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Emotional Functioning at age 7 years is Associated with C-Reactive Protein in Middle Adulthood

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Abstract

Objective—Few have considered whether and how child emotional functioning is associated with inflammation later in life. Therefore, we examined whether child emotional functioning at age 7 is associated with C-reactive protein (CRP), an indicator of systemic inflammation, in middle adulthood.

Methods—We studied adult offspring (mean age=42.2 years) of participants in the National Collaborative Perinatal Project, a national cohort of pregnant women enrolled between 1959 and 1966. Three measures of child emotional functioning were derived from psychologist ratings of child behavior at age 7: inappropriate self regulation (ISR), distress proneness, and behavioral inhibition. Multiple linear regression models were fit to investigate the association between childhood emotional functioning and adulthood CRP, and also to evaluate potential mediators of this association. Model n's ranged from 400-379 depending on covariates included and missing data on those covariates.

Results—Children with high ISR and distress proneness at age 7 had significantly higher CRP as adults (ISR b=0.86, SE=0.28, p=0.002; distress proneness b=1.23, SE=0.57, p=0.03). In contrast, children with high levels of behavioral inhibition had lower CRP as adults (b= −0.58, SE=0.38, p=0.04). Further, there was evidence that associations of ISR and distress proneness with CRP may be mediated in part by adulthood body mass index (Sobel significance tests of mediation: ISR p=0.003; distress proneness p=0.07).

Conclusions—Findings suggest that poor childhood emotional functioning is associated with inflammation in adulthood. These results suggest a potential childhood origin of adult inflammatory risk.

Keywords

Child emotional functioning; C-reactive protein; body mass index; life course

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INTRODUCTION

Increasing evidence suggests that psychological functioning is associated with a range of physical health outcomes including neoplastic, infectious and cardiovascular diseases (1–3) as well as other adverse conditions such as impaired wound healing (4). Biological mechanisms linking psychosocial factors to physical health are not well understood. Inflammation has received much attention as one potential pathway as it is implicated in the pathophysiology of various conditions, including cardiovascular disease (1, 5–7). One of the most studied inflammatory markers is C-reactive protein (CRP). CRP is of particular interest as elevated CRP has been found to be associated with atherosclerosis and incident coronary events (5, 6), though there is ongoing debate as to whether increases in CRP are in fact, causally associated with cardiovascular disease (8–10). Regardless, elevated levels of CRP are consistently associated with higher risk of cardiovascular and other diseases, and as such remains a useful inflammatory biomarker that can give insight into both chronic states of inflammation and subsequent risk for disease development.

Results from several studies suggest that poor emotional functioning activates the inflammatory system as indicated by elevated levels of CRP (1–4) in many (11–16) but not all cross-sectional studies (17, 18) that have examined this question. Studies that temporally isolate emotional functioning from CRP are rare. One study among Whitehall II participants observed positive associations between adulthood psychological distress and incident coronary heart disease over 12 years of follow-up, but no association with inflammatory markers including CRP (17). The sample did not include blue collar workers or the unemployed which may have biased results toward the null as those with lower socioeconomic status could have poorer emotional functioning and higher CRP.

Given that adverse social and psychological experiences occurring early in life can exert significant effects on later health and development (19–21), elevated adulthood CRP may reflect damage to body systems attributable to poor emotional functioning that began early in life. Indeed, recent work in this area strongly suggests the importance of a developmental perspective when considering the relationship between early emotional functioning, adult inflammation and physical health (21–27). Previous studies have found child emotional functioning (usually measured at age 7 or 8) to be associated with a range of adult physical health outcomes such as obesity, migraines, or asthma (22), as well as self-rated health and number of physical illnesses at age 35 (23). Only a few studies have examined child emotional functioning in relation to adulthood CRP. Odgers et al. (24) found that persistent conduct problems (assessed repeatedly between ages 7–26) were associated with poor health and elevated CRP in adulthood among males. Some work has examined the role of child maltreatment, which likely yields considerable emotional distress, on adulthood CRP (25–27). In these studies, childhood maltreatment occurring between ages 3–11 was significantly associated with elevated adulthood CRP independent of adult physical health, stress, and early life risk factors (25), and also adult depression (26). Finally, a recent study among adults found retrospectively assessed early life stress and adversity to be associated with high concentrations of adulthood inflammatory markers, including CRP, among African Americans (28). These studies suggest a potential childhood origin for adult inflammation related to child emotional functioning, although no studies have examined this question in a US sample.

The present study adds to this emerging literature by examining whether emotional functioning directly assessed at age 7 (as measured by inappropriate self regulation, distress proneness, and behavioral inhibition) was associated with CRP approximately 35 years later, while taking into account a range of potential confounders and mediators from across the life course. We hypothesized that those with poor childhood emotional functioning would

have elevated levels of adulthood CRP. Additionally, we examined whether adulthood factors mediated associations between childhood emotional functioning and adulthood CRP. This study adds to the literature in several ways. This study is among the first to link several domains of childhood emotional functioning to an adult biomarker of inflammation. Where previous work has focused specifically on child maltreatment or conduct disorder in relation to adulthood CRP, this study examines several aspects of childhood externalizing and internalizing problems in relation to adulthood inflammation. Thus, relative to prior literature, we are considering a broader range of less extreme forms of emotional dysfunction which are likely to be more representative of child emotional dysfunction experienced in the general population. Also, few US samples include measures of prospectively assessed childhood emotional functioning and inflammation in adulthood. Thus, this study provides insight into how psychological characteristics assessed early in the life span may be related to inflammation-related processes in middle adulthood.

METHODS

Study Population

The study population comes from the Boston and Providence offspring participants of the National Collaborative Perinatal Project (NCPP). Pregnant women enrolled in the NCPP between 1959–1966 (29, 30). Women were enrolled during pregnancy, and their offspring were regularly assessed from birth through age 7. Detailed medical and social histories were obtained from mothers at the time of enrollment. Information on child birth outcomes and subsequent growth and development, including psychologist ratings of child emotion and behavior, were obtained several times during the first year of life and at age 7.

The New England Family Study (NEFS) was established to locate and interview the now adult NCPP offspring from the Providence, RI, and Boston, MA sites. The current sample comes from a recent NEFS project designed to examine the pathways linking education and health (EdHealth), described in detail elsewhere (31). Briefly, EdHealth subjects were sampled from a larger NEFS follow-up study (n=1674; the Brown-Harvard Transdisciplinary Tobacco Use Research Center (32)), with preference for racial/ethnic minorities and those with high and low levels of education. During 2005–2007, 618 subjects participated in the three-hour in-person interview, at which time extensive education, socioeconomic, psychological and cognitive information was collected. Subjects also participated in a clinical assessment which consisted of a blood sample and anthropomorphic measurements obtained by trained study personnel. Informed consent was obtained at the time of interview. The study protocol was approved human subjects committees at the Harvard School of Public Health and Brown University.

Of the 618 subjects interviewed, 430 participated in the clinical assessment. Subjects were included in analysis if they had available childhood emotion and adult CRP data. Individuals with CRP levels >10mg/L were removed from the sample (n=16) as such levels are indicative of current illness or infection. In multivariate analyses, sample sizes per model ranged from 400 to 379 depending on the number of covariates included and individuals missing data on those covariates.

Measures

Child Emotional Functioning—When the NCPP went into the field in the late 1950's, no standard measures of child emotional functioning existed for population based research. Measures of child emotional functioning were derived from psychologist behavioral observations of NCPP children at the age 7 assessment. Trained psychologists administered a two-hour battery of cognitive, sensory and motor tests without the mother present and

rated the children on 15 behaviors observed during those tests. Domains of emotional functioning identified included inappropriate self regulation, distress proneness, and behavioral inhibition (33). Past work has documented the validity of these scales against a contemporary gold standard for assessing child behavior and emotion (Achenbach Child Behavior Checklist; CBCL) (34) and has found that these scales predict poor emotional functioning in adulthood (33). In this sample, Cronbach's alphas were 0.50 for distress proneness, 0.71 for inappropriate self regulation, and 0.83 for behavioral inhibition. Detail on scale construction and component items can be found elsewhere (33).

Inappropriate self regulation (ISR) reflects emotional functioning in children whose behavior was unrestrained and impulsive. Distress proneness reflects emotional functioning in children who were emotionally labile and easily frustrated. Both scales positively correlate with externalizing behavior problems as assessed by the CBCL (33), and can be considered domains of externalizing behavior. Behavioral inhibition reflects emotional functioning in children who were shy, withdrawn, and fearful. This scale positively correlates with CBCL internalizing behavior problems (33) and can be considered a domain of internalizing behavior.

Scale scores were each standardized to have a mean of 0 and standard deviation of 1. ISR ranged from −0.54–3.03; distress proneness ranged from −0.19– 3.76; behavioral inhibition ranged from −0.92–3.69. As would be expected in a normative population, the distribution of scores for each emotion attribute was somewhat skewed with fewer people at the high end of the distribution (e.g. fewer people with high levels of dysfunction). Following other work in this area (33, 35, 36), ISR and behavioral inhibition scores were dichotomized with the top 15% as the indicator category. This cut-point reflects a higher level of dysfunction different from the rest of the distribution, which was hypothesized to be relevant for systemic inflammation. Theoretical and empirical work by Kagan and colleagues (37) suggest that domains of emotionality can be grouped into meaningful subgroups at the extreme ends of the distribution; emotional functioning is not necessarily a continuous construct. Given this theoretical perspective and that the distributions were skewed yielding fewer people with emotional dysfunction, we dichotomized the scale scores. For distress proneness, the distribution was truncated and as a result, the cut point reflects the top 3% of the distribution. Given the lower reliability and truncated distribution, results for distress proneness should be interpreted cautiously. As distress proneness is positively correlated with ISR and both are domains of externalizing problems (33), results for distress proneness can be viewed as underscoring ISR findings. Models predicting CRP were fit separately using continuous and dichotomous emotion variables.

C-Reactive Protein (CRP)—CRP was the primary outcome variable. The concentration of CRP was determined using an immunoturbidimetric assay on the Hitachi 917 analyzer (Roche Diagnostics - Indianapolis, IN), using reagents and calibrators from DiaSorin (Stillwater, MN). This assay has a sensitivity of 0.03 mg/L. The day-to-day variabilities of the assay at concentrations of 0.91, 3.07 and 13.38 mg/L are 2.81, 1.61 and 1.1%, respectively. In this sample, CRP levels ranged from 0.07mg/L to 80.10 mg/L. Individuals with CRP levels >10mg/L were removed (n=16) as such levels are considered to be indicative of current illness or infection. Primary analyses treated CRP continuously. Additional analyses treated CRP dichotomously using the CDC/American Heart Association cut point for high cardiovascular risk (CRP>3mg/L) (6).

Covariates—Following other work in this area (25, 26), variables from across the life course were examined to determine whether child emotional functioning was associated with adulthood CRP net of other life course factors, or whether such associations could be

partly explained by adulthood factors. Demographics, childhood and adulthood variables were included in analysis.

Demographics included adulthood age, gender, self reported race (white, not white), and study site (Boston, Providence).

Child covariate data was collected during childhood and included being born small for gestational age, body mass index at age 7 years, IQ at age 7, physical heath from birth to age 7, and childhood SES at age 7. Small for gestational age (SGA) was calculated as whether or not the child's birth weight obtained at birth was less than or equal to the 10^{th} percentile for gestational age at delivery. Body mass index (BMI) at age 7 was calculated as the ratio of weight in kilograms to the square of height in meters (kg/m^2) as obtained by study personnel. Weight and height were measured as part of a scheduled study visit using instruments implemented in standard clinical practice at the time. Child IQ was assessed at age 7 using the Wechsler Intelligence Scale for Children (38). Scores were standardized to have a mean of 100 and standard deviation of 15. Child health was a summary measure indicating whether or not the child experienced one or more chronic physical health conditions from birth to age 7 as identified by a study pediatrician or maternal report. Categories of conditions included: abnormalities of the liver, cardiovascular conditions, hematologic conditions (e.g. anemia), lower respiratory tract abnormality (e.g. asthma), neoplastic disease, neurologic abnormality, and prolonged/recurrent hospitalization. Childhood SES was measured at age 7 using an index adapted from the US Bureau of the Census which reflects the education, occupation and household income of the head of household when the child was 7 years old (39). This index ranges from 0 (low) to 100 (high).

Adulthood factors included current smoking, depressive symptoms, education attainment, and body mass index. Current smoking in adulthood was assessed by a single self report item "Do you smoke cigarettes now?" (yes/no). Depressive symptoms in adulthood were assessed by the 10-item Center for Epidemiologic Studies of Depression scale (40) (CESD; Cronbach's alpha=0.88). Educational attainment was assessed as the total years of education and was categorized into four groups corresponding to highest level completed: Less than high school (< 12 years), high school graduate/GED (12 years), some college (more than 12 years but less than 16) and college or more (16 years or more). Adulthood BMI was calculated as the ratio of weight in kilograms to the square of height in meters (kg/m^2) using from height and weight measurements obtained by study personnel.

Statistical Analyses

First, those with available CRP (n=430) were compared to those who were excluded due to missing CRP (n=188) to determine if there were significant demographic differences using chi square and independent t-tests. Next, correlations among emotional functioning variables were assessed. Third, associations between child emotional functioning, CRP and other study variables were assessed with chi-square and independent t-tests. Associations between adulthood factors and CRP were also assessed via correlations, independent sample t-tests and ANOVA. Finally, four linear regression models were evaluated for each measure of child emotion. Model 1 was the unadjusted association between child emotion and CRP. Model 2 included the child emotion variable plus demographics. Model 3 also included childhood covariates: SGA, child BMI, child IQ, child health and child SES. Model 4 additionally included adulthood factors: smoking, depressive symptoms, education attainment and adult BMI. All models were fit in SAS using PROC GENMOD to adjust variance estimates for the presence of multiple siblings from the same family in the sample. A site variable (Boston vs. Providence) was included in all models to adjust for potential differences between study sites.

Covariates from childhood were considered as potential confounders, while covariates from adulthood were considered as possible mediators of the primary association between child emotions and adulthood CRP. Additional analyses were conducted to examine effect mediation by adult factors as well as to assess cardiovascular risk using a dichotomous CRP variable. Evaluation of potential mediators of the child emotion and adulthood CRP relations was conducted in two steps: (1) evidence of mediation was evaluated via coefficient changes according to Baron and Kenny (41), and (2) Sobel tests were conducted to statistically determine whether observed mediated effects were significantly different from zero.

To assess the association between child emotional functioning and elevated CRP that may signal increased risk for cardiovascular disease, models were refit with logistic regression using a dichotomous CRP variable. CRP was dichotomized according to the CDC/American Heart Association criteria for high and low risk for CVD (6) (High risk: CRP>3mg/L; low risk: CRP≤3mg/L) (6).

RESULTS

Descriptive Analyses

Chi-square and t-tests for the 430 individuals with CRP data and the 188 excluded due to missing CRP indicated no significant differences by age, race, gender or education level (all $p>0.05$; data not shown). Emotion scores correlated in the expected directions, but correlations were moderate underscoring previous factor analytic work (33) indicating each scale represents a different construct. ISR was positively correlated with distress proneness ($r=0.17$, $p=0.008$) and negatively correlated with behavioral inhibition ($r=-0.30$, $p<0.001$). Distress proneness and behavioral inhibition were not correlated ($r=0.02$, $p=0.68$).

Table 1 summarizes the sample characteristics and Table 2 displays the subject characteristics by levels of child emotional functioning. Subjects were mostly white, were more likely to be female than male, and in their early 40's at follow-up. As children, males were significantly more likely to have high ISR and distress proneness than females whereas females were significantly more likely to be behaviorally inhibited. BMI in adulthood was significantly elevated among those with ISR, and a trend for elevated adult BMI was evident among those high in distress proneness. Some significant associations between adulthood factors and CRP were also observed. Adulthood BMI and depressive symptoms were significantly correlated with CRP (BMI: $r=0.51$, $p<0.0001$; CES-D: $r=0.12$, $p=0.02$). Education attainment was marginally associated with CRP ($F(3, 391)=2.51$, $p=0.06$) with those with the lowest level of education having higher mean CRP relative to other education groups. Smoking in adulthood was not associated with CRP ($t=-1.05$, $p=0.29$). Though some covariates were not significantly associated with CRP or child emotion variables, all were included in multivariate analyses to be conservative.

Child Emotional Functioning and Adulthood CRP

Controlling for demographics, children high in ISR had significantly higher CRP in adulthood (Table 3). Further adjustment for childhood covariates did not attenuate this association. However, adding the adulthood covariates reduced the coefficient for ISR by more than half. Adult BMI was the only adulthood factor significantly associated with CRP in the fully adjusted model ($b=0.14$, $SE=0.01$, $p<0.001$).

Results for the associations between childhood distress proneness and adult CRP were similar (Table 3). Controlling for demographics, those high in child distress proneness had significantly higher CRP in adulthood, and further adjustment for childhood covariates did not attenuate this association. As with ISR, however, adulthood covariates attenuated the association between high childhood distress proneness and adult CRP to a trend. Again,

adulthood BMI had a strong, positive association with CRP in the fully adjusted model (b=0.14, SE=0.01, p<0.001).

The relationship of CRP with childhood behavioral inhibition differed in that it was associated with significantly lower levels of CRP in adulthood. Controlling for childhood covariates reduced this association somewhat, and further adjustment for adulthood covariates fully attenuated the association. Adult BMI remained significantly and positively associated with CRP in the fully adjusted model (b=0.14, SE=0.01, p<0.001).

Models from Table 3 were also examined including ISR, distress proneness and behavioral inhibition simultaneously. Results indicated that ISR (b=0.71, SE=0.29, p=0.01) and distress proneness (b=1.10, SE=0.56, p=0.05) but not behavioral inhibition (b=−0.44, SE=0.29, p=0.13) were associated with CRP after adjusting for demographics and child covariates, indicating ISR and distress proneness have independent effects on CRP.

When emotion was measured continuously the pattern of associations with CRP was similar to when dichotomous emotion measures were used (Table 4). Both ISR and behavioral inhibition were significantly associated with CRP when controlling for demographics and child covariates (positive association for ISR; negative association for inhibition), and effects were attenuated when adulthood factors were added to the models. When measured continuously, the magnitude of the effect of distress proneness was substantially lower, and distress proneness measured in this way was not significantly associated with CRP. Perhaps worth noting, however, is that the pattern of effects is similar to those seen with a dichotomous measure of distress proneness; the magnitude of effect across models 1 to 3 was similar, and the parameter estimate was strongly attenuated when adulthood factors were added to the model.

Additional Analyses

As results were largely similar when emotion was measured categorically and continuously, additional analyses were conducted only among the categorical emotion measures.

Mediation Analyses—The significant attenuation of the relationship between CRP and ISR, distress proneness and behavioral inhibition after including adult covariates in the models suggested the possibility of effect mediation. As adult BMI was the only adulthood variable significant in final models, it was evaluated as a potential mediating factor. However, it is important to note that child BMI is included in the models as a covariate. The correlation between childhood BMI and adult BMI is 0.31 (p<0.0001). Thus, one possibility is that change in BMI over time rather than adult BMI per se that mediates the association between child emotion functioning and adult CRP. To assess this more carefully we also considered the role of adult BMI by refitting the models excluding child BMI.

Table 5 summarizes the models testing for mediation following Baron and Kenny (41). When adjusting for all covariates except adult BMI, ISR remained significantly associated with CRP. ISR was also significantly associated with adult BMI, and this association was maintained after adjusting for childhood BMI and other covariates. With adult BMI added to the CRP model, the coefficient for ISR was attenuated and no longer significant whereas the coefficient for adult BMI was remained strong. The Sobel test statistic for this association was 2.97 (p=0.003), providing some evidence that adult BMI is involved in mediating the association of childhood ISR with adult CRP.

Similarly, childhood distress proneness was strongly associated with CRP after adjusting for all covariates except adult BMI, and a somewhat weaker association between distress proneness and BMI in adulthood was also evident. With adult BMI added to the model for

CRP, the coefficient for distress proneness was attenuated whereas the coefficient for adult BMI remained strong. The Sobel test statistic for this association was 1.8 (p=0.07), providing some evidence that adult BMI is involved in mediating the association between childhood distress proneness and adult CRP.

Refitting models excluding child BMI yielded results that were largely unchanged (data not shown) from models including child BMI, suggesting that adulthood BMI rather than change in BMI is the primary mediator. Thus, later life BMI may be a key mechanism by which ISR and distress proneness are associated with higher CRP, whereas childhood BMI may be most relevant insofar as it contributes to setting up adulthood BMI.

There was no evidence to suggest that adulthood BMI might mediate a relationship between behavioral inhibition and adult CRP.

High Risk CRP: Approximately 17% of the sample had high-risk CRP (>3mg/L). The pattern of relationships observed in logistic models was consistent with the linear models, and magnitudes of associations were strong. The odds of having high-risk CRP in adulthood among those with high child ISR was 2.26 (95%CI: 1.15,4.46) controlling for demographics, 2.24 (95%CI: 1.11,4.53) additionally adjusting for childhood risk factors, and 1.29 (95%CI: 0.56,2.98) with adult factors added to the model. Similarly, the odds of having high-risk CRP in adulthood among distress prone children was 3.74 (95%CI: 1.15,12.25) controlling for demographics, 3.85 (95%CI: 1.15,12.88) additionally adjusting for childhood covariates, and 2.82 (95%CI: 0.73,10.81) with adult factors added to the model. Those who were behaviorally inhibited as children had a 60% (95%CI: 0.15,1.04) reduced odds of high-risk CRP in adulthood after controlling for demographics, although these relationships were largely attenuated after adjusting for childhood (OR=0.42, 95%CI: 0.16,1.14) and adult factors (OR= 0.49, 95%CI: 0.17,1.44).

DISCUSSION

This study provides evidence that child emotional functioning is associated with CRP in adulthood. Specifically, those who were high in ISR and distress proneness as children had significantly elevated CRP in adulthood, even after controlling for potential confounders measured at birth and during childhood. Further, associations of ISR and distress proneness with adult CRP may be mediated in part by adulthood BMI. This finding is consistent with the emerging literature suggesting externalizing problems in childhood are associated with adult health and inflammation (22, 24). The analogous odds ratios for these relationships were large and suggest that poor child emotional functioning is associated with levels of CRP consistent with the CDC/American Heart Association's cut-point for high risk of cardiovascular disease (6).

Another primary finding was that childhood ISR and distress proneness were strongly associated with BMI in adulthood, net of child BMI and other life course factors. Childhood emotional problems could influence adult BMI through both behavioral and physiologic pathways, which in turn may affect CRP risk. Early adversity and emotional distress can have lifelong health consequences through altering body systems during sensitive periods of development, and also through accumulated damage over time (21). Poor childhood emotional functioning may disrupt developing metabolic and related processes early in life, and set in motion a chain of detrimental behaviors, leading to obesity and elevated CRP. As this study is among the first to link child emotional functioning to adulthood BMI and CRP, future research must formally examine these associations and test specific pathways through which these factors are related.

A surprising finding was that child behavioral inhibition was inversely associated with CRP, though this relationship was attenuated in final models. It is possible that adults who were behaviorally inhibited as children abstain from risk behaviors that affect inflammation. In this sample, behavioral inhibition was not associated with adult BMI. Inhibited children may not engage in behaviors that would lead to overweight/obesity and as a result, may be less likely to experience elevated adulthood CRP. However, given that some studies have observed negative associations between other measures of inhibition and health (23, 42–44), this finding should be interpreted cautiously.

Though we observed a significant association between distress proneness and CRP using the dichotomous emotion measure, no association was observed when treating distress proneness continuously. The lack of consistency across the different analyses may raise questions about the reliability of this finding. In this sample, the distress proneness distribution was heavily skewed towards those who were not distressed which resulted in little variability to power continuous analyses and only a small number of the most distressed individuals available for categorization in the indicator group (n=13 or 3%). As such, we recommend caution when interpreting the results for distress proneness and call for future work to examine this relationship with a better characterized distribution of childhood distress.

The study findings are congruent with emerging work in this area indicating childhood emotional functioning may set the stage for adulthood physical health and inflammation. Odgers et al. identified subtypes of conduct problems and found that those with life course persistent conduct problems had nearly 3 times the odds of having high risk CRP as adults compared to those without conduct problems (24). In the current study, two domains of childhood externalizing problems (ISR and distress proneness) were associated with elevated CRP in adulthood. Together, both studies suggest that externalizing problems in childhood may lead to inflammatory risk in adulthood. Similarly, Danese et al. (25, 26) found childhood maltreatment to associate with higher adulthood CRP. Though the authors did not measure child emotional functioning, maltreatment likely induces significant psychological distress. Given the results observed here and in Odgers (24), poor child emotional functioning could be a mechanism linking early life maltreatment to adulthood inflammation. Future research should examine such potential linkages.

This study has several limitations. When the NCPP went into the field in the 1950s, there were no population-based research tools to assess child emotion. The scales used here were constructed from psychologist ratings of child behavior 30 years after observation. Though these scales perform moderately well, contemporary measures such as the Achenbach CBCL (34) may more accurately assess child emotion. Using imprecise measures could mask relationships with adulthood inflammation. As such, it is possible the observed associations between child emotional functioning and adult CRP are underestimates. Also, data on several potential confounders, including childhood CRP, genetics, medication use and other chronic health conditions were not included in analysis. Failing to adjust for such potential confounders could result in spurious associations between child emotional functioning and CRP. Also, though the statistical tests performed here suggest adulthood BMI may mediate the association between child emotional functioning and adulthood CRP, the observational study design precludes a rigorous test of effect mediation (45). Finally, no information is available on other life course influences occurring between age 7 and middle adulthood. While we can appropriately address factors from early childhood, 35 years of experiences remain unknown that could potentially help explain the observed relationships. Future work should incorporate information from all stages in life to more completely assess relations between child emotion, adult inflammation, and related pathways.

This study has a number of strengths. Biomarkers like CRP are not subject to reporting biases and provide insight into physiologic mechanisms through which emotional problems may harm health. Also, emotional functioning was assessed approximately 35 years prior to CRP. Not only was emotional functioning directly assessed in childhood, but such a lengthy follow-up allows for the examination of markers of chronic health conditions that emerge in midlife. Additionally, study variables were collected from multiple sources (e.g. biomarker, psychologist rating, anthropomorphic measurements), thereby protecting against common method bias that could result when relying on a single data collection method. Finally, this study controlled for a number of confounders and mediators measured across the life course. Few other data sources in the US can link such information from birth, childhood and adulthood.

This study demonstrated that childhood emotional functioning is associated with systemic inflammation in adulthood net of multiple risk factors from across the life course, and that adult BMI might mediate relations between child externalizing problems and CRP. Poor childhood emotional functioning is an important public health concern in its own right. This work additionally provides evidence that problems with childhood emotional functioning may also be related to cardiovascular risk markers (e.g. obesity and CRP) later in life. Identifying whether and how child emotional dysfunction leads to systemic inflammation and adult health outcomes will aid in developing new strategies for reducing the burden of chronic disease in the United States.

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Acronyms

CRP	C-reactive protein
BMI	body mass index
ISR	inappropriate self regulation
SES	socioeconomic status
SGA	small for gestational age
IQ	intelligence quotient
CES-D	Centers for Epidemiologic Studies Depression Scale

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Table 1

Descriptive Statistics

Characteristic (n)	n(%)/Mean (SD)[a] (base n=400)[b]
Adulthood Inflammation	
Adult C-reactive protein, mg/L (400)	1.7 (2.0)
Demographics	
Site, Boston (215)	215 (53.8)
Age, years (399)	42.2 (1.8)
Race, not white (82)	82 (20.6)
Gender, female (234)	234 (58.5)
Childhood Factors	
Born small for gestational age (41)	41 (10.3)
Childhood body mass index, kg/m^2 (398)	16.1 (1.6)
Childhood full scale IQ (400)	101.6 (13.7)
Childhood chronic condition (72)	72 (18.1)
Childhood socioeconomic index (396)	54.1 (22.9)
Adulthood Factors	
Adulthood current smoker (102)	102 (25.8)
Adulthood depressive symptoms, CES-D (397)	1.6 (0.5)
Adulthood education - Less than high school (23)	23 (5.8)
- High school or GED (196)	196 (49.6)
- Some college (68)	68 (17.2)
- College graduate (108)	108 (27.3)
Adulthood body mass index, kg/m^2 (396)	29.2 (7.6)

[a] Cell entries are n(%)/means (SD) for categorical/continuous variables

[b] The base n reflects the study inclusion criteria: those who had available child emotion data and CRP values ≤ 10 mg/L

Abbreviations: IQ=intelligence quotient; CES-D=Center for Epidemiologic Studies Depression Scale; GED=general equivalency diploma

Table 2

Characteristics of Study Participants by Level of Child Emotional Functioning[a]

Characteristic	Inappropriate Self Regulation			Distress Proneness			Behavioral Inhibition		
	High (n=64)	Low (n=336)	p-value[b]	High (n=13)	Low (n=387)	p-value	High (n=62)	Low (n=338)	p-value
Adulthood Inflammation									
Adult C-reactive protein, mg/L	2.3 (2.4)	1.6 (1.9)	0.009	2.9 (3.1)	1.7 (2.0)	0.04	1.3 (1.4)	1.8 (2.1)	0.01
Demographics									
Site, Boston, **n (%)**	49 (76.6)	166 (49.4)	<0.001	8 (61.5)	207 (53.5)	0.57	37 (59.7)	178 (52.7)	0.31
Age, years	42.1 (1.7)	42.3 (1.8)	0.67	41.5 (1.7)	42.3 (1.8)	0.15	42.5 (1.8)	42.2 (1.8)	0.16
Race, not white, **n (%)**	12 (18.8)	70 (21.0)	0.69	3 (23.1)	79 (20.5)	0.82	11 (18.0)	71 (21.1)	0.59
Gender, female, **n (%)**	28 (43.8)	206 (61.3)	0.009	4 (30.8)	230 (59.4)	0.04	44 (71.0)	190 (56.2)	0.03
Childhood Factors									
Born small for gestational age, **n (%)**	7 (10.9)	34 (10.2)	0.86	1 (7.7)	40 (10.4)	0.75	2 (3.2)	39 (11.6)	0.05
Childhood body mass index, kg/m^2	16.6 (1.7)	16.0 (1.6)	0.007	16.0 (1.1)	16.1 (1.6)	0.83	15.7 (1.1)	16.1 (1.7)	0.01
Childhood full scale IQ	107.3 (14.0)	100.5 (13.7)	<0.001	106.2 (13.3)	101.4 (13.7)	0.22	95.2 (12.8)	102.8 (13.5)	<0.001
Childhood chronic condition, **n (%)**	11 (17.2)	61 (18.2)	0.85	2 (15.4)	70 (18.1)	0.80	10 (16.1)	62 (18.4)	0.67
Childhood socioeconomic index	62.6 (24.0)	52.4 (22.3)	<0.001	55.9 (29.2)	54.0 (22.7)	0.77	53.7 (22.4)	54.2 (23.0)	0.89
Adulthood Factors									
Adulthood current smoker, **n (%)**	14 (22.2)	88 (26.5)	0.48	4 (30.8)	98 (25.7)	0.68	16 (26.2)	86 (25.8)	0.94
Adulthood depressive symptoms, CES-D	1.5 (0.46)	1.6 (0.56)	0.15	1.5 (0.5)	1.6 (0.6)	0.88	1.5 (0.5)	1.6 (0.6)	0.62
Adulthood education, < High School, **n (%)**	1 (1.6)	22 (6.6)	0.09	1 (7.7)	22 (5.8)	0.38	5 (8.3)	18 (5.4)	0.31
Adulthood body mass index, kg/m^2	32.1 (9.8)	28.7 (7.0)	0.01	32.9 (6.7)	29.1 (7.6)	0.08	28.0 (6.2)	29.4 (7.8)	0.11

[a] Cell entries are **n(column percents)**/means(SD) for categorical/continuous variables. Column percents reflect the percent of the characteristic within each level of emotional functioning.

[b] P-values correspond to chi square/independent t-tests for categorical/continuous variables

IQ=intelligence quotient; CES-D=Center for Epidemiologic Studies Depression Scale

Table 3

Multiple linear regression models for the association between poor childhood emotional functioning and C-reactive protein in adulthood

Variable	Model 1[a] (n=400)	Model 2[b] (n=397)	Model 3[c] (n=389)	Model 4[d] (n=379)
Inappropriate Self Regulation	0.71 (0.27) 0.009	0.86 (0.28) 0.002	0.86 (0.28) 0.002	0.25 (0.25) 0.31
Distress Proneness	1.18 (0.56) 0.04	1.23 (0.57) 0.03	1.26 (0.56) 0.03	0.79 (0.48) 0.10
Behavioral Inhibition	−0.55 (0.29) 0.05	−0.58 (0.28) 0.04	−0.54 (0.29) 0.07	−0.31 (0.25) 0.22

Top cell entries include B (SE); bottom cell entry includes p-value

[a] Model 1: Unadjusted association

[b] Model 2: Controls for demographics (study site, age, race and gender).

[c] Model 3: Controls for variables in Model 1 and childhood factors (SGA, childhood BMI, IQ, health, SES)

[d] Model 4: Controls for variables in Model 2 and adulthood factors (smoking, depressive symptoms, education, adult BMI)

Abbreviations: SGA=small for gestational age; BMI=body mass index; IQ=intelligence quotient; SES=socioeconomic status

Table 4

Multiple linear regression models for the association between continuous measures of childhood emotional functioning and adult CRP

Variable	Model 1[a] (n=400)	Model 2[b] (n=397)	Model 3[c] (n=389)	Model 4[d] (n=379)
Inappropriate Self Regulation	0.44 (0.13) 0.0005	0.44 (0.13) 0.0005	0.45 (0.13) 0.0005	0.20 (0.11) 0.08
Distress Proneness	0.23 (0.24) 0.33	0.25 (0.24) 0.28	0.25 (0.24) 0.28	0.07 (0.20) 0.73
Behavioral Inhibition	−0.39 (0.14) 0.01	−0.41 (0.16) 0.01	−0.41 (0.17) 0.01	−0.25 (0.14) 0.07

Top cell entries include B (SE); bottom cell entry includes p-value

[a] Model 1: Unadjusted association

[b] Model 2: Controls for demographics (study site, age, race and gender)

[c] Model 3: Controls for variables in Model 2 and childhood factors (SGA, child BMI, IQ, health, SES)

[d] Model 4: Controls for variables in Model 3 and adulthood factors (smoking, CES-D, education, adult BMI)

Abbreviations: SGA=small for gestational age; BMI=body mass index; IQ=intelligence quotient; SES=socioeconomic status

Table 5

Models examining adult BMI as a potential mediator in the childhood emotional functioning and adult CRP relation

Variable	Model 1[a] Emotion→CRP	Model 2[b] Emotion→BMI	Model 3[c] BMI→CRP	Model 4[d] Emotion→BMI→CRP	Sobel test (p-value)
Inappropriate Self Regulation	0.73 (0.28) 0.01	3.06 (0.99) 0.002	0.14 (0.01) <0.001	0.25 (0.25) 0.31	2.97 0.003
Distress Proneness	1.28 (0.55) 0.02	3.54 (1.94) 0.07	0.14 (0.01) <0.001	0.79 (0.48) 0.10	1.80 0.07
Behavioral Inhibition	−0.46 (0.29) 0.11	−0.76 (1.03) 0.46	0.14 (0.01) <0.001	−0.31 (0.25) 0.22	−0.73 0.46

Top cell entries for models include B (SE); bottom cell entry includes p-value

[a] Model 1: Beta coefficient represents change in adult CRP (mg/L) in relation to childhood emotional problems (high vs. low) when controlling for all covariates except for adult BMI.

[b] Model 2: Beta coefficient represents the change in adult BMI in relation to childhood emotional problems (high vs. low) controlling all covariates. CRP is not included in the model.

[c] Model 3: Beta coefficient represents the change in adult CRP (mg/L) in relation to adult BMI when controlling for all covariates including child emotion problems.

[d] Model 4: Beta coefficient represents the change in adult CRP (mg/L) in relation to child emotional problems (high vs. low) when controlling for all covariates including adult BMI.

Abbreviations: BMI=body mass index; CRP=C-reactive protein