Childhood and Adolescent Adversity and Cardiometabolic Outcomes:

A Scientific Statement From the American Heart Association

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Abstract

Adverse experiences in childhood and adolescence, defined as subjectively perceived threats to the safety or security of the child's bodily integrity, family, or social structures, are known to be associated with cardiometabolic outcomes over the life course into adulthood. This American Heart Association scientific statement reviews the scientific literature on the influence of childhood adversity on cardiometabolic outcomes that constitute the greatest public health burden in the United States, including obesity, hypertension, type 2 diabetes mellitus, and cardiovascular disease. This statement also conceptually outlines pathways linking adversity to cardiometabolic health, identifies evidence gaps, and provides suggestions for future research to inform practice and policy. We note that, despite a lack of objective agreement on what subjectively qualifies as exposure to childhood adversity and a dearth of prospective studies, substantial evidence documents an association between childhood adversity and cardiometabolic outcomes across the life course. Future studies that focus on mechanisms, resiliency, and vulnerability factors would further strengthen the evidence and provide much-needed information on targets for effective interventions. Given that childhood adversities affect cardiometabolic health and multiple health

domains across the life course, interventions that ameliorate these initial upstream exposures may be more appropriate than interventions remediating downstream cardiovascular disease risk factor effects later in life.

Keywords

AHA Scientific Statements; adolescent; cardiovascular diseases; child; diabetes mellitus; hypertension; obesity; stress; trauma

It is now well established that experiences in childhood and adolescence are associated with health over the life course.[1] Adverse childhood experiences, which we define as experiences that threaten the child's bodily, familial, or social safety or security, range from broad categories of maltreatment and household dysfunction[2] to more targeted experiences of bullying,[3] exposure to crime, victimization, and economic disadvantage[3–5] (Table). Adverse experiences are highly prevalent; recent data from the BRFSS (Behavioral Risk Factor Surveillance System) demonstrate that 59% of the US adult population has experienced at least 1 adverse childhood event.[6] Much of the existing literature on childhood adversities and health has focused on childhood maltreatment, including experiences of physical, sexual, and emotional abuse and neglect, and has shown that such adversities disrupt normative developmental processes and magnify risk for health consequences later in life.[7] Cumulative measures have also been common ways of capturing exposure to childhood adversity, with many studies aggregating across the 10 items defined by the ACE study (Adverse Childhood Experiences)[2]: witnessing a parent being abused, living with a mentally ill person, living with a substance abuser, imprisonment of a household member, emotional abuse, physical abuse, sexual abuse, emotional neglect, physical neglect, or parental separation or divorce. Additional research has expanded on the original set of ACE items to include adversities common in diverse, nonwhite, lower-socioeconomic-level communities, as well as adversities perpetrated by peers (eg, bullying).[8–10] Given the interindividual variation in threat perception, there is a lack of consensus on precisely what constitutes childhood and adolescent adversity. Nevertheless, there is general agreement that the accumulation of these experiences, across either time or multiple domains, during childhood and adolescence detrimentally affects health. Moreover, cardiometabolic health outcomes and adverse experiences are strongly patterned by sex, race/ethnicity, socioeconomic status (SES), and nativity (place of birth, eg, whether born in the United States or elsewhere). For example, children living in lower-SES households and from racial/ethnic minorities are more likely to experience multiple adversities in childhood in addition to having a higher prevalence of cardiometabolic health outcomes.[6,8,11] The relation between sex and immigration status and childhood adversity and cardiometabolic outcomes is more complex and is discussed in detail later.

The goal of this American Heart Association scientific statement is to review the scientific literature on the influence of childhood and adolescent adversity (hereafter referred to as childhood adversity) on cardiometabolic health outcomes, including obesity, hypertension, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD). Cardiometabolic diseases constitute the leading causes of morbidity and mortality for men and women in the

United States[12,13] and an escalating economic burden.[14,15] Our assessment draws from several recent systematic reviews focused on various forms of childhood adversity, including childhood maltreatment,[16] violence,[5] and cardiometabolic outcomes, to identify evidence gaps and to provide suggestions for future research needed to inform policy and practice. Our broad goal is to summarize evidence necessary to guide and inform multilevel interventions designed to prevent and mitigate childhood adversity and associated risk for cardiometabolic disease.

Our review of the literature and proposed next steps are guided by a conceptual model (Figure) that recognizes 3 potential mechanisms of how childhood adversity could affect cardiometabolic health: behavioral, mental health, and biological mechanisms. As detailed later, behaviors such as smoking, sleep, activity, and caloric consumption all worsen as a result of stressful events and household dysfunction. Mental health problems may be induced or exacerbated by childhood adversity, predisposing children and youth to early manifestations of cardiometabolic disease risk. Lastly, because childhood adversity disrupts many of the regulatory processes of the body, biological processes can be directly affected. All of these mechanisms (behavioral, biological, and mental) interact, affect other cardiometabolic factors (eg, blood pressure, adiposity, glucose), and, in turn, affect cardiovascular morbidity and mortality. We also recognize several immutable factors, including sex, race/ethnicity, nativity status, and genetic predisposition, that exacerbate or buffer the effect of childhood adversity on cardiometabolic risk factors and ultimately cardiometabolic morbidity and mortality.

CHILDHOOD ADVERSITY AND CARDIOMETABOLIC OUTCOMES

Influence of Childhood Adversity on Cardiometabolic Outcomes

Several review articles suggest that childhood adversity is associated with increased risk of cardiometabolic disease, including CVD mortality and numerous CVD outcomes such as myocardial infarction, stroke, ischemic heart disease, and coronary heart disease.[5,16,17] A recent systematic review found that childhood maltreatment was associated with CVD (myocardial infarction, stroke, ischemic heart disease, coronary heart disease) in 91.7% (22 of 24) of published studies.[16] Research has also examined the relation between childhood adversity and risk factors for cardiometabolic disease. For example, several studies suggest that childhood adversity is associated with increased risk of hypertension and high blood pressure levels, although findings are mixed.[5,16,18] Other studies also suggest that there may be an association between childhood adversity and obesity.[3,19,20] A recent meta-analysis noted a positive association between childhood adversity and childhood-overweight measures in a pooled estimate of reviewed longitudinal studies.[21] In addition, childhood adversity has been associated with increased risk of T2DM in adulthood.[16,22,23]

Severity, Timing, and Chronicity of Childhood Adversity on Cardiometabolic Outcomes

Childhood maltreatment (physical, sexual, or emotional abuse and neglect) is by far the most frequent operationalization of adversity, and this broad measure has been robustly associated with cardiometabolic risk.[2,16] Studies have documented a more consistent association between physical and sexual abuse and cardiometabolic disease risk compared with other

specific forms of adversity.[23–29] Although some work has examined individual adverse experiences, other work has focused on the accumulation of these experiences and frequently demonstrates a dose-response relation with cardiometabolic risk. Several studies examining maltreatment as part of a composite measure of adversity have reported a dose-response relationship between number of childhood adversities and heightened risk for cardiometabolic diseases.[2,27,30–34] This type of dose-response relationship suggests that reducing the number of co-occurring adversities could help to prevent the downstream cardiometabolic consequences of maltreatment. The ACE study, for example, noted a continuous dose-response relation between the number of childhood adverse experiences and the odds of ischemic heart disease.[2] However, some research suggests more of a threshold effect.[22] Data from the BRFSS note a relation between exposure to   4 childhood adversities and CVD.[31] More recent research has expanded the potential domains of adverse experiences and incorporated severity and intensity into an adversity score,[35] signaling a potential future direction in the assessment and modeling of adverse experiences and their relation with cardiometabolic risk.

In a recent review, all but 1 study considered adversities experienced before 18 years of age as 1 period without consideration for different developmental periods that may exist within childhood.[5] For example, results from the Bucharest Early Intervention Project, which randomized children from extremely deprived institutional environments to therapeutic foster care, found that, for cortisol and parasympathetic nervous system reactivity, intervention effects were evident only among children placed in foster care before 24 months of age, suggesting that there may be sensitive periods in childhood during which the environment is particularly likely to alter stress response system development.[36] Whether there are sensitive periods of exposure to adversity for the development of cardiometabolic outcomes remains unknown. Within the Nurses' Health Study, Riley and colleagues[37] noted that experiencing sexual abuse jointly in childhood and adolescence was associated with increased risk of hypertension in adulthood compared with not experiencing abuse at either time. A similar association was not noted among women who experienced abuse at only 1 time point, suggesting that chronicity of exposure, not timing, was relevant for the development of hypertension.[37] However, childhood and adolescence, as defined by this study, are still quite broad periods in terms of development. More precise work on whether exposure during specific periods has differential effects on cardiometabolic risk is warranted.

Modifying Factors

Sex—There are sex differences in exposure to childhood maltreatment and in cardiometabolic outcomes. However, investigation into whether sex modifies the relation between childhood maltreatment and cardiometabolic outcomes has been limited. With regard to exposure to adversity, data from the National Comorbidity Survey Adolescent Supplement indicate that girls are more likely to experience sexual abuse and rape, for example, and boys are more likely to report experiences such as exposure to accidents or disasters.[38] Maltreatment-specific data suggest that girls are more likely to experience sexual abuse and boys are more likely to experience physical abuse.[39] With regard to cardiometabolic outcomes, many recent reviews have discussed sex differences, including an

earlier age of onset of many cardiometabolic diseases in men, yet in adulthood, CVD mortality is higher in women.[40,41] Recent studies have postulated that psychosocial stress may be a more important risk factor for cardiometabolic disease in women than in men, either because women are exposed to more psychosocial stress or because they are more vulnerable to its effects.[42] For example, sex differences in T2DM in relation to depression and anxiety have been noted, with stronger associations observed in women.[43,44] Furthermore, among young children, sex differences have also been noted in the relation between adversity and obesity, with girls being at increased risk of obesity in relation to adversity in early childhood.[45] However, recent reviews have demonstrated that few studies have formally examined sex-related differences in the association between adversity and cardiometabolic outcomes. Among those that have, there was no consistent pattern of sex-related variations.[16] Similarly, a review by Slopen et al[46] of stress and cardiometabolic biomarkers in youth found that only 4 studies reported sex-stratified analyses with no consistent direction of effect. A recent meta-analysis also noted insufficient data to draw conclusions about sex-related differences based on adverse childhood events exposure and T2DM.[47] Taken together, these data suggest large gaps in our knowledge and that a more rigorous examination of sex differences in the relation between childhood adversity and cardiometabolic outcomes is warranted.

SES, Race, Ethnicity, and Immigration Status—Racial and ethnic minority children and children living in lower-SES households have a higher prevalence of childhood adversities; in addition, they experience a higher prevalence of cardiometabolic health outcomes across the life course.[6,11] SES may be an upstream determinant of adversities because socioeconomic constraints may put children at higher risk for experiencing adversities (ie, exposure to violence, household dysfunction).[17] Children living in lower-SES households may be more vulnerable to adverse experiences because potential economic, social, and emotional resources necessary to cope with and manage these adverse experiences may not be available to them as a result of their disadvantaged position. However, existing studies have rarely examined the potential modifying effect of race/ethnicity or lower SES on childhood adversities and cardiometabolic health relation. Immigration history has also been largely ignored as a potential modifying factor. A recent study of the National Survey of Children's Health noted that regardless of SES, children of immigrant parents had, counterintuitively, lower levels of adversities compared with children of US-born parents.[11] Similar associations were noted within participants of the Hispanic Community Health Study/Study of Latinos.[48] Previous work has documented that despite higher poverty rates, children of immigrant parents have health outcomes that are similar to or better than those of children of US-born parents. Whether immigrant status modifies the association between childhood adversity and cardiometabolic health is unknown and warrants further research.

Mechanisms

As depicted in the Figure, at least 3 pathways are commonly identified to explain how childhood adversity may increase the risk of cardiometabolic (and other) diseases: behavioral, mental health, and biological.

Behavioral Factors—Evidence suggests that childhood adversity is associated with adverse health behaviors that increase the risk of cardiometabolic disease, including smoking, overeating, consumption of energy-dense foods, and inactivity.[2,49,50] The association of childhood adversity with these behaviors was first tested by Felitti et al.[2] In their retrospective ACE study, Felitti et al hypothesized that greater childhood adversity occurs in a setting of parental dysfunction in which children experience greater levels of distress and lack adequate support and "psychological nourishment."[51] Thus, in response to high levels of distress, children experiencing adversity are at higher risk of adopting adverse coping mechanisms (eg, smoking, overeating). For example, Anda and colleagues[52] published data showing that exposure to 5 ACEs versus no exposure was associated with a 5-fold higher rate of early smoking initiation. Furthermore, the home environment is central to children's daily experiences, particularly with regard to meal and activity patterns. The home environment may affect practices such as meal preparation, use of television (and other digital media), consumption of food outside the home, and participation in physical activity.[8,27,33,34] Parental psychological distress is associated with lower consumption of fruits, vegetables, and high-calcium foods among children,[33] plus fewer physical and more sedentary activities,[25,35] each of which increases children's risk of obesity.[34,36,37] Childhood adversity has been associated with obesity in children as young as 5 years of age,[45] and prospective research shows that childhood obesity and adolescent obesity have been associated with increased risk of cardiovascular risk factors and CVD among adults.[53–55] Data also suggest that whereas an unhealthy diet and sedentary lifestyle adversely affect physical and mental health,[56,57] a healthy diet and plentiful activity reduce inflammation, depression, and anxiety.[58,59] Thus, evidence increasingly suggests that behavioral risk factors, in part, mediate the childhood adversity-cardiometabolic disease relationship. However, despite a strong retrospective association of trauma, stress, and adult obesity,[60] little is known about the prospective impact of childhood adversity on behavioral mediators that predict cardiometabolic disease across the life course. In addition to behavioral factors, other unmeasured behaviors or biological processes likely are involved in the pathway from childhood adversity to adverse cardiometabolic outcomes.

Mental Health Factors—The association between early adversity and subsequent mental health problems in youth and adulthood is well known.[61] It is thought to be moderated by genetic factors and mediated in part by neurobiological effects of trauma.[62–67] A recent systematic review noted that mental disorders were a partial mediator of the association between childhood maltreatment and cardiometabolic disease[16] but concluded that the findings should be interpreted with some caution because studies varied greatly in terms of how they modeled effects of mental disorders (eg, statistical models varied in their treatment of time, in combination with other disorders, or with health behaviors).[24,27,28,30,68,69] Many childhood adversities, including childhood maltreatment and exposure to violence, are traumatic events that may result in posttraumatic stress disorder in some individuals. Although investigators have examined posttraumatic stress disorder in relation to a range of health outcomes (including rheumatoid arthritis, stroke, heart disease, and cancer), some of the strongest empirical research, in terms of methodology and findings, has been with cardiometabolic diseases.[70,71] Numerous methodologically rigorous prospective population-based observational studies have found that posttraumatic stress disorder is associated with

increased risk of incident CVD[72–84] and T2DM.[85–87] However, whether and how much of the relation between childhood adversity and cardiometabolic disease may be explained by post-traumatic stress disorder is unclear, especially because these studies have included traumatic events over the life course, with a substantial proportion of studies focused on veterans and military service-related trauma, not just adversity during childhood.

Childhood adversity increases the risk of mood and anxiety disorders,[62,88] which are widely recognized as increasing the risk for cardiometabolic morbidity and mortality. A recent American Heart Association statement positioned major depressive disorder and bipolar disorder as conditions that predispose youth to accelerated atherosclerosis and early CVD.[89] Although an extensive amount of research has focused on depression, a recent review called for equal attention to anxiety disorders as risk factors for CVD given the state of the current evidence.[90] Childhood adversity converges with mental health problems in a number of ways that are relevant to cardiometabolic outcomes. For example, childhood adversity is an important indicator of a more persistent and treatment-refractory course of illness and affects response to both pharmacological and psychosocial treatment for youth and adults with mental health conditions.[91–95] Among people with mental health conditions, childhood adversity, compared with no childhood adversity, results in greater cumulative exposure to mental health symptoms, associated stress, and biological perturbations.[96–98]

Beyond the direct effects of mental health problems on cardiometabolic outcomes, there are also indirect effects that further exacerbate cardiometabolic risk factors. For example, youth with mood disorders are less likely to achieve recommended levels of physical activity and sleep and more likely to have suboptimal dietary habits, all of which impart cardiometabolic disease risk.[89] In addition, several pharmacological treatments used to treat mental health problems could contribute to cardiometabolic risk factor accumulation. Several second-generation antipsychotics and mood-stabilizing medications confer risk of weight gain and other cardiometabolic disturbances.[99,100] It is unlikely, however, that the link between mental health and cardiometabolic outcomes is fully explained by psychotropic medications. [77,101] In addition, contemporary medications used for the treatment of attention-deficit/hyperactivity disorder, anxiety, and depression in youth are not commonly associated with cardiometabolic risk factors.[102–105]

Biological Factors—Childhood adversities may disrupt many of the regulatory systems of the body, altering the immune, metabolic, neuroendocrine, and autonomic nervous systems.[36,46,106] In the short term, altered stress responses likely help children function while living in high-risk households, for example, by increasing alertness. However, in the long term, these responses could trigger health problems, including chronic hypertension.[107] Long-term hypothalamic-pituitary-adrenal axis activation, in response to prolonged experiences of stress, affects glucocorticoid metabolism and likely alters immune function. Studies document that childhood adversities predispose individuals to chronic inflammation, [108–110] with elevation of interleukin-6, C-reactive protein, fibrinogen, and other biomarkers associated with cardiometabolic disease. Childhood adversities are also related to adverse trajectories in traditional cardiometabolic factors; the Georgia Stress and Heart Study, for example, showed that individuals who experience childhood adversity have faster increases in blood pressure from childhood to young adulthood.[111] Similarly, a British cohort showed

that childhood maltreatment led to accelerated increases in body mass index from childhood to adulthood.[112] Several studies also demonstrated that childhood adversities increase markers of subclinical CVD, including markers of endothelial dysfunction (E-selectin, intercellular adhesion molecule-1),[108] arterial stiffness, and carotid intima-media thickness progression.[113,114] Preliminary data suggest that epigenetic changes may form part of the biological linkage between subjective experience of adversity and objective cardiometabolic derangement.[115–118] Methylation of genes regulating pathways to obesity and metabolic disorders in adults exposed to child abuse also has been identified.[119] However, research on DNA methylation is still an emerging field of study. Population-based studies are needed to clarify the role of epigenetics in the link between childhood adversities and CVD risk.

Finally, although beyond the scope of this review, behavioral factors such as diet and physical activity as outlined earlier can reflect stress-induced physiological changes. For example, ghrelin is a neurohormone that is upregulated under stress conditions and has mild anxiolytic and antidepressant properties[120]; however, ghrelin also increases appetite, food-seeking behavior, and food-associated reward.[121,122] In addition, maltreated children have been found to be deficient in leptin, a hormone that regulates energy balance.[123] On the other hand, physical activity increases endorphins, postpran-dial satiety-hormone levels (peptide YY3-36[124]), and affective mood.[125,126]

LIMITATIONS

Although an increasing body of work has documented a relationship between childhood adversity and cardiometabolic outcomes and suggests potential underlying pathways, certain limitations of the literature should be considered.

Lack of Agreement on Definitions

As noted, existing literature in this area is based on a collection of heterogeneous measures and definitions of childhood adversity. Although the accumulation of these heterogeneous adverse experiences consistently predicts worse outcomes, little work has considered the differential effects that some of these experiences may have. In addition, limited research has carefully evaluated differential effects on the basis of the timing of when these experiences occur, with some studies suggesting that exposures in early childhood appear to have a more enduring impact. Furthermore, other prevalent adverse experiences not originally considered in the ACE study need to be evaluated for their potential influence on cardiometabolic risk. For example, although child victimization at the hands of adults has received more attention, recent studies have highlighted the important role of bullying or victimization by peers in predicting obesity and inflammation in later life.[9,10] Other studies have highlighted the importance of experiences of racial discrimination in relation to health outcomes, which are more prevalent among racial/ethnic minorities.[8] Given the high prevalence of individuals experiencing these and other stressors, it is important to consider the sociodemographic characteristics of the population being considered because its experiences of adversity will vary. Finally, adverse environmental conditions are nonrandomly distributed, are experienced to a disproportionate degree by subgroups, and are associated with risk for long-term familial and interpersonal adversities.

Few Truly Prospective Studies

Although longitudinal studies based on prospective measures have appeared more frequently in recent years, most of the research in the area is based on cross-sectional studies using retrospective reports by adults. Most research on childhood adversity and CVD, T2DM, hypertension, and obesity has been cross-sectional and has relied on retrospective reporting of childhood adversity.[5,16] This is problematic because research shows that there is only moderate agreement between prospective and retrospective measures of childhood adversity, such that groups of individuals identified with these 2 different methods of assessment may show only limited overlap and different disease risk.[127] Longitudinal designs are increasing in frequency, and a few longitudinal studies have assessed adversity in childhood and/or adolescence.[4,9,10,29,68,109,111,128–131] As an example, the British National Child Development Study, a 50-year longitudinal study, assessed experiences of bullying when children were between 7 and 11 years of age. Bullying was associated with higher levels of C-reactive protein in midlife and, among women, with obesity in midlife.[9] Nevertheless, retrospective reporting of adversity remains the predominant approach to measurement, even in longitudinal research. Longitudinal studies would enable the identification and tracking of behavioral, mental health, and biological mechanisms over time that then lead to cardiometabolic disease. In addition to strengthening the causal links, research that examines associations between childhood adversity and cardiometabolic risk over the life course is critical for elucidating when the deleterious effects of childhood adversity may begin to appear and thus could be targeted for prevention. To date, most investigations have focused on understanding how childhood adversity is associated with cardiometabolic risk in adulthood, although a growing number of studies have found detectable divergence resulting from adversity in trajectories of health risk in adolescence.[106,128,131,132] However, other studies have not found clear evidence of divergence before adulthood[111,112] or have found evidence to be stronger in adult samples compared with child/adolescent samples.[20] Research explicitly investigating trajectories is limited, precluding firm conclusions on when excess risk resulting from adversity is reliably detectable. Prospective studies that begin during the prenatal period or preconception or follow cohorts from childhood through childbirth would also capture intergenerational adversity and perinatal programming.

Limited Identification of Mechanisms

As discussed, childhood adversity may provoke unhealthy behaviors and poor mental health or produce neurobiological alterations that initiate relevant pathophysiological processes. Few studies have explicitly tested the mechanisms linking childhood adversity and cardiometabolic disease with comprehensive mediation models.[133] Moreover, no study of which we are aware has tested a range of mechanisms and attempted to quantify which mechanism may be most important. Such research is critical both to inform whether childhood adversity is causal in cardiometabolic disease and to identify targets for intervention.

FUTURE DIRECTIONS

Determinants of Resilience

Not all individuals with a history of childhood and adolescent adversity develop cardiometabolic health outcomes, which raises the question of the determinants of resilience and cardiometabolic health. Rather than being inherent to the child, resilience, that is, good mental and physical health despite the assails of early adversity, results from a complex interplay among the child's genetics, natural temperament, knowledge and skills, past experiences, social supports, and cultural and societal resources.[134] Better integration of our understanding of modifiable resilience factors into interventions and routine care settings could improve outcomes for children who may face adversity in the future or have had past adversities. Information on determinants of resilience may also offer important insights into the mechanisms underlying the relationships between childhood adversity and cardiometabolic health outcomes. Finally, information on determinants of resilience may improve the tailoring of interventions to those who can most benefit from them. Because no intervention is universally effective, understanding why certain interventions benefit some children and not others will enable the matching of interventions. Moreover, identification of modifiable factors that buffer the effects of adversity or improve resilience could provide targets for interventions.[135] Few studies have focused on resilience factors such as positive coping, social support, and family dynamics that could modify the impact of childhood adversity on cardiometabolic health.[136]

Modifiers of Vulnerability

There has been limited examination of individual characteristics such as sex, race/ethnicity, and genetic factors in modifying the risks posed by childhood adversity. Among women, experiences of stress are most often associated with a higher prevalence and incidence of cardiometabolic outcomes compared with men, which may be attributed to differential behavioral or biological responses to stress. For example, some research suggests that the impact of childhood adversity on obesity[3,20,137] is stronger or more consistent among women than men. However, consistent patterns of sex-related differences in the associations between childhood adversity and cardiometabolic diseases have not been observed.[16] Similarly, there are important environmental factors, including individual, family, neighborhood, and community characteristics, that could modify the effects of childhood adversity on cardiometabolic outcomes and should be further characterized. For example, residential segregation, crime, and discrimination could be barriers to the adoption of healthy lifestyles (eg, physical activity and healthy dietary patterns), thereby contributing to poor cardiovascular health. Finally, several studies suggest that genes may influence how children interact with their environment, biasing their biological responses and affecting risk of clinical outcomes.[138] Studies of gene-environment interplay, which includes genotype-environment and epigenetics, have, to date, focused largely on mental health outcomes. Future research should explore how childhood adversity may interact with genetic vulnerability in producing cardiometabolic health outcomes. Epigenetic approaches might examine how childhood adversity alters gene expression and whether such alterations influence cardiometabolic outcomes.

Mechanisms

To reverse or remediate biological risk for health outcomes among those exposed to childhood adversity (secondary prevention), it is important to better understand the mechanisms through which childhood adversity leads to cardiometabolic outcomes. On the one hand, childhood adversity begets psychosocial adversity and worse mental health in later life. Future research should test whether adult psychosocial adversity and mental health explain why individuals with a history of childhood adversity develop cardiometabolic health outcomes. These studies might highlight targets for interventions. On the other hand, we are only beginning to understand the biological mechanisms through which childhood adversity brings about cardiometabolic outcomes (biological embedding),[139] including inflammation, abnormal neuroendocrine function, and others.[139] Future research should test comprehensive biological mediation models to uncover intervention targets. Research clearly demonstrating that childhood adversity alters known mechanisms of cardiometabolic risk would provide compelling evidence that childhood adversity is indeed involved in the pathogenesis of cardiometabolic disease. However, rigorous evidence demonstrating these causal associations is limited.

Application of Modern Epidemiological Methods

Confounding bias, that the relation between childhood adversity and cardiometabolic disease is explained by a third variable, has not been fully accounted for in many studies beyond consideration of childhood SES, thus limiting our ability to make causal inferences on the adversity and cardiometabolic health relation. State-of-the-art epidemiological methods such as marginal structural models have transformed the epidemiological approach to time-varying confounding of time-varying exposures over the past 25 years, but to the best of our knowledge, these methods have not been applied to childhood adversity research. The possibility of time-varying confounding, that the behaviors and risk factors that are subsequently affected by exposure to childhood adversity may also increase the risk of adversity, is a major threat to causal inference. For example, findings in a genetically informative British cohort indicated that child characteristics such as intelligence quotient and adjustment problems predicted exposure to maltreatment by adults[140] and chronic peer victimization (bullying).[141] Others have shown the adverse effects of maltreatment and peer victimization on child adjustment. Childhood intelligence quotient and adjustment have been linked to cardiometabolic disease in adulthood.[142,143] Marginal structural models can be used to account for the potential for dynamic feedback processes by which certain factors can act as either confounders or mediators of the effects of the childhood adversity-cardiometabolic disease relationship.[144]

Interventions

Another outstanding question is whether an effective reduction in childhood adversity or interventions aimed at buffering the effects of exposure to adversity can prevent or mitigate the likelihood of developing cardiometabolic disease.[145] Only a few studies have examined the role of early intervention on the reduction of childhood adversities and cardiometabolic health.[146,147] The Carolina Abecedarian Project noted lower levels of blood pressure among adults in their mid-30s who received early childhood intervention compared with a randomly

allocated control group.[146] Future research should also examine the potential benefit of preventive interventions targeting mental health, behavioral, and biological sequelae of childhood adversity that could buffer the effects on cardiometabolic health. The same questions can be raised about screening for childhood adversity. The National Council for Behavioral Health, in partnership with and sponsored by Kaiser Permanente National Community Benefit Fund, selected 14 organizations through a competitive process to pilot the Trauma Informed Primary Care Project with the goal of integrating the assessment of trauma into primary care to tailor patient care while addressing the consequences of past trauma.[148] However, at this time, the benefits of such screening have not been quantified. As previously noted, SES is a potential antecedent to the experience of childhood adversities; thus, addressing social factors could reduce both childhood adverse experiences and the risk of cardiometabolic disease.[147] Moreover, the benefit of screening for childhood adversities relies on an appropriate response to address the effects of any adversities identified. Addressing the effects of childhood adversity is complex and can pose challenges for providers.[149,150] For adults, a retrospective assessment of childhood adversities and current trauma could be coupled with mental health assessments and screenings for substance use, although the validity of retrospective recall of childhood adversity remains debated.[127] Newly identified mental health problems should lead to referrals and treatment for those conditions, in addition to already provided clinical care for physical health conditions. For minors, in addition to screening for adversity and behavioral and mental health issues, the safety and security of the child must be considered because the adversity identified may be ongoing. There are thus implications to screening, requiring proper training of providers not only on the assessment of the adversities but also on the necessary responses.

CONCLUSIONS

Childhood adversity is highly prevalent, with 59% of the US population reporting at least 1 adverse event experience.[6] Substantial evidence links childhood adversity to cardiometabolic disease later in the life course, including heart disease, T2DM, and stroke, which are 3 of the top 10 causes of mortality in the United States. Given the high variability of cardiometabolic aberration and the multiplicity of pathways activated by childhood adversity, modification of the downstream cardiometabolic consequences is less desirable compared with addressing upstream adversity exposures. However, there are no national guidelines or recommendations on systematic surveillance for childhood adversity in the healthcare system, in part because of a limited understanding of how to prevent or mitigate adversity and to build resilience. Toward this goal, additional research, including longitudinal prospective studies, designed to guide and inform effective and timely individual/clinical and population-level preventive interventions is required. Areas for such research, as highlighted in this review, include defining exposure intensity, duration, and vulnerable periods during the life course and across generations; characterizing resiliency against progression toward cardiometabolic consequences; identifying biological factors that modify response to adversity and elucidating pathobiological pathways linking adversity to cardiometabolic outcomes; and demonstrating which interventions on upstream childhood adversity exposure prevent progression to cardiometabolic disease.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

[*] Modest.

[†] Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Eric B. Loucks	Brown University	NIH 1R01AG048825-01 (This grant is focused on elucidating biological and behavioral mechanisms of how early life social adversity could influence later life obesity risk)[†]	None	None	None	None	None	None
Katie McLaughlin	University of Washington	None	None	None	None	None	None	None
Kathryn M. Rexrode	Brigham and Women's Hospital	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A

relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

[†]Significant.

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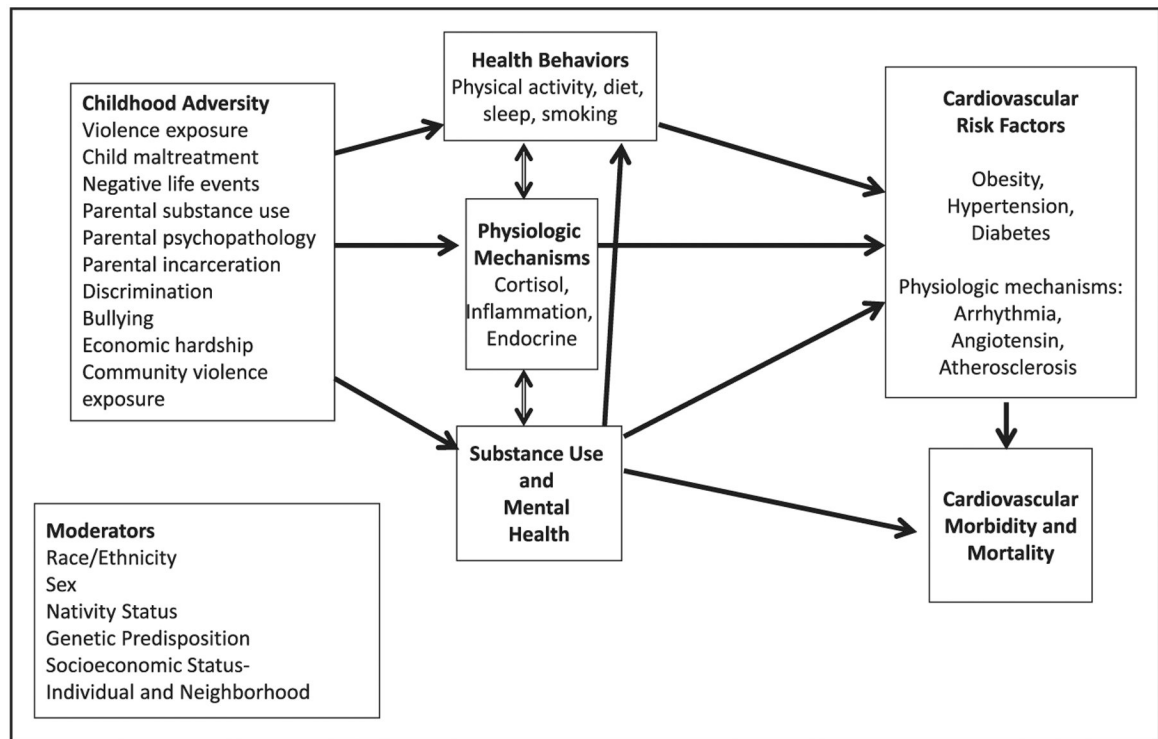
Figure.
Conceptual model of the relation between childhood adversities and cardiometabolic health.

Table.

Childhood Adversity Items Commonly Assessed for Association With Cardiometabolic Outcomes Individually or in Composite Scales

Construct	Individual Item
Household dysfunction	Parental substance abuse
	Violence at home
	Parental psychopathology
	Parental incarceration
	Parental death
	Parental separation or divorce
Violence (not childhood maltreatment or domestic violence at home)	Witnessing violence or violence victimization
	Dating violence
	Neighborhood safety
Childhood maltreatment	Emotional abuse
	Physical abuse
	Sexual abuse
	Physical neglect
Other	Homelessness
	Peer victimization (bullying)
	Discrimination
	Economic hardship
	Other traumatic event
	Death of close family friend or loved one