexts.

Method: The Bucharest Early Intervention Project is a longitudinal randomized trial of high-quality foster care as an alternative to institutional care. This report is based on 56 institutionalized children randomized to care as usual, 59 institutionalized children randomized to foster care, and 101 never institutionalized children who were recruited as an in-country comparison sample. Externalizing and internalizing behaviors were reported by parents and teachers at ages 8, 12, and 16. At age 16, C-reactive protein (CRP) was derived from blood spots in a subset of participants (n = 127). Multiple-group latent growth curve models were used to examine externalizing and internalizing trajectories and their associations with CRP.

Results: Among children assigned to care as usual, higher levels of externalizing behaviors at age 8, as well as smaller decreases in these behaviors from 8 to 16 years predicted higher levels of CRP at age 16. In the same group of children, higher internalizing behaviors at age 8, but not the rate of change in these behaviors, also predicted higher levels of CRP. In contrast, these relations were not observed in the children assigned to foster care and never institutionalized controls.

Conclusions: Early institutional rearing is associated with a coupling of psychopathology and inflammation, whereas early placement into foster care buffers against these risks. These findings have implications for promoting healthy mental and physical development amongst institutionalized children.

1. Introduction

Inflammation is thought to play a role in the pathogenesis of mental and physical illness, including cardiovascular and autoimmune disorders, which are more prevalent in populations exposed to adverse childhood experiences, such as child maltreatment and social disadvantage (Anda et al., 2006; Baumeister et al., 2016; Miller et al., 2011). Studies examining child maltreatment (Baumeister et al., 2016; Coelho et al., 2014), parental separation (Lacey et al., 2013), social inequality (Liu et al., 2017; Schmeer and Yoon, 2016), and experiments using maternal separation in animal models (Cole et al., 2012; Wieck et al., 2013) suggest that these early adversities trigger chronic low-grade immune activation which results in elevated levels of pro-inflammatory markers. Elevated levels of pro-inflammatory markers are also evident in both externalizing conditions (Mitchell and Goldstein, 2014; Pajer et al., 2002; Slopen et al., 2013), including attention deficit hyperactive disorders (ADHD) (Avcil, 2018; Ceylan et al., 2014; Darwish et al., 2019; Mitchell and Goldstein, 2014), and internalizing conditions (Copeland et al., 2012; da Silva et al., 2017; Mitchell and Goldstein, 2014; Slopen et al., 2013) in children and adolescents. However, findings across studies of youth have not been consistent, because null results have also been reported. More robust results of elevated inflammation have been reported in subgroups, such as individuals who are depressed and resistant to treatment (Chamberlain et al., 2019; Raison et al., 2013), or individuals who experienced exposure to both psychopathology (i.e., depression) and childhood

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adversities (Danese et al., 2008, 2011; De Punder et al., 2018; Grosse et al., 2016; Miller and Cole, 2012; Moreira et al., 2018).

Accumulating evidence indicates that childhood adversity contributes to the co-occurrence of inflammation and depression (Mitchell and Goldstein, 2014), though the literature in youth is sparse (Slopen et al., 2012). Elevated levels of c-reactive protein (CRP)— a reliable indicator of systemic inflammation and risk factor for cardiovascular disease (American Heart Association, VA)— has been observed in adolescents (Danese et al., 2011; Miller and Cole, 2012) with a combination of exposure to early adversity *and* depression, relative to individuals with only one of these conditions. Similar results have been reported in adults, as higher levels of CRP is observed in adults who were exposed to child maltreatment and depressed in the past year (Danese et al., 2008). Also, elevated inflammation, including CRP and other cytokines (interleukin-6), is present in adults with a current mood disorder who retrospectively reported high, but not low, levels of childhood trauma (De Punder et al., 2018; Grosse et al., 2016; Moreira et al., 2018). This coupling between inflammation and psychopathology in subgroups exposed to childhood adversities have led to a transactional hypothesis for the development of mental and physical illness in individuals exposed to childhood adversities (Nusslock and Miller, 2016). This hypothesis asserts that stress linked to early adversity is biologically embedded through epigenetic and biological changes in the stress and immune systems influencing pro-inflammatory tendencies by exaggerated inflammatory responses to challenges and reduced responsiveness to inhibitory hormonal signals. In turn, bidirectional influences between increased inflammation and differential functioning of neural reward, threat, and executive control networks would underly and sustain maladaptive behaviors and greater risk for mental and physical illness.

To date, work on the coupling effect between psychopathology and inflammation has been based on observational studies and restricted to internalizing conditions (i.e., depression), exposure to child maltreatment, and relatively common forms of adversity (e.g., socioeconomic disadvantage, parental separation). For several reasons, it remains important to determine the effects of early psychosocial deprivation due to early institutional rearing on the development of inflammation and psychopathology with consideration of externalizing conditions, including ADHD. First, children reared in institutions often experience poor caregiver quality and inadequate social, cognitive and linguistic stimulation (Zeanah et al., 2003, 2017), which places them at greater risk for various forms of psychopathology, including externalizing (i.e., disruptive behavior, conduct problems and inattention/ overactivity) and internalizing disorders (i.e., depression and anxiety) in childhood and adolescence (Gunnar and Van Dulmen, 2007; Humphreys et al., 2015; Rutter et al., 2007). Notably, among children and adolescents exposed to deprivation from institutional rearing, externalizing and ADHD behaviors are the predominant form of psychopathology (Gunnar and Van Dulmen, 2007; Humphreys et al., 2015; Rutter et al., 2007). Second, externalizing, ADHD (Avcil, 2018; Ceylan et al., 2014; Darwish et al., 2019; Mitchell and Goldstein, 2014; Pajer et al., 2002; Slopen et al., 2013) and internalizing (Copeland et al., 2012; da Silva et al., 2017; Mitchell and Goldstein, 2014; Slopen et al., 2013) behaviors are associated with inflammation in youth. The core process spanning both externalizing and internalizing problems, emotion dysregulation, has also been associated with elevated inflammation and other health risks in youth (Chen et al., 2015; Jones et al., 2018) and adults (Appleton et al., 2012, 2013, Gianaros et al., 2014). As such, examining the associations among the development of externalizing and internalizing behaviors and inflammation might reveal dynamic relations between the development of psychopathology and health risks in children exposed to institutional rearing across the world.

The present study used data from the Bucharest Early Intervention Project (BEIP), the only randomized controlled trial of foster care as an alternative to institutional care. We examined whether psychopathology and higher levels of inflammation can be mitigated in a cohort of adolescents with similar experiences of severe deprivation during early infancy followed by either care as usual or foster care intervention, as well as a demographically-matched group of never-institutionalized children. Previous work by our group examining direct effects of early deprivation due to institutional rearing on cardiometabolic risk at age 16 reported no differences in CRP across the three groups, and no effect of the timing of foster care placement (Slopen et al., 2019). In the present report, we extend our previous work by assessing whether the development of psychopathology accounts for individual differences in the association between institutional rearing and inflammation, as well as the role of early intervention. We examined the effects of early institutionalization and foster care intervention on externalizing and internalizing trajectories across middle childhood to adolescence, and whether stability/change in externalizing and internalizing behaviors was associated with CRP in late adolescence.

2. Method

2.1. Participants

Trial design and participant selection of the BEIP (ClinicalTrials.gov, NCT00747396) have been previously reported (Zeanah et al., 2003) and are summarized in the consort diagram (Fig. 1). In the year 2000, 187 infants ranging from ages 6 to 31 months who were living in one of six institutions in Bucharest, Romania, completed physical examinations; 51 children were excluded for serious medical conditions (e.g., genetic and fetal alcohol syndromes). Accordingly, 136 children (ages 6–30 months) were recruited. After the baseline assessment, half of the children were randomly assigned to care as usual (CAUG: $n = 68$) and half to foster care (FCG: $n = 68$). The age of foster care placement ranged from 6.81 to 33.01 months (M age = 22.63 months, $SD = 7.33$). The BEIP principal investigators and staff members performed the randomization procedures by randomly drawing numbers from a hat. Children were alternately assigned to the two groups, with the first number drawn assigned to CAUG and the next number drawn assigned to FCG. At baseline, a group of sex- and age-matched never institutionalized children (NIG: $n = 72$) was recruited from pediatric clinics in Bucharest, and additional NIG were recruited at age 8 ($n = 61$) and age 16 ($n = 2$).

Participation varied across data collection. The reported results based on latent growth curve models included 216 participants (CAUG: $n = 56$, 30 male; FCG: $n = 59$, 32 male; NIG: $n = 101$, 48 male) with at least one data point of problem behaviors. At age 16, a subsample of participants ($n = 127$: 44 CAUG, 41 FCG, 42 NIG) from our larger study provided blood spots, which were used to derive CRP. This subgroup who provided blood samples is representative of the larger sample of participants who participated in other assessments of the larger study at age 16 (range = 15.49–17.97 years) (see Fig. 1). The reasons for not participating in the blood spot collection were largely because they were unavailable or they declined, n = 13. Among the FCG and CAUG who provided blood samples at age 16 compared to those who did not, there were no differences in sex ($p = .97$), ethnicity ($p = .08$), birth weight ($p = .49$), baseline BMI ($p = .32$), baseline age ($p = .56$), externalizing ($p = .84$) and internalizing ($p = .42$) behaviors at 54 months. Similarly, there were no differences in externalizing ($p = .58$) or internalizing ($p = .15$) behaviors at 54 months or sex ($p = .24$) in FCG and CAUG with missing data for behavioral problems at age 16 versus those with data. Among the NIG who provided blood samples at age 16 compared to those who did not, there were no differences in sex ($p = .30$), ethnicity ($p = .89$), birth weight ($p = .34$), baseline BMI ($p = .84$), baseline age ($p = .68$), externalizing ($p = .55$) and internalizing ($p = .61$) behaviors at 54 months. There were no differences in externalizing ($p = .58$) or internalizing ($p = .61$) behaviors at 54 months, or sex ($p = .07$) in NIG with missing data for behavioral problems at age 16 versus those with data. These descriptions suggest

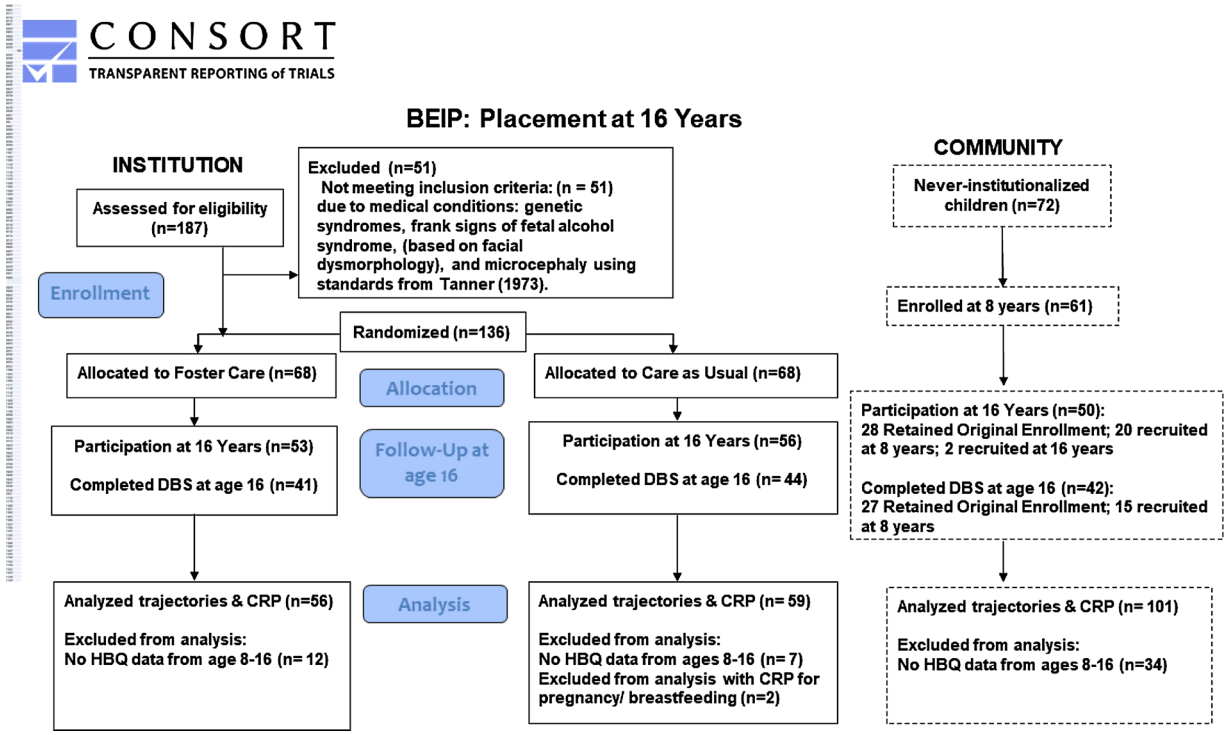

Fig. 1. CONSORT for the randomized controlled trial and follow-up.
Note. Never-institutionalized children were not part of the randomization but were recruited as a comparison group.

that missingness was not contingent on the outcomes themselves. Study procedures were approved by local commissions on child protection in Bucharest, the Romanian Ministry of Health, an ethics committee of Bucharest University, and institutional review boards of the institutions of the three principal investigators. Consent was obtained from children's legal guardian and assent was obtained from the children at age 8, 12, and 16 for each procedure.

2.2. Externalizing and internalizing behaviors

Problem behaviors were reported by teachers at age 8 (*M age* = 8.46; *SD* = .41) and by both teachers and parents at ages 12 (*M age* = 12.64; *SD* = .53) and 16 (*M age* = 16.55; *SD* = .60) using the MacArthur Health and Behavior Questionnaire (HBQ) (Essex et al., 2002). The HBQ measures symptoms of mental and physical health problems and provides composite scores for externalizing/ADHD and internalizing behaviors. The externalizing composite consisted of oppositional defiance, conduct problems, overt aggression, relational aggression, inattention, and impulsivity subscales; the internalizing composite consisted of depression, social anxiety, and anxiety subscales. In this sample, the externalizing/ADHD (α = .92–.94) and internalizing (α = .72–.87) subscales demonstrated strong internal consistency. Composite scores were averaged across the multiple informants whenever possible to reduce the likelihood of reporter bias.

2.3. Inflammatory outcome (CRP)

To measure inflammation, we used a minimally invasive technique, dried blood spots (DBS). Trained research assistants wiped participants' finger with isopropyl alcohol then pricked with a sterile, disposable, micro-lancet. Four blood drops (each about 50 µL) were applied to filter paper. The blood drops saturated the paper and was air-dried for a minimum of 4 h. After drying, DBS samples were placed into a resealable plastic bag and stored at −24 °C until they were shipped to the Laboratory for Human Biology Research (Evanston, IL) for processing. The time period of CRP analyses was between January to November 2016. CRP was measured using a high-sensitivity CRP assay method (McDade et al., 2004). The means of low, mid, and high samples were 0.40, 1.24, and 3.45 pg/ml. Between-assay coefficients of variability of low, mid, and high samples were 12.35, 4.23, 6.98%. No CRP values exceeded 10 mg/L. Within-assay coefficients of variability was 1.94%. CRP assay results below the limit of detection (< 0 mg/L) were winsorized with the nearest value within the limit of detection (n = 14); 2 outliers above 3 *SD* were winsorized with the nearest highest value (Horn et al., 2018). A log transformation was applied to reduce the positively skewed distribution.

2.4. Covariates

At the DBS collection, research assistants measured participants' height, weight, and body temperature. Height and weight were used to calculate body mass-index (BMI) at age 16. Participants provided some information about recent health behaviors using validated survey items from the National Longitudinal Study of Adolescent to Adult Health (Harris and Udry, 2018). This survey included items for regular cigarette-use, “Have you ever smoked cigarettes regularly - that is, at least one cigarette every day for 30 days?” and physical activity in the past day, “In the past 24 h, have you participated in vigorous physical activity long enough to work up a sweat, get your heart thumping, or get out of breath?”. Participants provided dichotomous responses (yes/no). Participants also reported their current medications, with frequently reported medications including nonsteroidal anti-inflammatory drugs, antibiotics, psychotropics, drugs for heart conditions, and glucose control. Given that many of the participants who were on medication were on more than one psychotropics and/or more than one drug category, we accounted for the use of any medication by using a dichotomous variable (yes/no). BMI, body temperature, use of any medication, regular cigarette-use, physical activity in the past day, and sex were potential covariates which we considered in fitting our models involving CRP. Furthermore, pregnant and breast-feeding females (n = 2) were excluded from all analyses involving CRP.

2.5. Data analyses

First, externalizing and internalizing trajectories were examined using separate Latent Growth Curve Models (LGCM) (Duncan and Duncan, 2009) in the R software package, "Lavaan" (Rosseel, 2012). We performed multiple-group LGCM which allowed simultaneous estimation of growth trajectories in each of the three groups (CAUG, FCG, and NIG) to examine the effects of institutional and foster care, as well as typical development. Multiple-group analysis is a well-established method for detecting moderating effects in structural equation modeling. In the models, the scores of externalizing or internalizing behaviors at ages 8, 12, and 16 were indicators of two latent factors: (a) an intercept centered at age 8, representing initial levels of externalizing or internalizing behaviors at age 8, and (b) a linear slope representing growth rates in externalizing or internalizing behaviors across 8 to 16 years. The covariance between the intercept and slope reflecting the strength and direction of association was estimated. Previous studies on externalizing and internalizing trajectories across childhood and adolescence in typical populations show that boys have higher mean levels of externalizing problems than girls, whereas sex differences for internalizing problems are mixed (Bongers et al., 2003; Leve et al., 2005). Based on *a priori* and empirical sex differences in mean levels of behavioral problems in our data (Tables 1 and 2), we allowed participant sex to covary with externalizing and internalizing behaviors.

Second, to examine whether externalizing and internalizing trajectories were associated with CRP at age 16 among groups, CRP was added into the models and regressed on the intercept and slope. Control variables, which showed significant correlations with CRP at age 16 (Tables 1 and 2) were incorporated into the models. Only BMI at age 16 correlated with CRP. Accordingly, CRP was regressed on BMI. The conceptual LGCM for externalizing trajectories is displayed in Supplemental Fig. S1. The LGCM for internalizing trajectories is the same, except the covariance between the intercept and slope was not statistically different from zero in all groups and was fixed to zero to improve model fit.

In all models, full information maximum likelihood estimation using all available data was used to handle missing data. Robust standard errors were used to correct for skewness and kurtosis in our variables. Fit indices, including the χ^2 goodness of fit, CFI, RMSEA, and SRMR, were used to determine the models' ability to reproduce the original variance/covariance matrix. Conventional thresholds indicating good model fit are CFI ≥ .95, RMSEA ≤ 0.05, SRMR ≤ .08 (Hu and Bentler, 1999).

We used χ^2 difference tests to evaluate whether the means of the intercepts and slope factors, the covariance between the intercept and slope, and path coefficients from the intercept and slope to CRP differed across the three groups. First, we compared χ^2 values between a null model, in which model parameters (intercept, slope, covariance between intercept and slope, path coefficients) were constrained to be equal across the three groups, and an alternative model, in which only one parameter (e.g., slope) was freely estimated across groups. This process was repeated to test each parameter of interest. A significant χ^2diff value between the null and alternative models testing the intercept and slope factors indicates that parameter was significantly different across groups. In the expanded models with CRP, a significant χ^2diff value between the null and alternative models testing path coefficients from the intercept or slope to CRP is evidence that group membership moderates the influence of externalizing or internalizing trajectories on inflammation. Pair-wise group contrasts were performed for the effects of early institutional rearing compared to foster care intervention (CAUG vs FCG), and compared to typical development (CAUG, FCG vs NIG), when the initial test revealed significant differences among the three groups. To control for Type-1 error due to multiple comparisons, we applied the Benjamini-Hochberg procedure (Benjamini and Hochberg, 1995) with a 0.05 false positive discovery rate.

3. Results

3.1. Preliminary analyses

Descriptive statistics of measures across the CAUG, FCG, and NIG are displayed in Table 1. As seen in Table 1, the health-related measures at age 16, including CRP, BMI, use of medication, and body temperature, did not differ among the three groups. Bivariate correlations among measures for all study groups combined are displayed in Table 2. As seen in Table 2, across 8 to 16 years, externalizing behaviors showed moderate temporal consistency (*r's* = .43–.68) and internalizing behaviors showed weak to moderate temporal consistency (*r's* = .11–.45). Higher levels of CRP were related to higher BMI, but not to participants' sex, use of medication, body temperature, regular cigarette-use or physical activity in the past 24 h. With the study groups

Table 1
Descriptive statistics across groups.

	M (*SD*)			P- values from group contrasts		
	CAUG	FCG	NIG	CAUG vs. FCG	CAUG vs. NIG	FCG vs. NIG
Externalizing/ADHD age 8	.67 (.42)	.61 (.48)	.29 (.35)	.434	< .001	< .001
Externalizing/ADHD age 12	.57 (.36)	.46 (.38)	.22 (.21)	.106	< .001	< .001
Externalizing/ADHD age 16	.56 (.39)	.44 (.35)	.16 (.20)	.078	< .001	< .001
Internalizing age 8	.55 (.26)	.51 (.33)	.36 (.31)	.475	.001	.006
Internalizing age 12	.44 (.27)	.36 (.21)	.29 (.25)	.107	.002	.108
Internalizing age 16	.44 (.24)	.39 (.23)	.23 (.18)	.277	< .001	.001
CRP age 16	.42 (.13)	.43 (.16)	.43 (.13)	.662	.612	.947
BMI age 16	21.05 (3.35)	22.38 (4.18)	22.07 (3.68)	.076	.187	.690
Body temperature °C age 16	36.65 (.43)	36.69 (.38)	36.64 (.40)	.591	.942	.549
Medication age 16 (yes n, %)	6 (13.6%)	10 (24.4%)	9 (22.0%)	.210	.319	.794
Current regular cigarettes use age 16 (yes n, %)	17 (38.6%)	11 (26.8%)	12 (29.3%)	.249	.364	.806
Performed vigorous physical activity in past 24 h age 16 (n, %)	11 (25.0%)	7 (17.1%)	17 (41.4%)	.374	.109	.018
Sex (female n, %)	26 (46.4%)	27 (45.8%)	53 (52.5%)			
Ethnicity (n, %)						
Romanian	28 (50%)	36 (61%)	93 (92.1%)			
Roma	21 (37.5%)	15 (25.5%)	7 (6.9%)			
Other or unknown	7 (12.5%)	8 (13.5%)	1 (1%)			

Note. CAUG = care as usual group. FCG = foster care group. NIG = never-institutionalized group. ADHD = Attention deficit hyperactivity disorder. CRP = C-reactive Protein. BMI = body mass index. h = hours. Body temperature, use of medication and blood samples were collected on the same day in a subsample (n = 127: 44 CAUG, 41 FCG, and 42 NIG). Percentages of sex and ethnicity are based on participants in the latent growth curve analyses (n = 216: 56 CAUG, 59 FCG, 101 NIG).

Table 2
Bivariate correlations among variables and descriptive statistics.

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Externalizing/ADHD age 8	–												
2. Externalizing/ADHD age 12	.43**	–											
3. Externalizing/ADHD age 16	.51**	.68**	–										
4. Internalizing age 8	.56**	.28**	.26**	–									
5. Internalizing age 12	.11	.56**	.35**	.11	–								
6. Internalizing age 16	.25**	.48**	.61**	.19*	.45**	–							
7. Sex (male)	.12	.27**	.29**	.02	.14	.19*	–						
8. Log CRP age 16	−.07	.17	.03	.06	−.01	−.01	−.06	–					
9. BMI age 16	−.03	−.05	−.03	−.07	−.02	−.05	−.10	.40**	–				
10. Medication age 16 (yes)	.10	.20*	.07	.16	.06	.16	−.08	.07	.05	–			
11. Body temperature age 16 °C	−.08	−.10	−.20*	−.04	.05	.07	−.25**	.01	−.05	.11	–		
12. Current regular cigarettes use age 16	.19*	.19*	.31*	.05	.08	.17	.07	.09	−.03	.00	−.04	–	
13. Performed vigorous physical activity in past 24 h age 16	.12	.01	.01	−.04	−.19*	−.01	.30*	.15	.10	−.09	−.18*	.07	–
Skew (SE)	1.09 (.17)	1.23 (.19)	1.36 (.20)	.92 (.17)	1.33 (.19)	1.04 (.20)		1.78 (.22)	1.27 (.20)		−.05 (.22)		
Kurtosis (SE)	.63 (.03)	1.26 (.38)	2.01 (.39)	1.33 (.35)	2.70 (.02)	2.01 (.41)		3.28 (.43)	1.84 (.40)		−.16 (.43)		

Note. $^{**}p \leq .001$. $^{*}p < .05$. CAUG = care as usual group. FCG = foster care group. NIG = never-institutionalized group. ADHD = Attention deficit hyperactivity disorder. CRP = C-reactive Protein. BMI = body mass index. h = hours. Body temperature, use of medication, current cigarette smoking, physical activity in past 24 h and blood samples were collected on the same day in a subsample (n = 127: 44 CAUG, 41 FCG, and 42 NIG). Sample size varied for internalizing (age 8: n = 195; age 12: n = 158; age 16: n = 141) and externalizing (age 8: n = 195; age 12: n = 159; age 16: n = 150) behaviors.

combined, no consistent pattern of correlation among CRP, internalizing and externalizing behaviors emerged.

3.2. Externalizing/ ADHD trajectories and inflammation

Externalizing trajectories by group are displayed in Fig. 2A. Parameter estimates of externalizing trajectories are in Table 3A. The model showed good fit, χ^2 *goodness of fit* (6) = 5.68, p = .46, CFI = 1, RMSEA < .001, SRMR = .046. As shown in Table 3A, the CAUG and FCG showed similar levels of externalizing behaviors at age 8. Whereas the FCG showed decreases in externalizing behaviors across 8 to 16 years, b = −.018,*SE* = .007, p = .014, the CAUG remained stably high during this period, b = −.012, *SE* = .007, p = .076. There were significant differences in the initial levels of externalizing behaviors at age 8, $\chi 2diff$ (2) = 43.94, p < .001, and rate of change, $\chi 2diff$ (2) = 38.52, p < .001, across groups. Compared to the NIG, both CAUG and FCG showed greater externalizing symptoms at age 8 and greater decreases across 8 to 16 years. This steeper decrease observed in the ever-institutionalized groups compared to the NIG can be attributed to the fact that NIG started with relatively lower externalizing behaviors. Additionally, the positive covariance between the intercept and slope within the CAUG, but not FCG and NIG, indicates that CAUG who began with more externalizing behaviors at age 8 continued to exhibit more (less decrease in) externalizing behaviors across time.

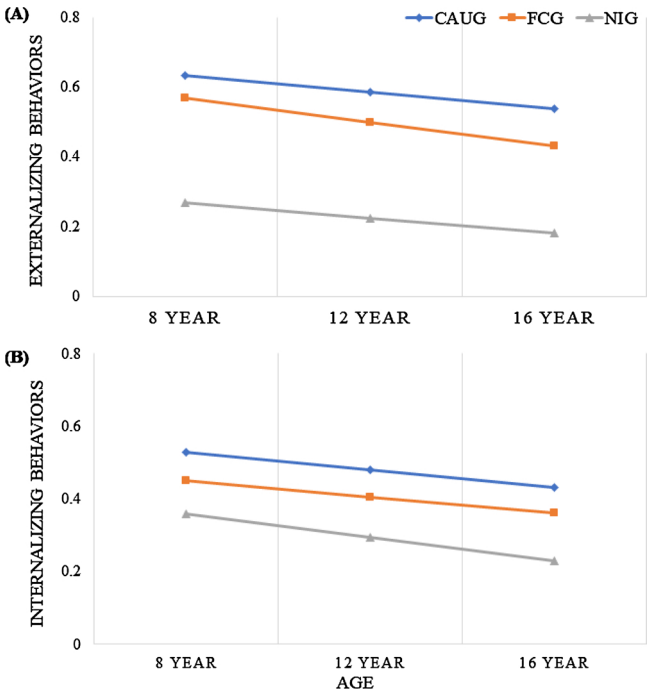

Fig. 2. Estimated (A) externalizing and (B) internalizing trajectories by groups. *Note*. CAUG = care as usual group. FCG = foster care group. NIG = never-institutionalized group.

Parameter estimates of the expanded model with CRP added as an outcome of externalizing trajectories by group are in Table 3B. This model showed good fit, χ^2 *goodness of fit*(27) = 21.42, p = .76, CFI = 1, RMSEA < .001, SRMR = .072. Within the CAUG, both externalizing behaviors at age 8 and less decrease in these behaviors across 8 to 16 years were significant predictors of higher levels of CRP at age 16. These relations were not statistically significant within the FCG or NIG. The path coefficient from the slope of externalizing behaviors to CRP was significantly different across the three groups, $\chi 2diff$ (2) = 38.03, p < .001. Pair-wise group contrasts for the path coefficient from the slope of externalizing symptoms to CRP showed differences between the CAUG and NIG, $\chi 2diff$ (1) = 8.57, p = .004, but not between the CAUG and FCG. There were no statistically significant group differences in the path coefficient from the intercept of externalizing behaviors to CRP across groups, $\chi 2diff$ (2) = 1.36, p = .505.

3.3. Internalizing trajectories and inflammation

Internalizing trajectories by group are displayed in Fig. 2B. Parameter estimates of internalizing trajectories are in Table 4A. This model showed good fit, χ^2 *goodness of fit* (9) = 7.85, p = .55, CFI = 1, RMSEA < .001, SRMR = .046. As seen in Table 4A, there were significant differences in the initial levels of internalizing behaviors at age 8, $\chi 2diff$ (2) = 19.86, p < .001, and rate of change, $\chi 2diff$ (2) = 12.18, p < .001, across groups. The CAUG showed more internalizing behaviors at age 8 but no difference in the rate of decrease across 8 to 16 years compared to the FCG. Compared to the NIG, both CAUG and FCG

Table 3
Parameter estimates from latent growth curve models for externalizing trajectories (A) and adding (B) CRP as the outcome.

	Within-group estimates (*SE*)						P-values from between-group $\chi 2$ difference tests		
Parameters	CAUG	p	FCG	p	NIG	p	CAUG vs. FCG	CAUG vs. NIG	FCG vs. NIG
(A) Model of externalizing trajectories									
Intercept (age 8)	.632 (.044)	< .001	.568 (.059)	< .001	.271 (.029)	< .001	.106	< .001	< .001
Slope	−.012 (.007)	.076	−.018 (.007)	.014	−.010 (.005)	.050	.153	< .001	.008
Covariance between intercept and slope	.016 (.007)	.031	−.004 (.006)	.466	.001 (.002)	.520	.011	.056	.520
(B) Expanded model of externalizing trajectories and effects on CRP									
Intercept (age 8)	.629 (.044)	< .001	.566 (.061)	< .001	.271 (.029)	< .001			
Slope	−.012 (.007)	.087	−.016 (.007)	.023	−.010 (.005)	.040			
Covariance between intercept and slope	.018 (.008)	.015	−.004 (.006)	.555	−.001 (.001)	.490			
Effect on CRP									
Intercept - > CRP	.274 (.139)	.051	−.031 (.081)	.598	.167 (.489)	.730			
Slope - > CRP	1.672 (.791)	.037	.185 (.507)	.625	−9.402 (10.087)	.350	.778	.004	.058[a]
BMI - > CRP	.012 (.004)	.001	.018 (.003)	< .001	.013 (.003)	< .001			

Note. Within-group estimates test whether effects are different from zero. CAUG = care as usual group. FCG = foster care group. NIG = never-institutionalized group. CRP = C-reactive Protein. BMI = body mass index. P values for group contrasts are unadjusted in the table. [a]*p*-adjusted = .087.

showed greater internalizing behaviors at age 8 and less decreases across 8 to 16 years.

Parameter estimates of the expanded model with CRP added as an outcome of internalizing trajectories by group are in Table 4B. This model showed good fit, χ^2 *goodness of fit* (30) = 30.43, p = .44, CFI = .99, RMSEA = .013, SRMR = .098. Within the CAUG, greater internalizing behaviors at age 8, but not the rate of change in internalizing behaviors, predicted higher levels of CRP at age 16. Again, these relations were not observed in the FCG or NIG. However, there were no statistically significant group differences in the path coefficients from the intercept, *χ2diff* (2) = 3.34, p = .188, or slope, *χ2diff* (2) = 2.14, p = .343, of internalizing behaviors to CRP.

4. Discussion

This study examined the effects of early institutional care and randomization to foster care on trajectories of behavioral problems across middle childhood to late adolescence and their associations with inflammation. In the trajectory analyses, we found that the care as usual and foster care groups exhibited similar internalizing and externalizing trajectories with slight differences. For externalizing trajectories, the care as usual and foster care groups both showed high levels of externalizing behaviors at age 8 and similar rates of change. However, the rate of decrease in externalizing behaviors from 8 to 16 years within the care as usual group was not statistically different from zero whereas the rate of decrease in externalizing behaviors within the foster care group was statistically significant. These findings suggest that the care as usual group showed relatively stable and high levels of externalizing behaviors over time, consistent with our previous report showing that the care as usual group shows high and stable levels of externalizing and general psychopathology across ages 8 to 16 (Wade et al., 2018). For internalizing trajectories, the care as usual group showed higher levels of internalizing behaviors than the foster care group at age 8, but the two groups showed similar levels of decrease across 8 to 16 years. When we further examined the relations between problem behavior trajectories and inflammation, we found that problem behavior trajectories were associated with inflammation in only the care as usual group, as the high-stable pattern of externalizing behaviors across 8 to 16 years predicted elevated inflammation, indexed by CRP, at age 16. Also, among the care as usual group, higher internalizing behaviors at age 8, but not the rate of change in these behaviors, predicted higher levels of CRP. In contrast, these relations between psychopathology and inflammation were not observed among the foster care or never-institutionalized groups. These findings suggest that early institutional rearing without early foster care intervention may shape the dynamic relations between the development of increased psychopathology and inflammation.

The coupling of high-stable externalizing and internalizing behaviors and elevated inflammation observed only in the care as usual group converges with studies reporting elevated inflammation in adolescents with high levels of childhood adversities and depression, compared to those with only one of these conditions (Danese et al.,

Table 4
Parameter estimates from latent growth curve models for internalizing trajectories (A) and adding (B) CRP as the outcome.

	Within-group estimates (*SE*)						P-values from between-group $\chi 2$ difference tests		
Parameters	CAUG	p	FCG	p	NIG	p	CAUG vs. FCG	CAUG vs. NIG	FCG vs. NIG
(A) Model of internalizing trajectories									
Intercept (age 8)	.530 (.032)	< .001	.450 (.036)	< .001	.359 (.029)	< .001	.029	< .001	< .001
Slope	−.013 (.006)	.032	−.011 (.006)	.061	−.015 (.005)	.002	.120	< .001	.003
Covariance between intercept and slope	–		–		–				
(B) Expanded model of internalizing trajectories and effects on CRP									
Intercept (age 8)	.523 (.034)	< .001	.448 (.036)	< .001	.361 (.030)	< .001			
Slope	−.012 (.006)	.046	−.011 (.006)	.072	−.016 (.005)	< .001			
Covariance between intercept and slope	–		–		–				
Effect on CRP									
Intercept - > CRP	.484 (.229)	.035	.061 (.304)	.690	.084 (.415)	.840			
Slope - > CRP	−.704 (1.540)	.648	2.555 (3.389)	.420	−2.787 (8.606)	.746			
BMI - > CRP	.007 (.005)	.165	.019 (.007)	.003	.016 (.004)	< .001			

Note. Within-group estimates test whether effects are different from zero. Covariance between intercept and slope was not different from zero in all groups and was fixed to zero to improve model fit. CAUG = care as usual group. FCG = foster care group. NIG = never-institutionalized group. CRP = C-reactive Protein. BMI = body mass index. P values for group contrasts are unadjusted in the table.

2011; Miller and Cole, 2012). These findings are also consistent with studies reporting elevated levels of inflammation in adults who were exposed to child maltreatment and depressed (Danese et al., 2008), and in adults with a current mood disorder who retrospectively reported high, but not low levels of childhood trauma (De Punder et al., 2018; Grosse et al., 2016; Moreira et al., 2018). Here, we extended this interaction effect to externalizing conditions, which are prevalent in children exposed to early psychosocial deprivation (Humphreys et al., 2015; Gunnar and Van Dulmen, 2007; Rutter et al., 2007).

In the literature of children and adolescents, the association between childhood adversity and inflammation has been inconsistent (Kuhlman et al., 2019; Slopen et al., 2012); different types of child maltreatment might be associated with different inflammatory markers (Baumeister et al., 2016); and many studies do not examine the possibility that inflammation can be modified by one's on-going mental health. We extend prior work by demonstrating that individual differences in the development of psychopathology plays a role in the etiology of heightened inflammation, or vice versa, among previously institutionalized children, whereas early institutionalization alone does not. It has been known that having a mental disorder increases the risk of having a medical disorder, and vice versa. Given that inflammation is moderately stable across childhood and adulthood (Juonala et al., 2006), the care as usual group who showed high-stable externalizing behaviors across ages 8 to 16 and high internalizing behaviors at age 8 may face elevated risk for chronic health problems that emerge in adulthood, such as cardiovascular disease.

Unfortunately, we are unable to untangle directionality in the present study as CRP was collected at one time point. Researchers suggest that the co-occurrence of psychopathology and inflammation might likely arise from bidirectional transactions among elevated proinflammatory cytokines, and differential brain, behavioral and cognitive functioning which contribute to psychopathology risk and sustain systemic low-grade inflammation in some individuals exposed to early adversity (Nusslock and Miller, 2016). Reciprocal interactions between immune mediators, such as cytokines, the central nervous and stress-response systems, are possible via neurochemical, neuroendocrine, and/or anatomical pathways that regulate motivation, sensitivity to threat and other physiological processes (Dantzer et al., 2008; Irwin and Cole, 2011; Miller et al., 2013; Sternberg, 2006; Wohleb et al., 2015). Mechanisms underlying the stress response system and peripheral inflammation are still under investigation, but may include increased density of sympathetic connections (Sloan et al., 2008), and post-translation modification of proteins involved in cytokine signaling (Pace et al., 2007). Additionally, epigenetic changes may play a role as alterations in methylation patterns involved in the hypothalamic-pituitary-adrenal (HPA) system and neuroplasticity are associated with early adversity, including individuals exposed to child maltreatment (Klengel et al., 2013; Labonté et al., 2012; McGowan et al., 2009) and a lack of parental care (Tyrka et al., 2012). These changes can influence self-regulation reflected in altered functioning of the stress-response and neural systems for processing threat, reward, and executive control, which might put children exposed to early adversities at risk for both psychopathology and heightened inflammation. Previous reports from the BEIP found that the care as usual group, but not the foster care group, had altered stress-response systems (McLaughlin et al., 2015), perturbed neural event-related potentials linked to poor executive control (Troller-Renfree et al., 2016) and a heighted attention bias to threat (Troller-Renfree et al., 2015). These correlates of emotion- and self-dysregulation may underlie both increased psychopathology and inflammation in the care as usual group.

Strengths of this study include an experimental randomized design to provide evidence of environmental enhancement on the recovery following early deprivation, as foster care intervention ameliorated risks for developing psychopathology and inflammation. However, there are several limitations. First, our conclusions and results are limited by our relatively small sample size. Notably, CRP was collected in a smaller subsample, even though we ensured that this subsample was representative of the larger sample, this relatively small sample size might limit the precision of our estimates for the relations between psychopathology and inflammation and effects that we could not detect. Accordingly, our results warrant future replication. Second, we cannot determine the temporal precedence of inflammation or psychopathology as CRP was measured at one time. Third, we used dried blood spots instead of venous blood draw to maximize participation. Although CRP measured in dried blood spots have been validated as proxies of levels in plasma serum, we acknowledge that there may be variability in dried blood spots (Bond and Richards-Kortum, 2015). Fourth, while the use of both parent- and teacher-reports provide a more holistic picture of children's problem behaviors in the home and the structured school contexts, we lacked parent-report measures at age 8 and the informants were not always the same individuals which could contribute to changes in the mean scores of problem behaviors over time. The teacher- or parent-reports of any one child in this sample could be from different teachers and different caregivers, particularly for the ever-institutionalized groups (care as usual and foster care groups) who often transition between foster homes, their biological family, or the institutions, as such new teachers or caregivers may not know the child well. These limitations highlight the advantages of using multi-informant data. Finally, psychopathology may arise earlier than age 8. Though we have discussed our previous findings with consideration of psychopathology in this sample at age 54 months, psychopathology at 54 months was assessed with a different measure and could not be directly incorporated into the trajectory analyses (Zeanah et al., 2009). Future studies, using larger samples with repeated measures of inflammation and psychopathology, should examine bidirectional associations, as well as the role of lifestyle mediators, including physical activity, diet, substance- and alcohol- use, and social support from friends.

In conclusion, this study provides initial evidence that early institutional rearing contributes to risk of high-stable externalizing and internalizing behaviors across middle childhood to adolescence, which are related to elevated inflammation in late adolescence. For children who have experienced early institutional rearing, placement into a sensitive caregiving environment might mitigate risk for a coupling of psychopathology and inflammation. These findings indicate that an early sensitive caregiving environment is essential in promoting mental and physical well-being across development and may have implications for chronic disease risk in adulthood.

Declaration of Competing Interest

The authors report no conflicts of interest in the conduct and reporting of this research.

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Appendix A. Supplementary data

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