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Childhood adversity and inflammatory processes in youth: A prospective study

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Summary
Background: Retrospective studies show that childhood adversity is associated with systemic inflammation in adulthood. Few prospective studies have examined whether childhood adversity influences inflammation in an observable manner during childhood or adolescence and if these effects are sustained over time.
Methods: Using longitudinal data from the Avon Longitudinal Study of Parents and Children, we examined associations between acute adverse events at seven time points prior to age 8 and inflammation at ages 10 and 15. Inflammatory markers at age 10 included interleukin-6 (IL-6; $N = 4655$) and C-reactive protein (CRP; $N = 4647$), and CRP was measured again at age 15 ($N = 3286$). We further evaluated whether body mass index (BMI), depression, or cigarette smoking mediated associations between adverse events and inflammation.
Results: Adverse events in middle childhood (occurring between ages 6 to 8), as well as cumulative adversity from birth to 8 years, were associated with higher levels of IL-6 and CRP at age 10. Adverse events reported in early childhood (1.5 years) or middle childhood, and cumulative adversity from birth through 8 years predicted increased levels of CRP at age 15, and these associations persisted after adjustment for CRP at age 10. Some, but not all, of these associations were mediated by BMI.

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Conclusions: This study documents that exposure to adverse events prior to age 8 is associated with elevated inflammation at age 10 and in mid-adolescence. These findings provide prospective evidence for a biological mechanism by which early experiences may shape long-term health. Future studies with earlier assessments of inflammation are necessary in order to elucidate potential sensitive periods and mechanisms that link childhood adversity to later disease vulnerability.

1. Introduction

Early life experiences have lasting effects on neurobiological functioning and health outcomes across the life course (Shonkoff et al., 2009; Taylor et al., 2011). Adverse childhood experiences — including low socioeconomic status (SES), maltreatment, or maladaptive early family environments — are associated with a broad spectrum of subsequent health problems in adulthood, including cardiovascular disorders (CVD) (Dong et al., 2004; Galobardes et al., 2006), metabolic abnormalities (Thomas et al., 2008; Danese et al., 2009), cancers (Felitti et al., 1998), arthritis (Dube et al., 2009; Von Korff et al., 2009) and mental illnesses (Chapman et al., 2004; Kessler et al., 2010). Evidence from both animal and human studies suggests that inflammation may be a central biological mechanism linking early adversity to a variety of health outcomes (Miller et al., 2009a). Although numerous studies show that low childhood SES and harsh early family environments are associated with elevated concentrations of inflammatory markers like circulating levels of C-reactive protein (CRP) and pro-inflammatory cytokines such as interleukin-6 (IL-6) among adults (Taylor et al., 2006; Danese et al., 2007; Pollitt et al., 2007), relatively few studies have examined whether childhood adversity is associated with inflammation during childhood or adolescence (Slopen et al., 2011). It is important to characterize the developmental progression of inflammatory processes in relation to adversity in children and adolescents in order to understand how exposure to childhood adversity may engender disease vulnerability over time (Danese et al., 2011). The aim of this study is to examine prospectively the relationship between adverse events that occur during childhood and inflammation in both childhood and adolescence.

Increasing evidence suggests that elevated levels of inflammation in childhood may provide an early marker of disease risk in adulthood. For example, elevated CRP in childhood is associated with elevated CRP in adulthood (Juonala et al., 2006); and CRP in childhood is also associated with a variety of cardiovascular (Cook et al., 2000) and atherosclerotic risk factors among youth, such as disturbed endothelial function and intima media thickening, even after adjustment for body mass index (BMI) (Jarvisalo et al., 2002). Although a number of studies have examined the relationship between childhood adversity on inflammation in child or adolescent samples, results have been inconsistent. In a recent systematic review of studies that examined childhood adversity, as measured by either socioeconomic or interpersonal stressors, in relation to inflammation in healthy children and adolescents, the pattern of findings was not clear (Slopen et al., 2011). Some of these studies documented associations between adversity and elevated levels of inflammation (Murasko, 2008; Fuligni et al., 2009a; Howe et al., 2010), while others found no associations (Cook et al., 2000; Gimeno et al., 2008; Miller et al., 2009b), conditional associations (Marin et al., 2007; Danese et al., 2011), or inconsistent associations depending on the measure of adversity (McDade et al., 2005; Dowd et al., 2010).

Some of the inconsistencies across studies may be due to aspects of adversity that prior literature has not been able to consider in detail in relation to inflammation. For example, variation in the type or severity of stressors, or differences in the proximity of stress exposure to assessment of inflammation may account for differences in the impact of adversity on inflammatory biomarkers. Furthermore, existing studies have rarely examined childhood adversity and inflammation prospectively in child and adolescent samples, with repeated measures of either the exposures or outcomes. Accordingly, we have limited evidence about whether childhood adversity has persistent effects on inflammation in youth, and whether adversity during early childhood, in contrast to later developmental periods, has a differential impact on later inflammation.

The present study utilized longitudinal data from the Avon Longitudinal Study of Parents and Children (ALSPAC). We used severity-weighted reports of acute adverse events as a measure of childhood adversity. The primary aim was to examine the association between adverse events, measured at seven time points between 1.5 and 8 years of age, and two commonly assessed measures of inflammation, CRP and IL-6. CRP and IL-6 were selected as these inflammatory biomarkers are indicative of systemic inflammation. As it is unclear as to whether CRP per se is causally associated with cardiovascular or other diseases (Casas et al., 2006; Kaptoge et al., 2010), we do not assume that they are on the causal pathway between adversity and coronary heart disease (C Reactive Protein Coronary Heart Disease Genetics Collaboration, 2011) or metabolic syndrome (Timpson et al., 2005). Rather, we consider them as a potential early marker of disease risk, based on prior work demonstrating that elevated levels of CRP are consistently associated with greater atherosclerosis and incident coronary events (Pearson et al., 2003; Danesh et al., 2004). Both IL-6 and CRP were measured at age 10 and CRP was measured again in mid-adolescence (age 15). Repeated assessment of adverse events allowed us to examine the associations of adverse events occurring in specific developmental periods as well as cumulatively with inflammatory processes in childhood and the persistence of those processes into mid-adolescence.

We hypothesized that adverse events at any time point prior to age 8 would be associated with inflammation at both time points, and the association would be greatest for a cumulative measure that incorporated all assessments of