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Social Determinants of Cardiovascular Health: Early Life Adversity as a Contributor to Disparities in Cardiovascular Diseases

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Social determinants of health (SDoH), factors related to the conditions in which people are born, live, work, play, age, and the systems that shape the conditions of daily life, have emerged as key drivers of health and health disparities.[1, 2] A strong body of research supports that SDoH are associated with cardiovascular risk factors and outcomes, independently or in conjunction with more traditionally recognized risk factors. As a result, efforts to improve cardiovascular health are predicated on improved understanding of the impact of SDoH on CVD over the life course.

Early life adversity encompasses a variety of SDoH and has been recognized as a contributor to poor cardiometabolic health.[3, 4] ELA and adverse childhood experiences (ACE) are terms often used interchangeably. ELA includes external stressors and experiences of child maltreatment, household dysfunction[5], bullying, exposure to crime, discrimination, bias, and victimization.[6-8] These are highly prevalent (46% of children, ages 0-17 and 61% of adults are estimated to have experienced at least one ELA[9]) and disproportionately affect racial/ethnic minorities and families of lower socioeconomic status (SES) [9]. ELA has been linked to an elevated risk of CVD outcomes in adults, including myocardial infarction, stroke, ischemic heart disease, and coronary heart disease, as well as type 2 diabetes mellitus (T2D).[10-13] The 2018 American Heart Association Scientific Statement on Childhood and

Adolescent Adversity and Cardiometabolic Outcomes highlighted three overall mechanisms of how ELA may impact cardiometabolic health, including behavioral, biological, and mental health pathways.[14] These mechanisms have also been implicated in stress research and influence interrelated physiological systems (eg, neural, autonomic, neuroendocrine, immune responses) through different pathways (i.e., direct biological pathways with feedback loops, gene-environment interactions, and indirect behavioral pathways).[15] Dysregulation of these systems early in life can result in biological imprints and behavioral patterns that have lasting effects over the lifespan and may be passed on to the next generation.[16]

Examining the role of ELA as a SDoH in the pathogenesis of CVD across the lifespan aligns with the National Heart, Lung, and Blood Institute (NHLBI) Strategic Vision.[17] To support this Strategic Vision, the NHLBI Division of Cardiovascular Sciences (DCVS) created an implementation plan that includes three priority areas applicable to this ELA topic: 1) addressing social determinants of cardiovascular health and health inequities, 2) promoting cardiovascular health and preventing CVD across the lifespan, and 3) enhancing resilience for cardiometabolic health.[18] In alignment with these priorities, NHLBI convened an interdisciplinary panel of experts in childhood adversity (https://www.nhlbi.nih.gov/events/2018/social-determinants-health-contributions-early-life-adversity-cardiovascular), SDoH, and CVD for a collaborative workshop on current research knowledge, opportunities for innovation and gap areas, entitled *the "Social Determinants of Health: Early Life Adversity as a Contributor to Disparities in Cardiovascular Diseases."* This manuscript reports workshop proceedings addressing key topics including: 1) disparities in ELA and CVD risk, 2) appropriate models to explain ELA contributions to CVD risk across the lifespan, 3) potential mechanisms underlying elevated risk of CVD (i.e., behavioral, inflammatory, genetic, and hormonal), 4) potential factors that may modify the impact of ELA on CVD risk, 5)understanding the role of resilience for CVD in the face of ELA, and finally 6) recommendations for future research to advance understanding of the impact of ELA on cardiovascular health across the lifespan.

Disparities in Early Life Adversity and CVD Risk

Disparities in cardiovascular health across the life course have been well documented. African American and Hispanic children, as well as children of lower SES, have a higher prevalence of obesity, diabetes, and hypertension.[19] Although obesogenic behaviors, such as low levels of physical activity, diets high in fat and sugar, and short sleep duration contribute to these associations, it is also important to focus on the antecedent causes of obesogenic behaviors, as well as other biological and behavioral factors that increase the risk of adverse cardiometabolic health outcomes[20] and disproportionally impact racial/ethnic minorities and children in lower SES households.

Studies of children[21, 22] and retrospective studies of adults[5, 23] indicate that childhood adversities are common in the U.S., with pronounced differences by race/ethnicity, and socioeconomic status.[16] For example, based on parental reports in the 2016 National Survey of Children's Health (NSCH), Black and Hispanic children had greater prevalence of exposure to one or more adverse experiences (i.e., 61% and 51%, respectively) relative to

non-Hispanic White and Asian children (i.e., 40% and 23%, respectively).[24] Merrick et al analyzed data from 214,157 adult respondents in the 2011-2014 Behavioral Risk Factor Surveillance System, (BRFSS) from 23 states, which indicated that ELA was highest among those with less than a high school education and those with a household income less than $15,000. [23]

Notably, disparities in exposure to ELA vary by country of birth, gender identity, and other factors. For example, children of foreign-born parents report experiencing fewer types of ELA relative to children of U.S.-born parents in the NSCH.[21, 25] Additionally, as reported in the 2011-2014 BRFSS, childhood adversities are disproportionately high among individuals identifying as a sexual minority.[23] Despite these reports of disparities in ELA exposure, there has been limited research to understand the variation in the associations between ELA and CVD risk across vulnerable populations, and even fewer prevention or treatment studies focused on these concerns. Innovative studies examining these associations and their underlying mechanisms specifically among racial and ethnic minorities [22, 26, 27], sexual minorities [28], and children with special health care needs [29], as well as consideration of intersectionality (e.g., synergy of multiple social identities), are needed for these most vulnerable groups.

Furthermore, research on ELA and CVD across population subgroups will need to extend beyond traditional measures of income and education to include the contextual factors (e.g., social environment and neighborhood physical conditions) that differ across groups.

Mechanisms Linking ELA with CVD Risk

There are several potential mechanisms, ranging from behavioral factors to dysregulation of physiological systems, that could explain how ELA increases the risk for CVD. We propose a few here, recognizing this is not an exhaustive list and future research is needed.

Behavioral and Psychological.

Studies in the field of psychology and psychiatry have shown that troubled early relationship experiences negatively impact mental health and health behaviors across the lifespan[30-34]; which can lead to increased risk of CVD.

ELA may lead to deficits in self-regulation, which is the ability to manage one's emotions, attention, and behavior in adaptive ways.[35] Individuals exposed to ELA are more likely to display poor self-regulatory behaviors that are consistent with higher reward thresholds, fewer pleasure responses to rewarding substances, and poorer regulation of appetitive behaviors.[36] This may translate into choices to engage in adverse health behaviors that contribute to increased CVD risk in longterm.[37-39] Nonetheless, individuals exposed to ELA who develop strong self-regulatory capacities do not experience reductions in CVD risk [40-42].

Systemic Inflammation.

Inflammation is a key mechanism underlying cardiovascular disease and is a potential mechanism linking ELA and CVD.[43] There is extensive evidence linking chronic stress and

depression, which are common outcomes with ELA, to systemic inflammation. [44] Furthermore,-although social support or positive quality relationships may buffer stress, individuals who report stressful relationships exhibit dysregulated immune function across the life-span, which can increase the likelihood of developing CVD and other chronic diseases [44] .

Epigenetics.

The molecular mechanisms that regulate gene expression without changing DNA sequences could be a potential explanation for the impact of ELA[45]. Specifically, studies in both animals and humans have found that exposure to ELA is associated with changes in DNA methylation levels in certain genes in the hypothalamus-pituitary-adrenal (HPA) axis and immune system, some of which may contribute to cardiometabolic disorders (e.g., *NR3C1, FKBP5, TLR2*, and *IL6*)[46-48]. Few studies, however, have extensively examined the relationships among ELA, DNA methylation, and cardiometabolic risks simultaneously, especially in the context of health disparities.

Hormonal.

ELA exposures also appear to shape the timing and pace of significant developmental transitions such as puberty [49], even independent of well-established correlates of pubertal onset such as pre-pubertal nutrition and body size and maternal menarcheal age. Specifically, ELA exposures have been related to earlier pubertal timing, which is a risk factor for post-pubertal weight gain, worsening CVD risk factor profiles, incident cardiometabolic disease, and early mortality [50-52]. Although the biological connections between ELA, pubertal development, and cardiometabolic risk have not been fully elucidated, particular pathobiological processes (i.e., hyperandrogenism, insulin resistance, and inflammation) may play a role [53-57] .

Further examination of the various factors that may mediate the relation between ELA and cardiometabolic health is neeed. Given that vulnerable populations are exposed to adversities at multiple levels along with other factors also detrimental to their mental and physical health, there is a need to design studies that examine potential mechanisms with consideration of other exposures that may impact similar pathways as those targeted by ELAs. This work may entail for example, the consideration of moderated-mediation models or the consideration of contextual factors as potential moderators in studies that examine mechanisms.

Models of Risk

Several life course theoretical models have described the emergence of health problems across the lifespan. Although not meant to be exhaustive, we highlight models pertaining to sensitive periods and the accumulation of risk- focused on the timing, frequency, and chronicity of relevant exposures over the life course, inclusive of a range of biological and socio-environmental factors.[58-61] Multiple life course frameworks exist for studying critical and sensitive periods (e.g., in utero, puberty) during which time the occurrence of risk exposures is hypothesized to be particularly salient in programming biological and cognitive

systems.[62-64] Using a developmental approach is key for identifying how the timing of risk exposure influences outcomes and when such effects emerge, including if there are delayed or "sleeper" effects.[65] Developmental approaches are inclusive of socioemotional, cognitive, and neurobiological outcomes and consider both maturational (e.g., normative brain development, pubertal timing) and environmentally-mediated effects (e.g., how early life experiences program biological and cognitive systems for future environments the individual is likely to encounter).

Cumulative risk life course models consider the total number of risk exposures [5, 66] and may include consideration of risk duration and severity, as well as sequence ("chains of risk") and potential clustering. [60, 67-69] One specific example of an accumulation of risk model that addresses social and racial health inequalities is the "weathering" hypothesis. This model proposes that stress exposures experienced disproportionately (and some uniquely—i.e., racial discrimination) in marginalized groups may accumulate over time, resulting in excessive wear and tear on the body, accelerated aging and sexual development including early puberty and childbearing, and subsequent increased risk for poor health and disease [70, 71]. In support of this model, a significant body of research has documented associations between experiences of racial discrimination and deleterious health outcomes among African Americans [16, 68, 72, 73]. Consideration of multiple models of risk may explain how early life risk factors across multiple developmental contexts may independently, in sequence, and/or in interaction with other social and biological risk factors increase the likelihood of disease, death, and disability across the life course.

Potential Moderators of the ELA and CVD Association

Associations between stress and disease are stronger among some individuals or groups than others in the empirical literature and have historically been treated as inevitable population variability, necessitating larger sample sizes to detect the expected stress-disease effects[74]. Thus, scholars have increasingly argued that understanding *why* stress impairs the health of some individuals more than others is a critical unanswered question in the field.

For example, although evidence for the link between ELA and increased inflammation exists, this pathway is not evident for all individuals. Numerous studies assessing childhood stress and inflammation have failed to find associations between these two variables, or have found this link only among select subsets of youths, such as those with high adiposity, certain cognitive appraisal styles, SES backgrounds, or among particular racial or ethnic groups.[75-80] Furthermore, differential response to ELA may be due to differences in biological sensitivity to a range of environmental influences. For example, the Biological Sensitivity to Context theory [81] proposes that children differ in their susceptibility to environmental influence in a "for better and for worse" manner, depending on their psychobiologic reactivity to stress.

Understanding why stress impacts the health of some but not others may also be explained by differential social context. Children who experience one ELA are often also experiencing additional hardships, such as poor housing conditions, poor neighborhood environments, and/or poor school environments, which exacerbate the potential effects of ELA on health.[82]

Children who belong to racial/ethnic minority and lower SES households may not only be experiencing ELA at the individual level but also disproportionally experience other societal adverse circumstances in their communities, at school and their neighborhoods further contributing to disparities in CVD.[40] The potential moderating effects of sex and gender is also an important consideration [83, 84].

Resilience

Although mechanistic studies of the ELA-CVD pathway are needed, so too are studies that elucidate resilience or protective factors within the ELA-CVD pathway. ELA contributes to adverse health outcomes, yet personal and social resources and the contexts within which they operate have the potential to offset adverse outcomes. Thus, resilience, or better than expected outcomes in the face of adversity or risk[85], can result through an intersection of individual, relational, and environmental characteristics. Research relies predominantly on group comparisons between ELA-exposed versus non-ELA-exposed individuals, rather than a focus on differences in protective and resiliency factors among ELA-exposed individuals who do not develop adverse outcomes such as CVD.[86] Therefore, research is needed to address this limited understanding of biological and psychosocial resilience among persons who have experienced ELA.

Resilience encompasses the factors that define both individual and collective resources [86, 87]. For example, Kim et al identified CVD resilient neighborhoods among the black population as those having a high percentage of persons with some college or college completion, fewer residents with incomes below the federal poverty threshold and significantly lower Gini index (measure of the distribution of income across population-level income percentiles) than at-risk census tracts.[87] Thus, research on the developmental pathophysiological mechanisms of ELA on CVD must appropriately address the psychosocial and biological mechanisms that can promote health and reduce CVD risks, at multiple levels, while taking into account the level, timing, and chronicity of ELA among exposed individuals.[78]

When addressing CVD and disparities, understanding individual and group differences is particularly salient for preventive intervention efforts. As argued by Sapolsky (2015), the robust evidence for the detrimental health effects of ELA is matched by similarly robust evidence for developmental plasticity in the expression of these effects. Hence, the earlier in life we can identify which individuals, under which stressors, develop biobehavioral CVD risk factors, the sooner we can tailor interventions to attenuate these effects and promote long-term cardiovascular health. Further, by understanding group differences in the stress-health link, we can more effectively tackle systemic health disparities disproportionately affecting low income and minority populations who historically face an increased burden of stressors.[40, 41]

Recommendations

Although a substantial body of research has established an association between ELA and CVD risk, research is needed to inform the development of public health and clinical

interventions. As summarized (Table), this workshop highlighted several gaps and opportunities for expanded research inquiry and reduce health disparities.

Explaining links between ELA and child and adult physical health benefits from a developmental approach, beginning with an understanding of biopsychosocial processes operating as early as the prenatal period and continuing into late adulthood. More consideration is also necessary to examine the individual and group differences in susceptibility, including individual, relational, and contextual promotors of resilience. Future research should also focus on resilience within high-risk populations as well as ELA that may be more prevalent in specific subgroups of the population (e.g., structural inequity, racial discrimination, bullying, immigration, sexual abuse). National, longitudinal, cohort study datasets should consider including questions that address social factors, as well as biological outcomes, to allow for the meaningful examination of ELA at the population level. Although measurement of ELA is beyond the scope of this manuscript, by leveraging these resources researchers can consider various factors related to the measurement and conceptualization of ELA, including but not limited to the use of retrospective vs prospective reports, exclusion of SES as an ELA and the use of traditional unweighted summary scores among other considerations. Considering that socioeconomic status can be both a moderator of the ELA and health relation as well as a contributor to increased exposure to ELAs, researchers should derive ELA measures that consider adversity apart from socioeconomic status and pursue refined measures that capture more information than traditional unweighted adversity summary scores. [88, 89] Furthemore, given the long latency period between ELA and CVD, prospective measures of adversity may not always be available, thus use of valid and reliable questionnaires to assess childhood experiences retrospectively is needed.

The study of ELA and CVD requires multiple disciplines and new approaches to advance the field. Translation of ELA research findings to practice and policy focused on CVD prevention or intervention has been limited. Addressing ELA through prevention efforts, mitigating the consequences and building resilience factors and buffers will be informed by longitudinal, prospective, and multilevel interdisciplinary studies. Multilevel interdisciplinary studies would include addressing all levels of the ecosystem including interpersonal, familial, community, and structural factors. The outcomes of these studies should be used to inform best practices for intervention research and then the translation to implementation science.

The NHLBI strategic vision addresses the scientific challenges related to elevated cardiovascular risk associated with SDoH and health inequities throughout the lifespan. The NHLBI encourages innovative, inspired, multidisciplinary research and evidence-based prevention and treatment strategies that advance the field towards implementation research to improve cardiovascular health starting in early life and continuing throughout the life span.

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Table:

Early Life Adversity (ELA) and Cardiovascular Disease Disparities: Research Gaps and Research Recommendations

IDENTIFIED RESEARCH GAPS	RESEARCH RECOMMENDATIONS
Developmental Timing	• Understand how ELA may differentially impact or imprint physiological systems at developmental time points, from the prenatal to late adulthood period, to influence CVD risk.
Interdisciplinary Approach	• Engage interdisciplinary approaches to examine the impact of ELA across multiple, related biological systems (genomic, neuroendocrine, cardiovascular, etc.), rather than examining individual systems using a silo-based approach. • Utilize an interdisciplinary approach that recognizes other SDoH factors (e.g., adverse physical environment) often co-occur with ELA exposure and can compound CVD risk.
Critical Populations	• Examine differential ELA impact and intersectionality considerations for racial and ethnic minorities, sexual minorities, and children with special health care needs as these populations may experience multiple and chronic forms of ELA and differential risk due to social and structural conditions.
Inclusion of Resilience	• Explore modifiable resilience factors in early life and investigate their impact on CVD. • Examine psychological, behavioral, neurological, genetic, biochemical or physiological factors that characterize the resilience pathway among persons with ELA histories who do not develop CVD.
STUDY DESIGN CONSIDERATIONS	
Prospective Cohort Studies	• Design studies staring in pregnancy or infancy to understand mechanisms by which ELA impacts cardiovascular health across the lifecourse as well as understand risk and protective factors which may inform intervention starting earlier in the lifecourse.
Natural Experiments	• Promote research studies that occur in traumatic and stressful environments settings, such as foster care, community-based resilience programs, home visiting programs, or after natural disasters as natural experiments for prospective data.
Intervention Studies	• Encourage studies aimed at prevention or reducing the impact of ELA to examine their impact on cardiometabolic health and health behaviors.. • Conduct intervention research studies on ELA that focus on multiple levels of analyses; i.e., individual or family levels, school/community levels, or at home.
Multi-level Studies	• Consider study designs that capture cumulative risk across all levels of the ecosystem (interpersonal, familial, community, and structural exposures).