Brain, Behavior, and Immunity 26 (2012) 239–250

Contents lists available at SciVerse ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Review

Childhood adversity and immune and inflammatory biomarkers associated with cardiovascular risk in youth: A systematic review

Natalie Slopen [a,b,c,*], Karestan C. Koenen [a,b,d], Laura D. Kubzansky [b]

[a] Center on the Developing Child, Harvard University, United States
[b] Harvard School of Public Health, United States
[c] Harvard Graduate School of Education, United States
[d] Mailman School of Public Health, Columbia University, United States

ARTICLE INFO

Article history:
Received 25 July 2011
Received in revised form 13 October 2011
Accepted 9 November 2011
Available online 25 November 2011

Keywords:
Children
Adolescents
Inflammation
Immune
Adversity
Stress
Systematic review

ABSTRACT

Background: Research suggests that adverse experiences in childhood affect the development of cardiovascular disease (CVD), and immune and inflammation dysregulation has been postulated to play role. However, it is unclear whether the effects of social adversity on immune-related biomarkers are evident in early life, and if these biomarkers may provide an early risk marker for targeting prevention and intervention. The purpose of this review is to evaluate research on the relationship between adversity and CVD-relevant immune biomarkers in youth, assess the consistency of the findings, and consider what additional research is needed.

Methods: PubMed and PsycINFO searches were conducted through September 2011. Studies were selected using criteria related to the childhood exposure, biomarker outcome, age range, and sample selection. Twenty articles were identified, examining associations between childhood adversity and immune biomarkers (assessed during childhood) that are potential risk markers for CVD later in life.

Results: Although childhood adversity was not consistently related to youth levels of inflammatory and other immune markers relevant to CVD, a trend toward positive findings was observed. No detectable patterns were evident based on measure of adversity, biomarker, study design, or sample size.

Conclusions: Overall, our findings suggest this avenue of research is worth continued investigation. We offer recommendations for future research related to (1) study design and sample, (2) definition and measurement of adversity, (3) statistical analysis, and (4) outcomes that will help distinguish whether there are immunologic alterations related to adversity and subsequent CVD risk that can be reliably detected in childhood.

1. Introduction

Over the past several decades, researchers have produced compelling evidence that adverse social conditions in early life strongly effect the development and progression of disease over the life course (Shonkoff et al., 2009). Evidence is particularly strong in relation to cardiovascular disease (CVD). Empirical studies show that children who experience various types of social adversity in early life, such as poverty, abuse, or neglect, have increased risk for CVD in adulthood, and have hypothesized that effects are due to increased psychological stress (Felitti et al., 1998; Galobardes et al., 2006). As research linking early life adversity to later cardiovascular health has advanced – in combination with an improved understanding of the atherosclerotic process – investigators are now focused on clarifying the mechanisms that underlie these associations (Taylor, 2010).

Accordingly, there is growing scientific interest in the relationship between social adversity and pre-clinical precursors to CVD, including biomarkers of systemic inflammation (Miller et al., 2009a). A number of studies have documented relationships between early adversity, such as childhood maltreatment (Danese et al., 2007) and family socioeconomic status (SES) (Brunner et al., 1996; Pollitt et al., 2008) and CVD-relevant immune dysregulation in adult populations, but fewer studies have examined these relationships within populations of children and adolescents. At the present time, it is unclear whether adversity-related biological alterations emerge close to the time of the adverse experiences (i.e., during childhood or adolescence), or whether the negative effects of early adversity are stored in a latent (undetectable) form and emerge as risk factors later in life (Ben-Shlomo and Kuh, 2002). This paper presents a systematic review of research that has examined social adversity in relation to immune biomarkers in youth that have been identified as either risk factors or risk

* Corresponding author at: Center on the Developing Child, Harvard University, 50 Church Street, 4th Floor, Cambridge, MA 02138, United States.
E-mail address: nslopen@hsph.harvard.edu (N. Slopen).

0889-1591/$ - see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.bbi.2011.11.003

markers for CVD. We use the term *immune biomarker* to refer to objectively measured indicators of normal or pathogenic immunological processes, including inflammatory outcomes.

CVD is the leading cause of death for both women and men in high (Kung et al., 2008) and middle to low income (Gazlano, 2007) nations. Social disparities in CVD are widely documented such that socially disadvantaged individuals are significantly more likely to develop CVD (Pollitt et al., 2005). Evidence suggests that atherosclerosis or its precursors begins to develop in children and adolescents, and progresses slowly into adulthood via hormonal, immunological, physiologic, and metabolic alterations (Aiello and Kaplan, 2009; Kavey et al., 2003). Inflammation is part of the immune response, and inflammatory and other immune-related markers have increasingly been recognized as playing an important role in the atherosclerotic disease process (Hansson and Hermansson, 2011; Pearson et al., 2003), as the development and progression of atherosclerotic plaque are products of inflammatory response to injury.

In 2003, the Centers for Disease Control and Prevention and American Heart Association jointly reviewed the literature and developed a consensus statement on the potential utility of inflammatory biomarkers for identifying at-risk populations (Pearson et al., 2003). While it is not yet fully established which markers participate in the causal pathway leading to CVD, it is clear that patterning in inflammatory biomarkers is evident with the disease and therefore may serve as a valuable marker of early risk. In their recommendations for research in population science, the joint committee suggested that a firm understanding of the distribution of inflammatory markers across populations is needed, and urgently so in particular subgroups such as children (Pearson et al., 2003). In addition, while recent research has begun to identify early life determinants of systemic inflammation and other markers of immune function in adulthood (Pollitt et al., 2008; Slopen et al., 2010), far less understanding is available among children. Given the challenges in conducting this work among children, a systematic review of the current literature may identify fruitful directions for future research by producing a more comprehensive overview of whether effects of social adversity on immune system processes are evident early in life and if these biomarkers may provide a useful early risk marker for evaluating potential effects of prevention and intervention strategies.

Based on the work of the Early Experience, Stress, and Neurobehavioral Development Research Network we have adopted a definition of adversity as comprised of the experience of social conditions or stressors that threaten, or are perceived to threaten, physiological equilibrium (Loman and Gunnar, 2010). Our definition refers to stressors that can be assessed by measuring aspects of the social environment or social experiences, such as low socioeconomic status, material hardships, stressful life events, institutional rearing, and family conflict. Stressful experiences early in life may be one mechanism by which the social environment becomes biologically embedded to increase risk for CVD among those who are socially disadvantaged. Experimental studies show that acute and chronic social stressors can produce biological stress reactions, which may alter regulation of the hypothalamic pituitary adrenal (HPA) axis and lead to stimulation of the sympathetic nervous system (SNS). These processes may lead to excessive glucocorticoid production, blunted HPA function, and excessive inflammation as measured by C-reactive protein (CRP), interleukin-6 (IL-6), and fibrinogen (McEwen, 1998). There is increasing evidence that psychosocial stressors influence these immune biomarkers, and that these biomarkers may mediate the influence of psychosocial stressors on CVD-related pathophysiological processes (Steptoe et al., 2007). Recently, investigators have proposed a biopsychosocial model which delineates psychological stress reactions as one important mechanism linking childhood social adversity with increased adult CVD risk (Taylor et al., 2004, 2006). For example, adults who reported greater adversity in childhood had more depressive symptoms and less mastery, which in turn were related to elevated concentrations of CRP (Taylor et al., 2006).

Fig. 1 illustrates potential interconnections between early life adversity, immune-related biological changes, and development of CVD. We recognize the importance of other pathways that might either directly (e.g., metabolic, cardiovascular) or indirectly (e.g., lack of physical activity, poor diet) mediate the effects of social adversity on CVD risk. To address directly the call for research on immune-related processes and CVD and to maintain a feasible scope for the present review, we focus on research directly linking adversity with immune mechanisms (linked to atherosclerosis) in childhood; however, we note the importance of considering other mechanisms with which adversity may interact to alter immunologic processes and recommend these as topics for further reviews.

Recent studies of adults have provided evidence that childhood adversity is significantly related to incident CVD (Fig. 1, path *a*) (Felitti et al., 1998; Galobardes et al., 2004), and suggest that inflammation and other immune-related changes are mechanisms by which early adversity may contribute to incident CVD (paths *b* and *c*) (Albert et al., 2006; Graham et al., 2006; Ridker et al., 2002; Sorlie et al., 2000). Thus, one question is how early in life dysregulation in immune processes become evident (path *e*). Another question is whether early dysregulation provides early indication of CVD risk (path *d*). At present, there is limited work clearly demonstrating that immune or inflammatory dysregulation assessed in childhood influences CVD in adulthood. However, investigations using child and adolescent samples show that several immune biomarkers are correlated with traditional cardiovascular risk factors also measured in childhood (e.g., BMI, cholesterol, blood pressure) that are (a) known to track into adulthood and (b) common among adults with CVD (da Silva et al., 2010; Ford, 2003; Juonala et al., 2006; Steene-Johannessen et al., 2010). For example, among children ages 3–17 in the National Health and Nutrition Examination Survey, higher CRP was associated with greater BMI, systolic blood pressure, and triglyceride concentrations in both sexes. Other work shows that elevated CRP in children is associated with important preclinical indicators of atherosclerosis in children, including lower brachial artery flow-mediated dilation and greater carotid intima-media thickness (Jarvisalo et al., 2002). Taken together, these findings suggest that inflammation and other immune system dysregulation during childhood may provide a valid indication of early risk for (or of pathophysiologic processes involved in) the development of CVD in adulthood. Thus, although the other pathways depicted in Fig. 1 are not fully established, numerous studies have begun to investigate whether early adversity may lead to dysregulation in immune and inflammatory processes, predicated on the assumption that early dysregulation is linked to subsequent disease risk.

From a mechanistic perspective, it is important to gain an understanding of *when* the effects of early adversity on immune biomarkers can be expected to emerge. Early identification of risk or pre-disease processes may suggest the possibility of sensitive periods for risk of developing CVD and would facilitate development of more targeted and appropriately timed prevention and intervention strategies. Knowledge of biological alterations in childhood related to subsequent CVD risk could also be valuable for identifying children who should be prioritized for intensive social or medical intervention, or measuring the effectiveness of prevention efforts. Thus, greater understanding of how to assess risk and early onset of relevant pathophysiologic processes early in life is urgently needed.

The aims of the present review are to evaluate the published research on the relationship between social adversity and CVD-rele-

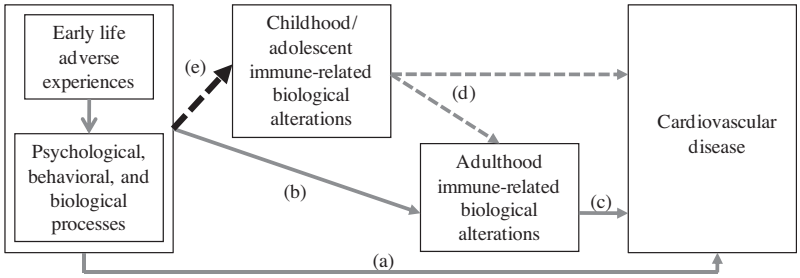

Fig. 1. Conceptual model: adverse experiences in childhood or adolescence, immune-related biological alterations, and incidence of cardiovascular disease. *Notes*: Arrow in black is the focus of the current literature review; solid lines are associations that have a substantial empirical basis; dashed lines are associations that require further empirical support.

vant immune biomarkers in child and adolescent populations, systematically assess the consistency of the findings, and consider what additional research is needed. To our knowledge, this is the first systematic review on this topic. We focus on immune biomarkers that are likely risk markers for CVD later in life. These include cytokines, acute-phase proteins, coagulation and adhesion molecules, and other markers of immune control that have been documented as risk markers for early and later atherosclerosis (Hansson and Hermansson, 2011; Stassen et al., 2006). Thus, we consider any markers that have previously been explored and documented as relevant to CVD risk and also considered in relation to adversity. Fig. 2 illustrates the central hypothesized biological pathways linking these biomarkers to CVD. Of note, a variety of other biological systems are involved in the up- and down-regulation of immune biomarkers that are not represented in Fig. 2; more extensive description of these systems can be found elsewhere (Black, 2003; Black and Garbutt, 2002). We do not review studies of cortisol (or glucocorticoid receptors) which is theorized to be more indirectly related to the etiology of CVD (Kubzansky and Adler, 2010; McEwen, 2007). For interested readers, the relationship between childhood adversity and cortisol has been discussed extensively in other recent review articles (Gunnar and Quevedo, 2007; McCrory et al., 2010).

2. Methods

We conducted systematic searches of PubMed and PsycINFO through September 2011 (see Fig. 3). PubMed includes coverage of the National Library of Medicine's bibliographic database, and PsycINFO is the American Psychological Association's bibliographic database; together, they provide comprehensive coverage of the life sciences and social science literature. We searched PubMed using the Medical Subject Heading (MeSH) terms *'Interpersonal Relations' 'Stress, Psychological', 'Socioeconomic Factors', 'Life Change Events', 'Social Environment', 'Family Relations', 'Conflict (Psychology)', 'Aggression', 'Violence', 'Prejudice', 'Inflammation', Biological Markers/blood', 'Biological Markers/immunology', 'Acute-Phase Proteins', 'Cytokines', 'Cytomegalovirus'*. MeSH is a vocabulary thesaurus for indexing articles in PubMed, developed and updated by the National Library of Medicine. MeSH terms allow users to locate relevant articles when several terms may be used to refer to the same

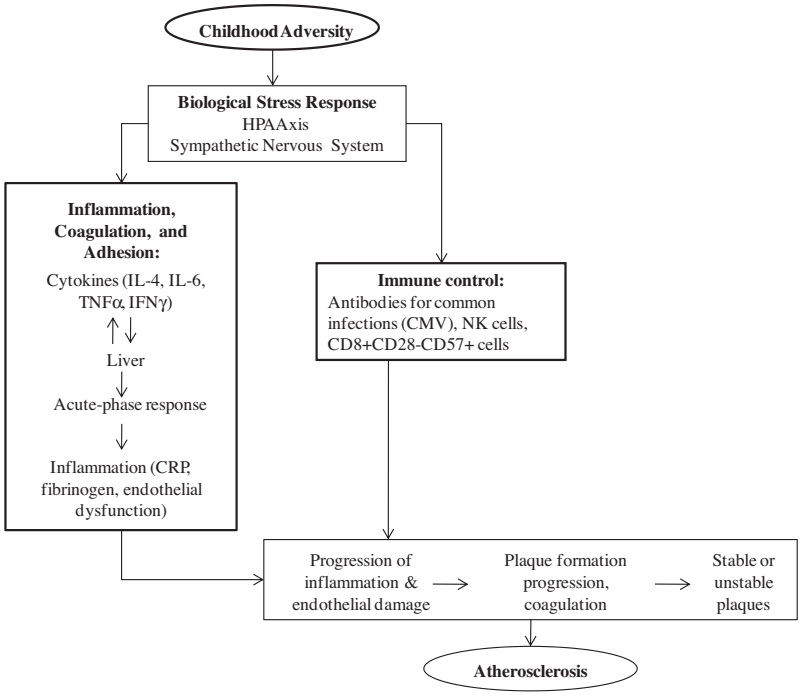

Fig. 2. Childhood adversity, immunological biomarkers examined in existing pediatric research, and development of atherosclerosis (Aiello and Kaplan, 2009; Black and Garbutt, 2002). *Note:* A variety of other biological systems are involved in the up- and down-regulation of immune biomarkers that are not represented; more extensive description of these systems can be found elsewhere (Black, 2003; Black and Garbutt, 2002).

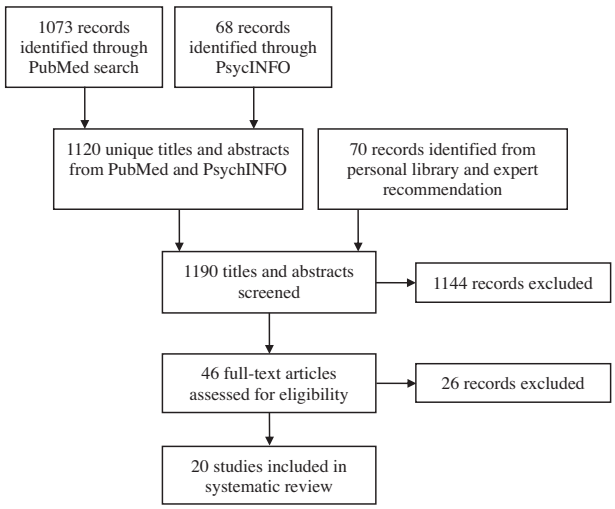

Fig. 3. Collection of studies for inclusion in systematic review.

concept. The terms are organized hierarchically by subject categories with more specific terms below the broader terms; narrower terms are automatically included in searches of broader terms. We supplemented the MeSH terms with similar words for key terms in the title or abstract, in order to identify any relevant recent publications that had not been indexed by MeSH. We also applied limits to the search to restrict the results to studies published in English, and studies with child and adolescent samples (i.e., less than 18 years). This search returned 1073 studies. In PsycINFO, we searched using a similar set of subject headings, keywords in the title/abstract, and limits, which resulted in 68 studies. After removing 21 duplicate studies, our searches returned a total of 1120 studies. We also searched our personal libraries for potential articles, and consulted with experts in this topic area.

All returned abstracts were read, and we selected studies using four criteria. The first criterion was that studies had to include a measure of adversity in childhood or adolescence (i.e., birth to age 18). We define adversity as a condition or experience marked by misfortune (either relative or absolute, as described above); however, this criterion was not met if the stressor is a part of the process of normal expected healthy child development, such as starting kindergarten. The second criterion required that the sample was not selected based on an existing physical illness (i.e., asthmatic children). The third criterion required that the study included a biological measure of the immune or inflammatory processes in childhood or adolescence. This criterion was met by inclusion of an enumerative or functional immune assay. Of note, clinical disease outcomes did not meet this criterion. The fourth criterion required that the immune outcome is a recognized risk marker for CVD. This criterion was met if a given inflammatory (Hansson and Hermansson, 2011; Hansson, 2005) or viral (Aiello and Kaplan, 2009; Galkina and Ley, 2009; Stassen et al., 2006) immune marker has been identified as relevant to atherosclerotic processes in peer-reviewed literature. Our search was 'data-driven' in the sense that used very broad MeSH terms to identify all studies with potentially relevant biomarkers, and then examined whether the markers in a given study fit the criteria necessary for inclusion.

For the selected studies, we searched the reference sections for additional relevant publications. We then reviewed the full manuscripts of the selected studies for key information: study design, source of population, sample size, age, nationality, type and measurement of adversity and immune outcomes, statistical methods, stratification and control variables, and findings. In light of the marked variation in study designs, participants, predictor variables, and outcomes across the identified studies, we describe the studies and their results using a qualitative synthesis, rather than a quantitative meta-analysis to aggregate effect sizes across studies.

3. Results

We identified 20 studies for inclusion in this review. This includes studies from North America ($n = 11$), Europe ($n = 8$), and South America ($n = 1$). Sample sizes for studies ranged from 54 (Birmaher et al., 1994) to 7772 (Howe et al., 2010) participants (median, $n = 282$). Approximately one third of the studies used samples where all participants were under the age of 13, while nearly one third of the studies used samples where all participants were between 13 and 18 years of age; the remaining studies included both child and adolescent aged children. The majority of studies in the current review were cross-sectional ($n = 14$). Four of the 20 studies were longitudinal and had repeated measures of the outcome (Caserta et al., 2008; Gimeno et al., 2008; Miller and Chen, 2010; Miller et al., 2009c). Of the remaining studies, one used a case-control design (Danese et al., 2011) and one study used a daily diary design, which required participants to complete a checklist about their experiences for 14 days (Fuligni et al., 2009). The samples for these studies were recruited from schools ($n = 8$), some form of area-probability sample ($n = 7$), or were recruited through clinics or another type of convenience sampling ($n = 5$).

There was extensive variation in the types and measures of adversity among the selected studies. Approximately half of the studies utilized a measure of family SES as a primary exposure variable (i.e., parental occupation, educational attainment, income; $n = 10$), while other studies utilized measures of interpersonal stressors and/or life events ($n = 10$), and area-level measures of economic deprivation ($n = 2$) as the primary exposures. The studies examined adversity in relation to a variety of immunologic biomarkers, including CRP; cytokines (IL-4), IL-6 interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α); fibrinogen; natural killer (NK) cell function; and, markers of immune control of cytomegalovirus (CMV). Of the 21 identified studies, 15 examined adversity in relation to one immune biomarker that met criteria for inclusion in the current review; five studies assessed two or more relevant biomarkers. In the following paragraphs, we present the results of our review organized by type of biomarker examined; the results are also summarized in Table 1.

3.1. Adversity and CRP

CRP is a pro-inflammatory molecule that is associated with increased risk for CVD (Ridker et al., 2002); it modulates leukocyte activities and endothelial functions, and has been shown to increase inflammation by catalyzing monocyte activation (Aiello and Kaplan, 2009; Galkina and Ley, 2009). Eleven studies investigated the association between adversity and CRP among children or adolescents; seven of these studies were cross-sectional, two studies had longitudinal designs with repeated measures (Gimeno et al., 2008; Miller et al., 2009c), one study used a prospective case-control design (Danese et al., 2011), and one study used the daily dairy method (Fuligni et al., 2009) Seven of the eleven studies used a measure of family SES as the primary exposure. In three of the eleven studies, adversity was associated with increased concentration of CRP (Fuligni et al., 2009; Howe et al., 2010; Murasko, 2008). For example, in a cross-sectional study of 7772 children (age 10 years) in Avon County, England, Howe and colleagues found that lower maternal education was associated with higher CRP (Howe et al., 2010). Similarly, using a daily diary study design,

Table 1
Published research examining adversity/psychosocial stress and immune and inflammatory biomarkers of cardiovascular disease among healthy youth, organized by outcome and study design.

	Design, *N*	Country	Sample, age	Adversity	Findings	Expected direction
CRP						
Gimeno et al. (2008)	Longitudinal, *N* = 1484	Finland	Cardiovascular Risk in Young Finns Study; 3–9 years at childhood measure, 12–18 years at adolescent measure	Parental occupation	No social class variation in CRP observed at childhood or adolescent assessments	No
Miller et al. (2009c)	Longitudinal, *N* = 103	Canada	Subsample from study on depression and CVD risk in women at risk for affective disorders; 15–19 years at baseline	Chronic interpersonal stress	No association between chronic interpersonal stress and CRP	No
Danese et al. (2011)	Prospective, *N* = 174	England and Wales	Subsample from the Environmental Risk Longitudinal Twin Study; 12 years at baseline	Physical maltreatment	Children who experienced maltreatment and depression had greater CRP, while those who experienced maltreatment but no depression did not show elevated CRP	Conditional
Cook et al. (2000)	Cross-sectional, *N* = 699	England and Wales	Recruited from schools in 5 towns; 10–11 years	Parental occupation	No social class variation in CRP	No
Dowd et al. (2010)	Cross-sectional, *N* = 6004	US	NHANES; 3–16 years	Family income and education	Lower household income associated with greater CRP; no association for parental education	Mixed
Howe et al. (2010)	Cross-sectional, *N* = 7772	England	Avon Longitudinal Study of Parents and Children; 10 years	Maternal education	Higher maternal education was associated with lower CRP	Yes
Marin et al. (2007)	Cross-sectional, *N* = 104	Canada	Subsample from study on depression and CVD risk in women at risk for affective disorders; 15–19 years	Acute events and chronic interpersonal stress	Statistical interaction between acute events and chronic interpersonal stress: as chronic interpersonal stress increased, an inverse association between # of acute events and CRP increased in magnitude	Conditional
McDade et al. (2005)	Cross-sectional, *N* = 536	Bolivia	Census sample from Bolivian Amazon, 2–15 years	Family economic resources	Greater household wealth associated with lower CRP; no association for other indicators of economic resources (i.e., agricultural plots, wages, goods bartered)	Mixed
Murasko (2008)	Cross-sectional, *N* = 4788	United States	NHANES; 12–17 years	Family income	Lower income associated with greater CRP in full sample; association greater for females compared to males	Yes
Thomas et al. (2005)	Cross-sectional, *N* = 208	Britain	Children recruited from 2 schools; mean age = 12.9 years	SES of school	High SES boys had higher CRP than low SES girls & boys; pattern not present when CRP values > 10 removed	No
Fuligni et al. (2009)	Daily diary, *N* = 69	US	Subsample from larger study of high school students; mean age = 17.8 years	Interpersonal stress	Greater frequency of daily interpersonal stress associated with greater CRP	Yes
Cytokines						
Interleukins						
Miller and Chen (2010)	Longitudinal, *N* = 135	Canada	Subsample from study on depression and CVD risk in women at risk for affective disorders; 15–19 years	Family climate; life events	Circulating IL-6 not associated with harsh family climate. Harsh family climate positively associated with (a) production of IL-6 following lipopolysaccharide (LPS) stimulation, and (b) resistance to gluccocorticoids (sample coincubated by LPS and cortisol). Interaction between harsh family climate and life events for IL-6 following LPS stimulation but not other IL-6 outcomes (i.e., effect of acute events on stimulated IL-6 greater among females in harsh family environment)	Mixed
Miller et al. (2009c)	Longitudinal, *N* = 103	Canada	Subsample from study on depression and CVD risk in women at risk for	Chronic interpersonal stress	Greater chronic interpersonal stress was associated with increased stimulated IL-6	Mixed

(*continued on next page*)

Table 1 (*continued*)

	Design, *N*	Country	Sample, age	Adversity	Findings	Expected direction
			affective disorders; 15–19 years at baseline		production; however, no association with circulating IL-6	
Herberth et al. (2008)	Cross-sectional, *N* = 234	Germany	Leipzig participants in the Life style Immune System Allergy Study; 6 years	Life events	Divorce/separation of parents in past year associated with higher concentrations of IL-4; no associations for death or disease in family, or parental unemployment	Mixed
Howe et al. (2010)	Cross-sectional, *N* = 7772	England	Avon Longitudinal Study of Parents and Children; 10 years	Maternal education	Higher maternal education associated with lower IL-6 among males; marginal association among females	Conditional
INF-γ						
Herberth et al. (2008)	Cross-sectional, *N* = 234	Germany	Leipzig participants in the Life style Immune System Allergy Study; 6 years	Life events	Parental unemployment in the past year associated with lower INF-γ; no association for divorce/separation, or death or disease of a family member	Mixed
TNF-α						
Dixon et al. (2009)	Cross-sectional, *N* = 112	US	School children from three communities in South Florida; 5–10 years	Life events	Stressful events score associated with higher TNF-α	Yes
Fibrinogen						
Cook et al. (1999)	Cross-sectional, *N* = 641	England and Wales	Children recruited from schools in 5 towns; 10–11 years	Parental occupation	No social class variation in fibrinogen	No
Thomas et al. (2005)	Cross-sectional, *N* = 208	Britain	Children recruited from 2 schools; mean age = 12.9 years	SES of school	In gender stratified analyses, males at high SES school had greater fibrinogen than males at low SES school; no difference identified among females	Conditional
Goodman et al. (2005)	Cross-sectional, *N* = 758	US	Students recruited from high schools in a suburban Midwest; 13–19 years	Parental education	No social class variation in fibrinogen	No
Morley et al. (2000)	Cross-sectional, *N* = 330	England	Sample of students from 7 high schools; 11–15 years	Area-level deprivation	Area-deprivation score associated with increased fibrinogen; association was stronger for females compared to males	Yes
Natural killer cells						
Caserta et al. (2008)	Longitudinal, *N* = 169	US	Children identified from a larger study through a hospital, 5–10 years	Parental psychopathology; life events; family conflict	Parental psychiatric symptoms was associated with enhanced NK cell activity, while family conflict had significant negative association with NK cell activity; no association for stressful life events	Mixed
Birmaher et al. (1994)	Cross-sectional, *N* = 54	US	Adolescents recruited from a psychiatric clinic; 11–18 years	Life events; family SES	Past year and lifetime events negatively associated with NK cell activity; no association between NK cell activity and SES. No associations between past year or lifetime events or SES and lymphocyte proliferation in response to PHA	No
Immune control of CMV						
Caserta et al. (2008)	Longitudinal, *N* = 169	US	CMV seropositive children (*N* = 40) identified from a larger study through a hospital; 5–10 years	Parental psychopathology; life events; family conflict	Greater parental psychiatric symptoms associated with increased CD8+CD28-CD57+ cells; no associations for stressful life events or family conflict	Mixed
Dowd et al. (in press)	Cross-sectional, *N* = 2272	US	CMV seropositive children from NHANES; 6–16 years	Family income	Poverty associated with increased CMV antibodies; threshold effect (i.e., no association with continuous income)	Yes

Abbreviations: CMV = cytomegalovirus; CRP = C-reactive protein; IFN-γ = interferon-gamma; NHANES = National Health and Nutrition Examination Survey; NK = natural killer; PHA = phytohaemagglutinin; TNF-α = Tumor Necrosis Factor-alpha.

Notes: Mixed = significant association present for at least one of the adversity exposures examined, but not significant for at least one of the adversity exposures tested. Conditional = adversity is unrelated to the biomarker in the overall sample, but an association exits only for some sub-group.

investigators found that greater frequency of daily interpersonal stressors in the past two weeks was associated with higher levels of CRP in a small sample of high school students ($n = 69$) (Fuligni et al., 2009). In contrast, however, another three of the eleven studies showed a null relationship between adversity and CRP (Cook et al., 2000; Gimeno et al., 2008; Miller et al., 2009c) and one study found a relationship opposite to the expected direction (i.e., boys from high SES schools had higher CRP than boys and girls from low SES schools) (Thomas et al., 2005).

In two of the eleven studies, the association between adversity and CRP was conditional on some other individual characteristic (Danese et al., 2011; Marin et al., 2007). For example, Danese et al. (2011) found that physical maltreatment was associated with elevated CRP, but only among children who were experiencing depression. In the other study, investigators found a significant interaction between episodic stressors (i.e., acute events) and chronic interpersonal stress on levels of CRP in a sample of adolescent females ($n = 104$) (Marin et al., 2007); however, the pattern of results was not in the expected direction. Among girls with low chronic stress, there was no relationship between episodic stressors and CRP; yet, in the context of high chronic stress, higher episodic stressors were associated with lower CRP (Marin et al., 2007).

In the remaining two studies, the presence of an association varied depending on how the exposure was measured (Dowd et al., 2010; McDade et al., 2005). For example, in a study of 6004 children (ages 6–13 years) in the National Health and Nutrition Examination Survey (NHANES) that examined parental socioeconomic position in relation to child CRP, a significant negative association between household income and CRP was evident, but there was no association between parental education and CRP (Dowd et al., 2010).

3.2. Adversity and pro-inflammatory cytokines

Pro-inflammatory cytokines are regulatory peptides that promote systemic inflammation, and can affect the expression of adhesion molecules, endothelial permeability, lipid metabolism, and other processes relevant to the development and progression of CVD (Galkina and Ley, 2009). Five articles reported associations between adversity and pro-inflammatory cytokines in youth (IL-6, $n = 3$; IL-4, $n = 1$; INF-γ, $n = 1$; and TNF-α, $n = 1$). One article (Herberth et al., 2008) examined both IL-4 and INF-γ, therefore we refer to six studies in this section. Two studies utilized a repeated measures design (Miller and Chen, 2010; Miller et al., 2009c) and the other four studies were cross-sectional (Dixon et al., 2009; Herberth et al., 2008; Howe et al., 2010). Five of the six studies used measures of interpersonal stressors and chronic or acute life events, and the remaining study examined family SES as the primary exposure (Howe et al., 2010). One study showed a clear association between adversity and cytokine concentration in the expected direction (Dixon et al., 2009) among 112 school children (ages 5–10 years) in South Florida, Dixon and colleagues found that a greater number of stressful life events was associated with higher TNF-α levels (Dixon et al., 2009). In two separate studies using the same sample of female adolescents (15–19 years) from Vancouver, Canada, researchers documented positive associations between chronic interpersonal stress (Miller et al., 2009c) and harsh family climate (Miller and Chen, 2010) and IL-6 production in response to a bacterial stimuli; however, the associations between these exposures and circulating levels of IL-6 were null.

The other studies showed mixed results. For example, in a study of 7772 children (age 10 years), researchers found that lower maternal education was significantly associated with higher concentration of circulating IL-6 among boys, but not among girls (Howe et al., 2010). Herberth et al. (2008) examined both IL-4 and INF-γ in 234 children (6 years of age) in Leipzig, Germany, and found that associations varied by type of exposure and outcome. Specifically, IL-4 concentration was positively associated with parental divorce or separation, but not with the three other stressful events that were considered (i.e., death of a family member, illness of family member or parental unemployment). In contrast, INF-γ was positively associated with parental unemployment, but not with parental divorce or separation, death of family member, or illness of a family member.

3.3. Adversity and fibrinogen

Fibrinogen is a protein that contributes to clotting of blood and blood thickness, is integral to thrombolytic events that trigger stroke and myocardial infarction, and can indicate the level of inflammation occurring in the body (Aiello and Kaplan, 2009; Danesh et al., 1998). Four cross-sectional studies examined the association between adversity and fibrinogen concentration. Two of the four studies used a measure of family SES as the primary exposure (Cook et al., 1999; Goodman et al., 2005) while two studies used area-level measures of social deprivation (Morley et al., 2000; Thomas et al., 2005). One of the four studies documented a significant association in the expected direction: greater area-level deprivation was associated with elevated fibrinogen among high school students (11–15 years) ($n = 330$), and this association was stronger among females compared to males (Morley et al., 2000). Two studies found no association between family SES and fibrinogen (Cook et al., 1999; Goodman et al., 2005). The remaining study found a conditional association, whereby higher school-level SES was associated with greater fibrinogen among boys (i.e., opposite to the expected direction), while no association was present among girls (Thomas et al., 2005).

3.4. Adversity and natural killer cells

NK cells are lymphocytes that are believed to play a role in promoting both earlier and later stages of atherosclerotic lesion development (Galkina and Ley, 2009; Whitman and Ramsamy, 2006). Two studies examined adversity in relation to NK cell function (Birmaher et al., 1994; Caserta et al., 2008). In both studies, the results were mixed. Using a longitudinal design over a three year period, Caserta and colleagues examined parental psychiatric symptoms, family conflict, and stressful life events in relation to NK cell activity among 169 children (ages 5–10 years at baseline) (Caserta et al., 2008). Parental psychiatric symptoms significantly predicted enhanced NK cell activity, family conflict was significantly negatively associated with NK cell activity, and no association between stressful life events and NK cell activity was evident. In a cross-sectional study of adolescents (11–18 years), Birmaher et al. (1994) found that having more adverse life events (past year and lifetime) was significantly associated with lower NK cell activity, even after adjustment for mental health status and family SES; there was no association between family SES and NK cell activity.

3.5. Markers of immune control of viruses

Immune activation following CMV infection may promote the development and progression of atherosclerosis (Stassen et al., 2006), and elevated CMV antibodies have been identified as risk marker for the development of CVD (Sorlie et al., 2000; Stassen et al., 2006; Zhu et al., 2001). We identified two studies of adversity in relation to markers of immune control of CMV: one study of CMV antibodies (Dowd et al., in press), and one study of percentages of CD4 and CD8 cells (CD8+CD28-CD57+ cells which are associated with immune control of CMV) (Caserta et al., 2008). In a cross-sectional study of 2272 CMV seropositive youth (6–16 years) in NHANES, Dowd and colleagues (Dowd et al., in press) found

poverty status was significantly associated with greater CMV antibody levels; however, a threshold effect was detected, whereby additional income beyond the poverty line was not associated with CMV antibody levels (i.e., there was no association when a continuous variable for income was used). In another study, the association between adversity and percentages of CD8+CD28-CD57+ cells depended on the measure of adversity that was used (Caserta et al., 2008). In the same longitudinal study described above, Caserta et al. (2008) found that parental psychiatric symptoms was associated with increased levels of CD8+CD28-CD57+ cells among 40 children seropositive for CMV over the three-year study (ages 5–10 years at baseline), but this association was not evident with family conflict or stressful life events.

4. Discussion

The aim of the current review was to assess systematically the scientific literature describing the relation between early adversity and immune biomarkers associated with risk for CVD in children and adolescents. We provide a condensed summary of the results in Table 2. While the overall evidence for a relationship between adversity and immune biomarkers of CVD risk in youth is somewhat inconsistent, there seems to be a trend toward positive findings suggesting this is an avenue of research that is worth continuing to investigate. Among the studies reviewed, CRP was the most common biomarker investigated, while the other immune biomarkers have received less research attention. The small number of studies for several of the biomarkers limited our ability to form conclusions about the consistency of results for each outcome, particularly in light of the variation in study designs and measures.

The less than definitive results of this review point towards three possible conclusions: (a) adversity is not related to immune alterations related to CVD risk in a manner that can be reliably detected in childhood or adolescence; (b) adversity is related to at least some immune alterations that can be reliably detected in children and adolescents, however these associations are difficult to detect in the current literature due to methodological issues in existing studies; or, (c) adversity is related to immunologic dysfunction in youth, but this dysfunction is reflected by immune parameters other than the ones considered in the present review. Additional research is needed to discern which of these possibilities is correct. Based on our review, we offer recommendations for future research that will help distinguish whether there are immunologic alterations related to adversity and subsequent CVD risk that can be reliably detected in childhood. We discuss issues related to (1) study design and sample, (2) definition and measurement of adversity, (3) statistical analysis, and (4) outcomes.

4.1. Study design and sample

Only a minority of studies in this review had a longitudinal design with multiple waves of follow-up. The majority of studies used a cross-sectional design; in this design it is not possible to directly assess whether exposure to adversity actually causes change in immunologic functioning, the fundamental hypothesis of this research. While concerns about reverse causality are not high (it is unlikely that dysregulated immune functioning leads to childhood adversity), it is possible that adversity does not influence dysregulated immune functioning but rather there is a third underlying factor driving both childhood adversity and immune dysregulation (e.g., poor parental health). To address this concern, future research should examine change in adversity in relation to changes in immune biomarkers over time; this design allows for a temporal assessment of the hypothesized relationship between the exposure and the outcome, and can decrease bias in non-randomized studies by reducing variability caused by stable individual traits since the comparisons are within individuals (Raudenbush, 2001). It may also be valuable to evaluate trajectories of immune biomarker levels within a randomized control design that includes an intervention to address some form of childhood adversity. For example, researchers have shown that interventions for foster parents can improve their ability to regulate the level of stress in their child (Fisher et al., 2006). In one randomized trial of a family-based therapeutic intervention, diurnal cortisol activity among foster children (ages 3–6 years) in the intervention condition became less dysregulated and more similar to the comparison group over the 12 months of the study (Fisher et al., 2007).

There was large variation in the sample sizes across the studies, and it is possible that some of the inconsistency in the existing literature can be attributed to inadequate statistical power. Due to the limited amount of previous research and knowledge about expected effect sizes, there are no established guidelines for optimal sample sizes in this field of research. According to Cohen (1992), a multiple regression analysis with conventional levels of alpha (0.05) and beta (0.20), a small effect size ($d = 0.02$) and three control covariates would require a sample of 599 individuals. On this basis, more than half studies in the present review were not powered to detect associations if the effect sizes were small. Also related to sample design, we recommend that researchers continue to investigate the relationship between adversity and immune function across the spectrum of child and adolescent ages; it is important to include children and adolescents at varying stages of maturation (e.g., especially pre- and post-puberty), in order to observe whether associations are present at some periods of development, but not others.

4.2. Measurement and definition of adversity

In the present review, we defined adversity broadly, and included any type of stressful experience or material hardship that is not considered to be a normative part of child development. The identified studies included a wide range of stressors, the most common being family SES, stressful life events, and chronic interpersonal stress. There was also substantial variation in how the different stressors were measured, with some studies using dichotomous indicators (to reflect high or low SES, or discrete

Table 2
Summary of findings.

Biomarker	Number of studies that included marker	% of those (*N*) studies that found significantly higher level associated with adversity		% of those (*N*) studies that found mixed results[a]		% of those (*N*) studies that found conditional associations		% of those (*N*) studies that found null associations	
CRP	11	27.27	(3)	18.18	(2)	27.27	(3)	27.27	(3)
Cytokines	5	60.00	(3)	20.00	(1)	20.00	(1)	0.00	(0)
Fibrinogen	4	25.00	(1)	0.00	(0)	25.00	(1)	50.00	(2)
Natural killer cells	2	0.00	(0)	100.00	(2)	0.00	(0)	0.00	(0)
Immune control of CMV	2	50.00	(1)	50.00	(1)	0.00	(0)	0.00	(0)

[a] "Mixed" refers to inconsistent results across multiple measures of adversity.

interpersonal events), while other studies used multiple-item scales, or inventories to assess cumulative adversity. Variation in the types of adversities based on chronicity and severity, combined with differences in the specific measures that were used, likely contributed to the inconsistent findings. The current review did not suggest that acute stressors are more strongly related with changes in immunologic functioning than chronic stressors, or vice versa, but this may be due in part to the fact that few studies considered the effects of acute stressors or compared effects of acute and chronic stressors directly. Given the potential implications of this information from both a mechanistic and intervention standpoint, future studies should examine this issue directly. It will also be useful to further investigate how acute and chronic adversities combine to affect immune processes; although several studies in our review examined interactions between acute and chronic forms of adversity (Marin et al., 2007), more research is needed to characterize the nature of these relationships.

The majority of studies in the review considered stressors for which severity level was unspecified. Given that many studies used SES as a proxy measure for adversity, it is likely that exposure to adversity ranged broadly across these studies from relatively minor to more substantial. However, we were generally unable to determine which studies were capturing a more versus less severe adversity experience. In one study that examined physical maltreatment as the exposure this was more easily assessed, and this study found a positive association with CRP (Danese et al., 2011). Further support of the relevance of severity may be provided by findings from another study which found that poverty, but not a continuous measure of household income, was associated with elevated concentration of CRP among youth (Dowd et al., 2010) Thus, our review suggests that the severity of the adversity may be important. Research is needed to establish whether there is some kind of threshold effect such that adversity influences immunologic dysregulation in a more consistent manner at severe levels but not at lesser levels. Finally, it will be important for future studies to clarify the expected temporal relationship between adverse exposure and outcomes (i.e., the "incubation period" (Miller et al., 2009c)). For example, how soon after an adverse event can we expect to observe a change in biological functioning, and will this change persist for a limited time, or indefinitely? Longitudinal studies with multiple waves will be required to address this issue.

4.3. Statistical analysis

Our review also highlighted a high degree of variability in the potential confounders that were included in each study, and in consideration of potential effect modifiers of the association. Such heterogeneity makes it difficult to compare findings across studies. For increased comparability between studies and an improved understanding of the relationship between adversity and CVD-related immune functioning in youth, researchers will need to adjust for a consistent set of potential confounders and consider relevant effect modifiers. Thus, we first recommend that researchers develop guidelines for standard control variables to be used in research on adversity and immune functioning in youth (e.g., age, race, gender, medications); for now, researchers can adapt guidelines that have been developed for adult populations (O'Connor et al., 2009) Based on the existing literature, we also recommend that at a minimum, researchers test and report interactions between adversity and sex and psychological functioning, and consider other relevant theoretically-identified characteristics (e.g., age as a potential effect modifier in a study of parental divorce on immunologic markers). If moderating factors exist and are not accounted for, true associations that are specific to a subset of the sample may be obscured (Fitzmaurice, 2000). In the present review, several studies provided evidence that the association between adversity and biological functioning varied based on an individual characteristic (i.e., sex (Howe et al., 2010; Thomas et al., 2005), mental health (Danese et al., 2011)); however, not all studies found evidence of effect modification, and many simply did not test the possibility. Related, in studies that have samples with a wide range of ages, researchers should test for interactions between adversity and pre- and post-pubertal age, in the case the relationships of interest vary depending on stage of physical development. This will allow researchers to determine whether there are sensitive periods when effects of adversities may be particularly potent.

4.4. Immune biomarkers of CVD risk

Our search identified studies that examined adversity in relation to CRP, pro-inflammatory cytokines, fibrinogen, natural killer cells, and markers of immune control of viruses. It is a priority to establish which of these immune biomarkers measured in childhood and adolescence are in fact related to long-term risk for CVD in adulthood. One challenge for addressing this is the need for prospective data on individuals followed over many decades. Some research has investigated the value of CRP measured in childhood or adolescence for predicting other risk factors for CVD in youth (da Silva et al., 2010; Guran et al., 2007). We are not aware of similar research for any of the other biomarkers, but this might be an alternative approach to assessing these relationships when longitudinal data are not available. If child or adolescent measures of these immune parameters are confirmed as valuable markers of health, risk-thresholds may be developed for use by clinicians, as well as researchers. Clinical risk thresholds will improve the interpretability and practical implications of research in this area.

Another challenge for researchers studying inflammation and other immune activity in childhood is that because injury and infections are frequent occurrences among children, acute elevations in immune markers are common and may not be indicative of, and in fact may obscure ability to detect the presence of, low grade chronic inflammation. However, a number of techniques may be used to address this concern. For example, researchers may ask about recent infection (Caserta et al., 2008) and control for this or exclude anyone with relevant history of infection from the analysis. Investigations can also exclude individuals whose inflammation levels are suspected to be indicative of infection when relevant cut-points for those markers are available (e.g., CRP > 10 mg/L) (Jaye and Waites, 1997). Another approach is to assess and control for body temperature in order to account for the potential effect of unrecognized injury or infection (Danese et al., 2011).

Several immune biomarkers of CVD risk that have been examined in adults in relation to stressors were not included in any of the studies identified for this review (e.g., soluble intercellular adhesion molecule-1, monocyte chemoattractant protein-1 (Albert et al., 2006; Loucks et al., 2006)). New research in youth populations may reveal other immune biomarkers that are more directly affected by adverse experiences. Progress in this research area may occur through the consideration of other immune parameters that can be measured with existing technology, development of techniques for measuring immunologic parameters that are not currently measurable, or through use of alternative methods of assessing known biomarkers (e.g., laboratory manipulations of established immune biomarkers, such as exposure to a microbial challenge). For example, two studies included in this review found that harsh family climate was significantly related to cytokine response to lipopolysaccharide exposure (a bacterial stimulus) but not with ongoing inflammatory activity (i.e., circulating levels of IL-6) under normal conditions (Miller and Chen, 2010; Miller et al., 2009c) This work suggests that among young healthy individuals, exposure to adversity may initially amplify the inflammatory

response to exogenous immunologic stimuli but not alter basal levels of inflammation. However, over time, repeated hyperinflammatory responses may lead to chronically-elevated levels of inflammation.

An emerging field of research has begun to examine more integrated models of how psychosocial factors influence the development and progression of disease, moving beyond the assessment of individual biomarkers (Miller et al., 2009a). These models posit that social stress induces epigenetic changes in neurobiological signaling systems involved in regulating inflammation (Miller et al., 2009a). It is these epigenetic changes that lead to the changes in gene expression that increase susceptibility to cardiovascular (and other) diseases. Thus, the long-term impact of childhood adversity is posited to occur through early biological programming of adult health.

Only a handful of studies have examined interactions between the social environment and molecules that regulate inflammatory processes (Cole et al., 2010, 2011; Marin et al., 2007; Miller and Chen, 2007, 2010; Miller et al., 2009c). For example, in a cohort of female adolescents, Miller and Chen (2007) examined associations of SES at various times in childhood and adolescence with expression of genes that code for the glucocorticoid receptor (GR) and toll-like receptor 4 (TLR4), which regulate inflammation. They found that current SES (at the time of blood collection) did not predict gene expression patterns; however, individuals from lower socioeconomic conditions during years 2 and 3 of life had reduced expression of GR and increased expression of TLR4, a pattern which suggests poorer regulation of inflammatory responses. In another study, Miller et al. (2009c) followed 103 healthy female adolescents over 6 months, and found that chronic interpersonal stress was associated with greater expression of pro-inflammatory molecules (GR-β, nuclear factor-κB) and of inhibitor of κB, a molecule whose activation facilitates pro-inflammatory signaling. These findings are further complemented by research which demonstrated an interaction between adverse socioenvironmental conditions and a genetic polymorphism in the IL-6 promoter among adolescents (Cole et al., 2011); one form of the gene appeared to be protective with lower levels of inflammation (measured by CRP) evident as compared with other forms of the gene, in the context of greater social adversity. Taken together, these studies suggest that considering interactions between the social environment and genes that regulate inflammatory processes may enhance our understanding how early life experiences are embedded to affect immune system regulation and health decades later.

5. Conclusions

The present review systematically examined published research on the relationship between adversity and immune processes in youth that may be related to the likelihood of developing CVD in adulthood. Although we found tremendous variation across the empirical studies in this area, we did identify a positive trend in the findings suggesting that this is a promising avenue for research. Moreover, this review clearly points to important methodological and substantive considerations that will strengthen future studies and facilitate greater comparability among them. Such recommendations are based on the existing literature and thus must be considered in light of several limitations of the existing literature. One limitation is the potential for publication bias towards positive results, which may have led to over-representation of studies with significant associations. Second, the quality of the identified studies varied (e.g., sample selection criteria, measures of adversity, etc.), which may account for some of the variability in the results that are observed. Third, there were few studies for some of the biomarkers that were considered, and it was not possible to assess our findings according to type of adverse exposure.

Also important to note is that given the broad range of types of adversities that were assessed in this review, it is likely that there are substantive differences in how various forms of adversity operate to affect immune and inflammatory markers. However, because pathways were rarely evaluated in the studies included here, we could not evaluate these potential differences. For example, the association between elevated levels of immune biomarkers and low SES could result in part from greater exposure to second-hand cigarette smoke and higher incidence of acute illness. In contrast, psychosocial stress reactions may play a stronger role in the relation between elevated levels of immune biomarkers and acute life events. Future research will be informed by more explicit consideration of the mechanisms by which adversity influences immune and inflammatory dysregulation. Research in this area will also be greatly enhanced by definitive evidence to support which biomarkers measured in childhood or adolescence have the strongest causal or predictive relevance to cardiovascular outcomes in adulthood.

Our findings should be interpreted in light of the constraints we imposed on the present review. For example, we restricted the scope of our review to studies of healthy youth populations, therefore our conclusions may not generalize to youth populations with chronic health conditions, such as samples of children with asthma, which has been a focus for a substantial portion of the research on this topic (Kang et al., 1998; Marin et al., 2009; Miller et al., 2009b; Wolf et al., 2008). In addition, this review considered only studies that assessed social adversities (i.e., those assessed by measuring aspects of the social environment or social experiences), and did not include studies with adversities defined by compromised physiological health (e.g., under-nutrition, infectious disease). Of note, physiological adversity, which can impact immune function in childhood, may also be a consequence of social adversity and therefore may be a worthy topic for a separate review.

In summary, to advance knowledge about the biological consequences of adversity among youth, we recommend that future research should: (1) utilize adequately-powered multi-wave longitudinal samples to assess change within individuals; (2) examine whether associations are limited to the most severe and/or chronic forms of adversity; (3) explore individual and contextual variables that may affect the strength of potential associations; (4) develop clinically-relevant risk-thresholds for immune-related biomarkers that can be used in both research and clinical settings; and (5) explore alternative biomarkers that may be more directly associated with adverse experiences among youth. This work holds promise for addressing gaps in the literature regarding the mechanisms that link early life adversity to CVD in adulthood, and developing strategies for early targeted prevention and intervention strategies to reduce risk for CVD over the life course.

6. Funding

This work was supported by a postdoctoral fellowship to the first author from the Robert Wood Johnson Foundation to support research on early adversity and biomarkers of risk over the life course.

Acknowledgements

The authors thank Allison Aiello, PhD, Michelle Albert, MD, MPH, Stephen Gilman, ScD, and members of the Biomarkers Working Group at the Center on the Developing Child at Harvard University for their assistance conceptualizing the review. The authors also thank Carol Mita for her assistance in conducting the literature search.

References

Aiello, A.E., Kaplan, G.A., 2009. Socioeconomic position and inflammatory and immune biomarkers of cardiovascular disease: applications to the panel study of income dynamics. Biodemogr. Soc. Biol. 55, 178–205.

Albert, M.A., Glynn, R.J., Buring, J., Ridker, P.M., 2006. Impact of traditional and novel risk factors on the relationship between socioeconomic status and incident cardiovascular events. Circulation 114, 2619–2626.

Ben-Shlomo, Y., Kuh, D., 2002. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int. J. Epidemiol. 31, 285–293.

Birmaher, B., Rabin, B.S., Garcia, M.R., Jain, U., Whiteside, T.L., Williamson, D.E., Alshabbout, M., Nelson, B.C., Dahl, R.E., Ryan, N.D., 1994. Cellular immunity in depressed, conduct disorder, and normal adolescents – role of adverse life events. J. Am. Acad. Child Adolesc. Psychiatry 33, 671–678.

Black, P.H., 2003. The inflammatory response is an integral part of the stress response: implications for atherosclerosis, insulin resistance, type II diabetes and metabolic syndrome X. Brain Behav. Immun. 17, 350–364.

Black, P.H., Garbutt, L.D., 2002. Stress, inflammation and cardiovascular disease. J. Psychosom. Res. 52, 1–23.

Brunner, E., Davey Smith, G., Marmot, M., Canner, R., Beksinska, M., O'Brien, J., 1996. Childhood social circumstances and psychosocial and behavioural factors as determinants of plasma fibrinogen. Lancet 347, 1008–1013.

Caserta, M.T., O'Connor, T.G., Wyman, P.A., Wang, H., Moynihan, J., Cross, W., Tu, X., Jin, X., 2008. The associations between psychosocial stress and the frequency of illness, and innate and adaptive immune function in children. Brain Behav. Immun. 22, 933–940.

Cohen, J., 1992. A power primer. Psychol. Bull. 112, 155–159.

Cole, S.W., Arevalo, J.M.G., Takahashi, R., Sloan, E.K., Lutgendorf, S.K., Sood, A.K., Sheridan, J.F., Seeman, T.E., 2010. Computational identification of gene-social environment interaction at the human IL6 locus. Proc. Natl. Acad. Sci. USA 107, 5681–5686.

Cole, S.W., Arevalo, J.M.G., Manu, K., Telzer, E.H., Kiang, L., Bower, J.E., Irwin, M.R., Fuligni, A.J., 2011. Antagonistic pleiotropy at the human IL6 promoter confers genetic resilience to the pro-inflammatory effects of adverse social conditions in adolescence. Dev. Psychol. 47, 1173–1180.

Cook, D.G., Whincup, P.H., Miller, G., Carey, I.M., Adshead, F.J., Papacosta, O., Walker, M., Howarth, D., 1999. Fibrinogen and factor VII levels are related to adiposity but not to fetal growth or social class in children aged 10–11 years. Am. J. Epidemiol. 150, 727–736.

Cook, D.G., Mendall, M.A., Whincup, P.H., Carey, I.M., Ballam, L., Morris, J.E., Miller, G.J., Strachan, D.P., 2000. C-reactive protein concentration in children: relationship to adiposity and other cardiovascular risk factors. Atherosclerosis 149, 139–150.

da Silva, I.T., Sanches, L.B., Mello, A.P.D., Damasceno, N.R.T., 2010. Impact of C-reactive protein on cardiovascular risk in adolescents. Arq. Bras. Cardiol. 94, 585–591.

Danese, A., Pariante, C.M., Caspi, A., Taylor, A., Poulton, R., 2007. Childhood maltreatment predicts adult inflammation in a life-course study. Proc. Natl. Acad. Sci. USA 104, 1319–1324.

Danese, A., Caspi, A., Williams, B., Ambler, A., Sugden, K., Mika, J., Werts, H., Freeman, J., Pariante, C.M., Moffitt, T.E., Arseneault, L., 2011. Biological embedding of stress through inflammation processes in childhood. Mol. Psychiatry 16, 244–246.

Danesh, J., Collins, R., Appleby, P., Peto, R., 1998. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 279, 1477–1482.

Dixon, D., Meng, H., Goldberg, R., Schneiderman, N., Delamater, A., 2009. Stress and body mass index each contributes independently to tumor necrosis factor-[alpha] production in prepubescent latino children. J. Pediatr. Nurs. 24, 378–388.

Dowd, J.B., Zajacova, A., Aiello, A.E., 2010. Predictors of inflammation in U.S. children aged 3–16 years. Am. J. Prev. Med. 39, 314–320.

Dowd, J.B., Palmero, T.M., Aiello, A. E., in press. Family poverty is associated with cytomegalovirus antibody titers in US children. Health Psychol., doi:10.1037/a0025337.

Felitti, V.J., Anda, R.F., Nordenberg, D., Williamson, D.F., Spitz, A.M., Edwards, V., Koss, M.P., Marks, J.S., 1998. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am. J. Prev. Med. 14, 245–258.

Fisher, P.A., Gunnar, M.R., Dozier, M., Bruce, J., Pears, K.C., 2006. Effects of therapeutic interventions for foster children on behavioral problems, caregiver attachment, and stress regulatory neural systems. In: Lester, B.M., Masten, A.S., McEwen, B. (Eds.), Resilience in Children, pp. 215–225.

Fisher, P.A., Stoolmiller, M., Gunnar, M.R., Burraston, B.O., 2007. Effects of a therapeutic intervention for foster preschoolers on diurnal cortisol activity. Psychoneuroendocrinology 32, 892–905.

Fitzmaurice, G., 2000. The meaning and interpretation of interaction. Nutrition 16, 313–314.

Ford, E.S., 2003. C-reactive protein concentration and cardiovascular disease risk factors in children – findings from the National Health and Nutrition Examination Survey 1999–2000. Circulation 108, 1053–1058.

Fuligni, A.J., Telzer, E.H., Bower, J., Cole, S.W., Kiang, L., Irwin, M.R., 2009. A preliminary study of daily interpersonal stress and C-reactive protein levels among adolescents from Latin American and European backgrounds. Psychosom. Med. 71, 329–333.

Galkina, E., Ley, K., 2009. Immune and inflammatory mechanisms of atherosclerosis. Annu. Rev. Immunol. 27, 165–197.

Galobardes, B., Lynch, J.W., Davey Smith, G., 2004. Childhood socioeconomic circumstances and cause-specific mortality in adulthood: systematic review and interpretation. Epidemiol. Rev. 26, 7–21.

Galobardes, B., Smith, G.D., Lynch, J.W., 2006. Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. Ann. Epidemiol. 16, 91–104.

Gazlano, T.A., 2007. Reducing the growing burden of cardiovascular disease in the developing world. Health Aff. 26, 13–24.

Gimeno, D., Ferrie, J.E., Elovainio, M., Pulkki-Raback, L., Keltikangas-Jarvinen, L., Eklund, C., Hurme, M., Lehtimaki, T., Marniemi, J., Viikari, J.S.A., Raitakari, O.T., Kivimaki, M., 2008. When do social inequalities in C-reactive protein start? A life course perspective from conception to adulthood in the Cardiovascular Risk in Young Finns Study. Int. J. Epidemiol. 37, 290–298.

Goodman, E., McEwen, B.S., Huang, B., Dolan, L.M., Adler, N.E., 2005. Social inequalities in biomarkers of cardiovascular risk in adolescence. Psychosom. Med. 67, 9–15.

Graham, J.E., Christian, L.M., Kiecolt-Glaser, J.K., 2006. Stress, age, and immune function: toward a lifespan approach. J. Behav. Med. 29, 389–400.

Gunnar, M., Quevedo, K., 2007. The neurobiology of stress and development. Annu. Rev. Psychol. 58, 145–173.

Guran, O., Akalin, F., Ayabakan, C., Dereli, F.Y., Haklar, G., 2007. High-sensitivity C-reactive protein in children at risk for coronary artery disease. Acta Paediatr. 96, 1214–1219.

Hansson, G.r.K., 2005. Inflammation, atherosclerosis, and coronary artery disease. N. Engl. J. Med. 352, 1685–1695.

Hansson, G.K., Hermansson, A., 2011. The immune system in atherosclerosis. Nat. Immunol. 12, 204–212.

Herberth, G., Weber, A., Roder, S., Elvers, H.D., Kramer, U., Schins, R.P.F., Diez, U., Borte, M., Heinrich, J., Schafer, T., Herbarth, O., Lehmann, I., Grp, L.I.S., 2008. Relation between stressful life events, neuropeptides and cytokines: results from the LISA birth cohort study. Pediatr. Allergy Immunol. 19, 722–729.

Howe, L.D., Galobardes, B., Sattar, N., Hingorani, A.D., Deanfield, J., Ness, A.R., Davey-Smith, G., Lawlor, D.A., 2010. Are there socioeconomic inequalities in cardiovascular risk factors in childhood, and are they mediated by adiposity? Findings from a prospective cohort study. Int. J. Obes. 34, 1149–1159.

Jarvisalo, M.J., Harmoinen, A., Hakanen, M., Paakunainen, U., Viikari, J., Hartiala, J., Lehtimaki, T., Simell, O., Raitakari, O.T., 2002. Elevated serum C-reactive protein levels and early arterial changes in healthy children. Arterioscler. Thromb. Vasc. Biol. 22, 1323–1328.

Jaye, D.L., Waites, K.B., 1997. Clinical applications of C-reactive protein in pediatrics. Pediatr. Infect. Dis. J. 16, 735–747.

Juonala, M., Viikari, J.S.A., Ronnemaa, T., Taittonen, L., Marniemi, J., Raitakari, O.T., 2006. Childhood C-reactive protein in predicting CRP and carotid intima-media thickness in adulthood - The Cardiovascular Risk in Young Finns Study. Arterioscler. Thromb. Vasc. Biol. 26, 1883–1888.

Kang, D.H., Coe, C.L., Karaszewski, J., McCarthy, D.O., 1998. Relationship of social support to stress responses and immune function in healthy and asthmatic adolescents. Res. Nurs. Health 21, 117–128.

Kavey, R.E.W., Daniels, S.R., Lauer, R.M., Atkins, D.L., Hayman, L.L., Taubert, K., 2003. American heart association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. Circulation 107, 1562–1566.

Kubzansky, L.D., Adler, G.K., 2010. Aldosterone: A forgotten mediator of the relationship between psychological stress and heart disease. Neurosci. Biobehav. Rev. 34, 80–86.

Kung, H.C., Hoyert, D.L., Xu, J., Murphy, S.L., 2008. Deaths: Final Data for 2005 (National Vital Statistics Reports 56). National Center for Health Statistics, Hyattsville, MD.

Loman, M.M., Gunnar, M.R., 2010. Early experience and the development of stress reactivity and regulation in children. Neurosci. Biobehav. Rev. 34, 867–876.

Loucks, E.B., Sullivan, L.M., Hayes, L.J., D'Agostino Sr., R.B., Larson, M.G., Vasan, R.S., Benjamin, E.J., Berkman, L.F., 2006. Association of educational level with inflammatory markers in the Framingham Offspring Study. Am. J. Epidemiol. 163, 622–628.

Marin, T.J., Martin, T.M., Blackwell, E., Stetler, C., Miller, G.E., 2007. Differentiating the impact of episodic and chronic stressors on hypothalamic-pituitary-adrenocortical axis regulation in young women. Health Psychol. 26, 447–455.

Marin, T.J., Chen, E., Munch, J.A., Miller, G.E., 2009. Double-exposure to acute stress and chronic family stress is associated with immune changes in children with asthma. Psychosom. Med. 71, 378–384.

McCrory, E., De Brito, S.A., Viding, E., 2010. Research review: the neurobiology and genetics of maltreatment and adversity. J. Child Psychol. Psychiatry 51, 1079–1095.

McDade, T.W., Leonard, W.R., Burhop, J., Reyes-Garcia, V., Vadez, V., Huanca, T., Godoy, R.A., 2005. Predictors of C-reactive protein in Tsimane' 2 to 15 year-olds in lowland Bolivia. Am. J. Phys. Anthropol. 128, 906–913.

McEwen, B.S., 1998. Protective and damaging effects of stress mediators. N. Engl. J. Med. 338, 171–179.

McEwen, B.S., 2007. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol. Rev. 87, 873–904.

Miller, G., Chen, E., 2007. Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolescence. Psychosom. Med. 69, 402–409.

Miller, G.E., Chen, E., 2010. Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. Psychol. Sci. 21, 848–856.
Miller, G., Chen, E., Cole, S.W., 2009a. Health psychology: developing biologically plausible models linking the social world and physical health. Annu. Rev. Psychol. 60, 501–524.
Miller, G.E., Gaudin, A., Zysk, E., Chen, E., 2009b. Parental support and cytokine activity in childhood asthma: the role of glucocorticoid sensitivity. J. Allergy Clin. Immunol. 123, 824–830.
Miller, G.E., Rohleder, N., Cole, S.W., 2009c. Chronic interpersonal stress predicts activation of pro- and anti-inflammatory signaling pathways 6 months later. Psychosom. Med. 71, 57–62.
Morley, R., Harland, P., Law, C.M., Lucas, A., 2000. Birthweight and social deprivation: influences on serum lipids and fibrinogen. Acta Paediatr. 89, 703–707.
Murasko, J.E., 2008. Male-female differences in the association between socioeconomic status and atherosclerotic risk in adolescents. Soc. Sci. Med. 67, 1889–1897.
O'Connor, M.F., Bower, J.E., Cho, H.J., Creswell, J.D., Dimitrov, S., Hamby, M.E., Hoyt, M.A., Martin, J.L., Robles, T.F., Sloan, E.K., Thomas, K.S., Irwin, M.R., 2009. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. Brain Behav. Immun. 23, 887–897.
Pearson, T.A., Mensah, G.A., Alexander, R.W., Anderson, J.L., Cannon, R.O., Criqui, M., Fadl, Y.Y., Fortmann, S.P., Hong, Y., Myers, G.L., Rifai, N., Smith, S.C., Taubert, K., Tracy, R.P., Vinicor, F., 2003. Markers of inflammation and cardiovascular disease application to clinical and public health practice – a statement for healthcare professionals from the centers for disease control and prevention and the American Heart Association. Circulation 107, 499–511.
Pollitt, R.A., Rose, K.M., Kaufman, J.S., 2005. Evaluating the evidence for models of life course socioeconomic factors and cardiovascular outcomes: a systematic review. BMC Public Health 5, 7.
Pollitt, R.A., Kaufman, J.S., Rose, K.M., Diez-Roux, A.V., Zeng, D., Heiss, G., 2008. Cumulative life course and adult socioeconomic status and markers of inflammation in adulthood. J. Epidemiol. Community Health 62, 484–491.
Raudenbush, S.W., 2001. Comparing personal trajectories and drawing causal inferences from longitudinal data. Annu. Rev. Psychol. 52, 501–525.
Ridker, P.M., Rifai, N., Rose, L., Buring, J.E., Cook, N.R., 2002. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N. Engl. J. Med. 347, 1557–1565.
Shonkoff, J.P., Boyce, W.T., McEwen, B.S., 2009. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. JAMA 301, 2252–2259.
Slopen, N., Lewis, T.T., Gruenewald, T.L., Mujahid, M.S., Ryff, C.D., Albert, M.A., Williams, D.R., 2010. Early life adversity and inflammation in African Americans and Whites in the midlife in the United States Survey. Psychosom. Med. 72, 694–701.
Sorlie, P.D., Nieto, F.J., Adam, E., Folsom, A.R., Shahar, E., Massing, M., 2000. A prospective study of cytomegalovirus, herpes simplex virus 1, and coronary heart disease – The Atherosclerosis Risk in Communities (ARIC) Study. Arch. Intern. Med. 160, 2027–2032.
Stassen, F.R., Vega-Córdova, X., Vliegen, I., Bruggeman, C.A., 2006. Immune activation following cytomegalovirus infection: more important than direct viral effects in cardiovascular disease? J. Clin. Virol. 35, 349–353.
Steene-Johannessen, J., Kolle, E., Reseland, J.E., Anderssen, S.A., Andersen, L.B., 2010. Waist circumference is related to low-grade inflammation in youth. Int. J. Pediatr. Obes. 5, 313–319.
Steptoe, A., Hamer, M., Chida, Y., 2007. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. Brain Behav. Immun. 21, 901–912.
Taylor, S.E., 2010. Mechanisms linking early life stress to adult health outcomes. Proc. Natl. Acad. Sci. 107, 8507–8512.
Taylor, S.E., Lerner, J.S., Sage, R.M., Lehman, B.J., Seeman, T.E., 2004. Early environment, emotions, responses to stress, and health. J. Pers. 72, 1365–1393.
Taylor, S.E., Lehman, B.J., Kiefe, C.I., Seeman, T.E., 2006. Relationship of early life stress and psychological functioning to adult C-reactive protein in the coronary artery risk development in young adults study. Biol. Psychiatry 60, 819–824.
Thomas, N.-E., Cooper, S.-M., Williams, S.R.P., Baker, J.S., Davies, B., 2005. Fibrinogen, homocyst(e)ine, and C-reactive protein concentrations relative to sex and socioeconomic status in British young people. Am. J. Hum. Biol. 17, 809–813.
Whitman, S.C., Ramsamy, T.A., 2006. Participatory role of natural killer and natural killer T cells in atherosclerosis: lessons learned from in vivo mouse studies. Can. J. Physiol. Pharmacol. 84, 67–75.
Wolf, J.M., Miller, G.E., Chen, E., 2008. Parent psychological states predict changes in inflammatory markers in children with asthma and healthy children. Brain Behav. Immun. 22, 433–441.
Zhu, J.H., Nieto, F.J., Horne, B.D., Anderson, J.L., Muhlestein, J.B., Epstein, S.E., 2001. Prospective study of pathogen burden and risk of myocardial infarction or death. Circulation 103, 45–51.