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## The Role of Adverse Childhood Experiences in Cardiovascular Disease Risk: a Review with Emphasis on Plausible Mechanisms

Shaoyong Su<sup>1</sup>, Marcia P. Jimenez<sup>2</sup>, Cole T. F. Roberts<sup>2</sup>, and Eric B. Loucks<sup>2</sup>

<sup>1</sup> Georgia Prevention Institute, Medical College of Georgia, Georgia Regents University, 1120 15th Street, HS 1721, Augusta, GA 30912, USA

<sup>2</sup> Department of Epidemiology, Brown University School of Public Health, Providence, RI, USA

### Abstract

Childhood adversity, characterized by abuse, neglect, and household dysfunction, is a problem that exerts a significant impact on individuals, families, and society. Growing evidence suggests that adverse childhood experiences (ACEs) are associated with health decline in adulthood, including cardiovascular disease (CVD). In the current review, we first provide an overview of the association between ACEs and CVD risk, with updates on the latest epidemiological evidence. Second, we briefly review plausible pathways by which ACEs could influence CVD risk, including traditional risk factors and novel mechanisms. Finally, we highlight the potential implications of ACEs in clinical and public health. Information gleaned from this review should help physicians and researchers in better understanding potential long-term consequences of ACEs and considering adapting current strategies in treatment or intervention for patients with ACEs.

### Keywords

Adverse childhood experiences; Childhood maltreatment; Cardiovascular disease; Risky behaviors; Depression; Intervention

### Introduction

Despite significant advances in treatment and secondary prevention over the past decades, cardiovascular disease (CVD) remains the major cause of mortality and morbidity for both men and women in the USA and worldwide [1]. Total direct and indirect costs of CVD are projected to increase from \$579 billion in 2012 to \$1.2 trillion in 2030. There is increasing evidence that early life factors may contribute to the development of CVD, such as findings

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Shaoyong Su, ssu@gru.edu.

Marcia P. Jimenez, marcia\_pescador\_jimenez@brown.edu

Cole T. F. Roberts, cole\_roberts@brown.edu

Eric B. Loucks, eric.loucks@brown.edu

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of early atherosclerotic lesions in adolescents and young adults [2], development of CVD risk factors such as obesity, blood pressure, and cholesterol in infants and children [3], and evidence that early life markers such as birth weight and childhood socioeconomic status (SES) may be risk markers for CVD [3]. As a critical developmental phase, environmental exposures in early life may have crucial impacts on adolescent and adult health [4]. Some compelling data have come from studies of children who grew up in poverty and show heightened vulnerability to negative health outcomes including CVD in adulthood [5]. However, low childhood SES is only one marker of early life stress and may not fully represent the psychosocial stress during childhood [6]. Emerging evidence now ties adverse childhood experiences (ACEs), characterized by multiple harsh conditions within the family, to adult health risks [7]. Understanding the burdens associated with ACEs and identifying their long-term effects on health are of grave importance in promoting cardiovascular health and reducing health care costs across the life course.

According to the World Health Organization (WHO), ACEs refer to some of the most intensive and frequently occurring sources of stress that children may suffer early in life [8]. Such experiences include abuse (physical, emotional, and sexual), neglect (emotional and physical), and household dysfunction (e.g., parental mental health and substance abuse problems, violence between parents or caregivers, having an incarcerated family member, and parental marital discord). The prevalence of ACEs is high among the US population. A nationally representative telephone health survey collected information on ACEs between 2009 and 2011 on 84,786 adult respondents, with the majority (58.5 %) reporting at least one ACE and 11.6 % reporting 5 ACEs [9]. Similarly, another national survey of children's exposure to violence in 2011 reported that 57.7 % of children and youth (aged 1 month to 17 years) experienced at least one ACE in the year prior to survey [10]. Of note, ACEs are interrelated rather than occurring independently. Exposure to one type of ACE increased the likelihood that a child or youth had exposures to other types as well. For example, Dong et al. reported that the prevalence of reporting physical abuse was 80.5 % among persons who reported emotional abuse compared to 20.1 % among persons who had not (with adjusted odds ratio of 17.7) [11]. A graded relationship between ACEs and negative health outcomes has also been reported. For example, the greater the number and severity of childhood adversities, the higher the likelihood of reported ischemic heart disease [12].

Growing evidence suggests that early adverse experiences can disrupt normal psychosocial development and increase vulnerability to a broad range of behavioral, mental, and physical health problems, which in turn leads to a higher risk of CVD. For example, it has been shown that exposure to repeated severe (e.g., abuse) and chronic (e.g., conflict between parents) stressful events in early life can result in abnormal behaviors in children and adolescents, who may try to reduce tension or stress through avoidant, self-medicating (e.g., smoking or alcohol abuse), compulsive (e.g., overeating), and/or self-injurious behaviors [13–15]. Traumatic experiences in childhood can also affect emotional and psychological development, increasing vulnerability to mental health problems such as major depression and posttraumatic stress disorder (PTSD) [16]. Moreover, emerging data suggest that adversity in early life is able to alter biological functioning in stress regulatory pathways, leading to long-lasting altered stress responsivity in adulthood [17]. Of note, these pathways influence each other rather than working independently. Indeed, they may form a complex

matrix of interrelationships and together contribute to the susceptibility to CVD. Given the long-term effect of ACEs, a lack of recognizing and addressing patient's poor psychosocial circumstances in early life may increase chances of unsuccessful treatments or interventions for CVD risk. For example, in a follow-up study of morbidly obese individuals who had lost >100 lb, Felitti and colleagues found that participants with a history of major childhood emotional trauma and household dysfunction were more likely to regain their weight within 18 months compared to those without exposure to ACEs [18]. Many of these patients considered “being obese” as a solution rather than a problem, keeping them safe from further harm [19]. A second example is a recent study showing lower statin medication adherence in male participants that experienced ACEs [20]. Lower medication adherence could, in part, be due to a present-focused orientation that may emerge early in life where because of adverse experiences, a child learns to focus on present challenges, with an uncertain future [20]. These studies and others that followed illustrate the role of screening and early detection of ACEs in developing trauma-informed care.

In the current review, we first provide an overview of the association between ACEs and CVD risk, with updates on the latest epidemiological evidence. Second, we briefly review plausible pathways by which ACEs could influence CVD risk, including traditional risk factors and novel mechanisms. Finally, we highlight the potential implications of ACEs in clinical and public health. Information gleaned from this review should help physicians and researchers in better understanding potential long-term consequences of ACEs and considering adapting current strategies in treatment or intervention for patients with ACEs.

## ACEs and Adult CVD Risk

Many researchers have long been interested in connections between the heart and psychosocial stress, including impacts of traumatic experiences early in life [21]. Over the past decade, a number of retrospective and prospective studies have assessed associations between ACEs and CVD risk. A landmark study is the ACE Study, which enrolled over 17,000 adults through a large health maintenance organization (HMO) [22]. A dose–response relationship was observed between the number of ACE categories experienced and increased ischemic heart disease risk [12]. However, the ACE study was retrospective, limited by self-reported cardiac outcomes without medical record confirmation. A subsequent prospective population-based study in Finland found a significant linear trend between the number of ACEs and risk of incident and confirmed CVD cases in 23,916 participants during a mean follow-up of 6.9 years [23]. Further evidence from the Nurses’ Health Study (NHS) found associations between severe childhood maltreatment and early-onset CVD events in 66,798 women [24]. Most recently, a nationally representative telephone survey collected exposure information on ACEs from 53,998 adults in ten US states and District of Columbia and found that exposure to 4 ACEs was associated with a higher likelihood of CVD compared to those with no ACE exposure [7]. Two studies in different US cohorts (New England Family Study and CARDIA Study) demonstrated significant associations of childhood family psychosocial environment with 10-year coronary heart disease risk, calculated using the Framingham algorithm [25, 26]. Mediation analyses in the CARDIA Study by Loucks et al. suggested that mechanisms may include the potential negative impact of childhood family psychosocial environment on later-life

socioeconomic position (e.g., education in men and women) and/or psychosocial functioning (e.g., depression and anger-out expression in women), which may in turn lead to higher coronary heart disease (CHD) risk, particularly through smoking (in men and women) and lipids (in women) [25].

## Possible Pathways Linking ACEs and CVD Risk

### Behavioral Factors

**Smoking**—A broad range of studies have consistently shown associations between ACEs and higher risk of adult smoking, after adjusting for demographic variables [22, 27, 28, 29, 30]. Specific ACEs have been evaluated, and findings suggest that childhood abuse [31], childhood residential mobility [32, 33], childhood household dysfunction [34], and parental divorce [35] are associated with higher risk of adult smoking, and these associations are independent of SES measures such as education level and employment status.

One possible mechanism for associations of ACEs with smoking is that nicotine has demonstrable psychoactive benefits that could unconsciously help regulate stress in those exposed to ACEs. In fact, a study found that participants with smoking-related illness (such as CVD) who persist in smoking are more likely to report ACEs than participants with similar illnesses who quit smoking [36]. Other studies found that childhood adversity was associated with lower likelihood of quitting smoking for women but not men [37, 38]. The role of childhood adversity in determining smoking behavior may indicate a “sensitive period” during which intervention could lead to improvements in adult health, especially for women.

As smoking remains a major CVD risk factor and nearly 90 % of adult smokers indicate that they first started smoking before the age of 18 years [39], it is of importance to examine whether smoking is a mediator of the relationship between ACEs and CVD. A recent study found that smoking fully mediated the effects of childhood adversity on acute myocardial infarction [40]. However, smoking may not be the only pathway. In an analysis by Loucks et al. in the New England Family Study, findings showed that associations of parental bonding with 10-year CHD risk calculated using the Framingham risk algorithm remained statistically significant in sensitivity analyses that removed smoking from the Framingham risk algorithm [25]. This suggests that the early family environment may impact CHD risk on pathways independent of smoking. Further work is needed to determine the importance of smoking as a primary or component mediator.

**Obesity and Type 2 Diabetes**—A systematic review on associations of childhood exposure to interpersonal violence with obesity observed that 29 of the 36 included studies reported positive associations between at least one measure of childhood interpersonal violence and obesity [41]. Furthermore, a recent meta-analysis of 41 studies ( $n=190,285$ ) demonstrated that childhood maltreatment was associated with an odds ratio of 1.36 (95 % CI 1.26, 1.47) for developing obesity across the life course [42]. This positive association was unaffected after adjustment for childhood and adult SES, while the effects were stronger in women and White participants [42]. Potential mechanisms of ACEs on obesity include negative affect (anger, perceived stress) [43] and disordered eating [44, 45], but there

remains mixed support of primary mediation by physical inactivity [46–48]. Longitudinal follow-up and implementation of targeted interventions may better demonstrate the direction of causation and prevention capabilities.

With regard to type 2 diabetes, a major CVD risk factor, there is little research on the relationship of ACEs with type 2 diabetes. Initial reports described associations of childhood physical abuse with elevated HbA1c, fasting glucose, or self-reported type 2 diabetes [48–50]. Analyses in the NHS II demonstrated dose–response associations of childhood physical abuse with type 2 diabetes [50]. Evidence suggested that body mass index accounted for roughly half of the observed associations between physical abuse and type 2 diabetes [50]. Further prospective and interventional research will clarify if ACEs are important in the development of obesity and type 2 diabetes.

**Physical Inactivity**—Another potential behavioral consequence of ACEs may be physical inactivity. Children who were sexually abused may avoid engaging in physical exercises with peers that could lead to being touched [51]. However, the results of relationship between ACEs and physical activity in adults are mixed. In the ACE Study, compared to participants who had no ACEs, those who had experienced four or more categories of childhood exposure had 1.4-fold higher likelihood of physical inactivity [22]. Similar results were observed in a recent WHO report which conducted ACE surveys in eight eastern European countries [52]. Compared with those who reported no adverse experiences, young adults who reported at least four ACEs were at significantly increased risk of many health-harming behaviors including physical inactivity (odds ratio 1.68; 95 % confidence interval 1.32–2.15). On the contrary, a nationally representative survey of adult resident in England found that ACEs were not related to physical exercise. Exploration of reasons for inconsistent findings could yield important information, such as evaluating the potential role of childhood adversity-induced physical fitness as a self-defense response, particularly to physical- and sexual-related adverse experiences [53, 54].

**Sleeping Behavior**—Several aspects of sleep behavior such as poor sleep quality, short sleep time, and sleep apnea syndrome have been linked to CVD risk in both adults and adolescents [55–57]. In recent years, there has been a growing body of epidemiological evidence documenting associations between childhood adversities and sleeping difficulties in adulthood. For example, using data obtained from 25,810 respondents of a national telephone survey, Chapman et al. found a significant, graded relationship between the number of ACEs and frequent insufficient sleep (< 14/30 days), after adjusting for demographic covariates and mental distress [58]. Similar results were reported from a recent study in 19,349 Canadian adults, in which for each additional childhood adversity experienced, the odds of having troubled sleep increased by 10 % (odds ratio=1.10) [59]. Most recently, Kajeepeta et al. conducted a systematic review, which showed that the majority of studies found significant associations of childhood adversity with multiple sleeping disorders [60]. These studies highlight the importance of early detection and intervention of sleeping disorders for children, adolescents, and adults, who experienced traumatic events in early life, to improve health and reduce risk of developing CVD.

## Emotional Factors

The long-term impacts of ACEs on emotional and mental development are well established [61]. At very early ages, children learn to express and regulate emotions by interacting with parents and caregivers. Child maltreatment (e.g., abuse or neglect) and household dysfunction (e.g., domestic violence) may disrupt this learning process, limiting children's abilities to develop adequate self-regulatory and coping mechanisms. Maltreated children may be more sensitive to independent adverse life events, as compared to those with no trauma history, requiring lower levels of threat to trigger the negative response [62]. Children who experience parental abuse and/or neglect are more likely to show problems with emotion regulation and develop mental disorders in adolescence and adulthood. For example, in an early longitudinal study, 80 % of young adults who had been abused before age 18 met the diagnostic criteria for at least one psychiatric disorder by the age of 21 [63]. Compared to their non-abused counterparts, abused subjects demonstrated significant impairments in functioning both at ages 15 and 21 years, including more depressive symptomatology, anxiety, psychiatric disorders, and emotional-behavioral problems [63].

In recent years, numerous epidemiologic and clinical studies provided compelling evidence for strong associations between various forms of childhood adversities and mental illnesses in adults, such as major depression. Using data from the ACE Study, Chapman et al. reported a dose-response relationship between the severity of experienced childhood adversities and the presence of a depressive episode in the past year or lifetime chronic depression [64]. Their findings are in line with other epidemiological studies. For example, in a 32-year prospective longitudinal study of a representative birth cohort, Danese et al. found that children exposed to adverse psychosocial experiences were at elevated risk of depression in adulthood [6]. Findings of the Canadian longitudinal survey [65], the Australian longitudinal study on women's health [66], and the Wisconsin longitudinal study [67] have provided concordant results. An interesting cohort study that used both retrospective and prospective assessments of childhood adversity showed strong associations with major depression, suggesting that this association is not merely artifact of recall bias [68]. Depression has long been recognized as a risk marker for CHD, although the causal role has been questioned due to depression interventions in participants with CHD often not being effective to reduce subsequent CHD events or mortality [69–72]. A recent study that intervened on depression showed significant protective effects against incidence of CVD events in participants without baseline CVD, which suggests that depression may indeed be on the causal pathway and interventions may be important if performed earlier on in the disease process [73]. Replication of these findings by other studies is needed.

PTSD is another common sequela of childhood maltreatment [74]. In a study of 1420 children and adolescents, Copeland et al. found that children displaying PTSD symptoms were more likely to have a history of exposure to trauma and to come from an adverse family environment [75]. Symptoms of PTSD in young children tend to be persistent over time [76]. Moreover, childhood maltreatment appears to make people more vulnerable to developing PTSD when exposed to a current life stressor [77]. PTSD also has a negative impact on health, likely including CVD. In a number of prospective observational studies, PTSD has been associated with incident CVD and mortality [78–83]. Recently, data are

emerging on the association between PTSD and objective measures of subclinical atherosclerosis. For example, Ahmadi et al. studied veterans who underwent clinically indicated computed tomography for evaluation of coronary artery calcification (CAC) and found that PTSD patients had twice the odds of CAC than those without PTSD [84]. Identification and prevention of depression and PTSD in young adults with experiences of childhood adversity may provide an important avenue for the prevention of CVD in later adult life.

### Biological Pathways

**Established CVD Biomarkers**—In addition to CVD events, the Study of Women's Health Across the Nation (SWAN) recently reported that midlife women with a history of childhood sexual abuse had greater carotid intima media thickness (IMT), a measure of subclinical CVD, compared to women without this history [85]. Loucks et al. [25] demonstrated that a risky childhood family psychosocial environment was associated with carotid IMT in White, but not Black, participants in the CARDIA Study ( $n=2659$ ). These findings suggest that early childhood adversity is linked with the long-term development of atherosclerosis.

Epidemiological studies also showed associations between ACEs and CVD risk factors, such as hypertension and diabetes. For instance, findings from the Nurses' Health Study (NHS) suggest that women exposed to severe physical and/or sexual abuse prior to age 18 were more likely to develop hypertension than women with no abuse history or less severe forms of abuse exposure [86]. These findings were supported by data from cross-national population surveys. In the WHO World Mental Health Surveys, which enrolled 18,630 adults from ten countries, the presence of three or more childhood adversities was found to be associated with adult-onset hypertension [87]. However, it is of note that most studies were conducted in middle-aged adults and relied on self-reported categorical measure of hypertension. Most recently, Su et al. [88] examined the long-term effect of ACEs on blood pressure (BP) trajectories from childhood to young adulthood using data from a longitudinal cohort of White and Black boys and girls followed for 23 years (1989–2012), with an average of 13 BP assessments during that time period. Significant associations were found between the number of ACEs and longitudinal BP trajectories, where the effect sizes increased as participants aged into the third decade of life [88]. These data suggest that individuals with ACE exposure may have elevated risk for developing hypertension, most likely at earlier ages, than those without a history of ACEs [88].

### Nervous, Neuroendocrine, and Immune Systems

As results from epidemiological studies have been fairly consistent in demonstrating associations of ACEs with CVD and CVD risk factors, neurobiological studies have simultaneously showed how childhood adversities, such as abuse, may trigger a cascade of molecular alterations in multiple systems that regulate stress responses, including nervous, neuroendocrine, and immune systems [89]. It is well known that the human brain is not fully developed at birth and undergoes profound changes through to young adulthood [90]. Traumatic experiences in early life can negatively affect the structure and function of the brain. For example, maltreated children and adolescents tend to have decreased volume in

the corpus callosum, which is the largest white matter structure in the brain and is responsible for interhemispheric communication and other processes (e.g., emotion, higher cognitive abilities) [91, 92]. Adults who were maltreated appear to have reduced volume in the hippocampus, which is central to learning and memory [92]. Compared to community controls, adolescents and young adults who experienced severe maltreatment early in life showed reduced frontal (anterior) interhemispheric coherence and poorer connections in white matter tract regions [92]. Similarly, the neuroendocrine and immune systems undergo age-dependent maturation after birth. In conditions of acute psychosocial stress, the hypothalamic-pituitary-adrenal (HPA) axis is activated and glucocorticoid hormones (e.g., cortisol) are released [17]. Maltreated children tend to have elevated basal cortisol levels, suggesting chronic activation of the HPA axis [17]. Similarly, adults with a history of childhood maltreatment also showed chronic activation of the HPA axis [17]. Remaining in a high level of stress for long periods of time can damage multiple physiological systems, including the brain. In addition, chronic activation of the stress response by trauma may have far-reaching effects on immune system functioning. Consistent with impaired functioning of the HPA axis, elevated inflammation levels have been observed in both children and adults who experienced maltreatment in early life [93]. Abnormal endocrine and immune functioning in children exposed to ACEs may impact on mental and cardiovascular health. The potential effects of ACEs on these systems have been reviewed elsewhere by Danese and McEwen [94] and more recently by Nusslock and Miller [89].

### Endothelial Function

A recent study in rats showed that maternal separation, a rodent model of early life stress, induced increased circulating endothelin-1 (ET-1) levels, and BP reactivity through the ET-1 pathway [95]. Furthermore, in a study of 221 healthy adolescents and young adults, Su et al. [96] found graded associations of ACE exposure with plasma ET-1 levels, which were, on average, 18 and 24 % higher in participants with 1 ACE and 2 ACEs, respectively, vs. those without ACEs ( $P=0.001$ ). ET-1 is well known as a potent vasoconstrictor with inotropic and proinflammatory properties [97–99]. Dysregulation of the endothelin pathway is considered to occur early during development of atherosclerosis and vascular complications. Elevated plasma ET-1 levels have been found in patients with CHD, heart failure, and pulmonary arterial hypertension [100]. These preliminary studies suggest that the endothelin pathway may, in part, underlie the link between ACEs and development of CVD; however, replication of findings is needed.

### Clinical and Population Health Implications

If the ACEs do indeed influence CVD risk, there is substantial literature on childhood interventions to help prevent or mitigate effects of ACEs on children, described in more detail elsewhere [101–104]. A number of specific prenatal and childhood programs, such as the Nurse–Family Partnership, Perry Preschool, Abecedarian Project, and Triple P programs, provide a nurturing environment to children and their families and have been shown to have lifelong positive effects on developmental and health outcomes [101–104]. These types of interventions could influence cardiovascular risk as suggested by the recent *Science* article on the Abecedarian project [101]. This was a randomized controlled trial showing impacts of



enriched preschool on blood pressure, metabolic syndrome, and Framingham risk score in participants in their mid-30s, with effects particularly strong in males [101]. However, replication and extension of findings on impacts of early life interventions on later life CVD risk are needed.

Aside from childhood interventions, an important question is “What, if anything, can be done in adult patients to reduce potential harmful effects of ACEs on CVD risk?” Furthermore, is it worthwhile for cardiologists to screen patients for ACEs if cardiologists are currently minimally equipped to mitigate effects of ACEs? These are important issues and are at the forefront of research at this time. For mental health outcomes, there are a range of adult interventions, including pharmaceutical and behavioral, designed to limit mental health effects of ACEs [105]. Some may be more effective than others. For example, a recent study in *The Lancet* suggested that while Mindfulness-Based Cognitive Therapy and antidepressant medication had similar effects on depression relapse, Mindfulness-Based Cognitive Therapy was significantly more effective than antidepressants in participants with severe childhood abuse [106]. The potential impacts of depression on CVD risk are reviewed above. These findings suggest that certain adulthood interventions may be effective at reducing ACE-related disparities in health. As cardiologists and other health professionals that treat adults consider screening adult participants for ACEs, it will be important to have a team that can support the patient if he or she is deemed at risk due to ACEs [107]. Furthermore, research evaluating adult intervention effectiveness to reduce impacts of ACEs on CVD risk would be beneficial at this time. Treatment options could include both pharmacological and behavioral approaches.

Finally, it is important to consider the social contexts in which ACEs manifest. For example, parents living in poverty, with few employment opportunities, low education, and inadequate support systems are more likely to express more adverse parenting styles, such as neglect, abuse, and lower parental monitoring [104]. Efforts to address upstream fundamental determinants of ACEs may help to break the intergenerational cycles that tend to link early life adversity with later life disease [108].

## Conclusion and Future Directions

ACEs are prevalent in the USA, exerting an enormous impact on individuals, families, and society. Findings to date suggest that ACEs may have an impact on CVD. The quality of research findings will be strengthened with further prospective studies, validated measures of ACEs, direct assessments of CVD events, and randomized controlled trials of interventions. In the mean time, clinicians might reflect on the potential benefits of considering the role of ACEs in CVD risk and explore plausible interventions to help mitigate these effects.

There is an emergent need to develop trauma-informed care (TIC) for CVD patients who experienced adverse events in early life. TIC is an approach to engaging people with histories of trauma that recognizes the presence of trauma symptoms and acknowledges the role that trauma has played in their lives [109••]. In recent years, the term of TIC has been widely used, particularly in behavioral health service [110]. Future research is needed to

implement TIC in clinical trial and daily health care practice [109••]. For example, it is important to critically examine if a more empathic and sensitive communication between patients and health care providers can encourage trauma survivors more likely to follow up on medical appointments and engage in preventive care and potential cost savings for these patients. It is also crucial to design clinical trials to examine if integrated TIC treatment or intervention can improve health outcomes and reduce CVD risk in patients with a history of ACEs and to identify the optimal strategies that can help these patients lead to healthier lives.

In addition to implementing TIC in the treatment of CVD, early intervention and increasing children's exposure to safe, stable, and nurturing environments may be more efficient than treating diseases as they arise later in life [103]. Recently, the American Heart Association released a science advisory, emphasizing the importance of greater efforts to preserve cardiovascular health from childhood and to treat health risk behaviors into older ages [111]. Consistent with the AHA's strategic impact 2020 goals and beyond, there is a need to develop research and programs preventing early adversity and promoting positive child development.

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