Mechanisms Underlying the Association Between Early-Life Adversity and Physical Health: Charting a Course for the Future

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ABSTRACT

Early-life adversities (ELA) are associated with subsequent pervasive alterations across a wide range of neurobiological systems and psychosocial factors that contribute to accelerated onset of health problems and diseases. In this article, we provide an integrated perspective on recent developments in research on ELA, based on the articles published in this Special Issue of *Psychosomatic Medicine*. We focus on the following: 1) the distinction between specific versus general aspects of ELA with regard to the nature of exposure (e.g., physical and sexual abuse, emotional abuse or neglect, relative socioeconomic deprivation), biological and behavioral correlates of ELA, and differences across diseases; 2) the importance of timing in the critical phases of exposure to ELA; and 3) adaptive versus dysfunctional responses to ELA and their consequences for biological and behavioral risk factors for adverse health outcomes. This article concludes with outlining important new targets for research in this area, including the neurobiology of affect as a mechanism linking ELA to adverse health outcomes, and the need for large-scale longitudinal investigations of multisystem processes relevant to ELA in diverse samples, starting prenatally, continuing to late adolescence, and with long-term follow-up assessments that enable evaluation of incident disease outcomes.

Key words: early-life adversity, adverse childhood experiences, health, disease, mechanisms, social determinants.

INTRODUCTION

The articles in the special issue demonstrate that increases in physical health problems emerge early in development among children exposed to adversity. These include global indices of health problems and health impairment (1,2), asthma (3,4), obesity (5), and pain conditions (6). Articles in this issue also provide evidence that a number of neurobiological mechanisms underlie the associations of adversity experienced in utero and in childhood with physical health problems across the life course, including inflammatory (7), cardiometabolic (8), epigenetic (9,10), gene expression (10), and cellular aging pathways (11). It is intriguing that in contrast to influential theories (e.g. 12), two articles failed to find evidence for cardiovascular mechanisms linking early-life adversity with child and adult physical health outcomes (1,13). In addition to these neurobiological mechanisms, articles in the special issue highlight the importance of psychosocial mechanisms in the association between early adversity and health. Most notably, multiple articles document a mechanistic role of psychological distress and mental health problems in the link between adversity and health. Psychopathology, particularly anxiety and depression, mediated the association between early-life adversity and postpartum weight retention (3), trajectories of health across childhood and adolescence (2), adult cardiometabolic risk (8), and risk of asthma and allergy in one's offspring (4). Social relationships also partially explained adversity-health associations (3). Not all examinations of social mediators produced positive findings, however. For example, negativity in the parent-child relationship did not mediate the association between family socioeconomic status (SES) and health impairment in young children (1). Finally, the special issue highlights the significance of chronic pain as an outcome associated with early-life adversity beginning early in the life course (6) and the role of central sensitization as a mechanism explaining this association (14).

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Together, these findings reveal pervasive alterations across a variety of neurobiological systems and psychosocial factors among individuals exposed to adverse early environments that, in turn, contribute to accelerated onset of health problems and disease. Yet, the pathways explored here are by no means exhaustive, some articles represent fields in their infancy in terms of bridging social and biological sciences (e.g. social epigenetics), and some articles failed to find support for mechanisms widely argued to play a role in the link between adversity and health despite strong study designs (e.g., (13)). A multitude of fundamental questions about the pathways linking adverse early environments to the onset of disease remain unanswered. We highlight some of the most pressing issues for the field with the goal of stimulating innovative research on these topics.

ARE THE ADVERSITY EXPOSURES AND MECHANISMS LINKING ADVERSITY TO HEALTH UNIVERSAL OR SPECIFIC?

Determining the degree of specificity with regard to exposures, mechanisms, and outcomes in the associations between early-life adversity and health is a critical issue for future research. First, the term adversity is used to refer to a broad range of experiences including child abuse and neglect, parental psychopathology, and poverty. Many studies, including some in this issue, combine these diverse experiences into a cumulative risk index and associate that index with health outcomes and underlying mechanisms. This approach has been advocated to address challenges in measurement, reporting, and statistical modeling of adversity (15). However, this approach has been critiqued for failing to distinguish between diverse experiences that may have differing associations with neurobiological and psychological development that contribute to psychopathology following adversity (16,17). For example, in some cumulative indices, an individual who experienced a singular experience of sexual abuse by a stranger would have the same adversity score as a child who was chronically abused by a parent for a decade or who had a parent with depression. Emerging evidence suggests that this type of approach clouds specificity in the associations of adversity with emotion, cognition, and at least some of the neurobiological pathways thought to play a role in the onset of disease, including regulation of stress response systems (18). Indeed, Chen et al. (7) demonstrate that, although two distinct dimensions of SES, prestige (parent education), and resources (assets) are each associated with asthma-related clinical outcomes, the mechanisms underlying these associations are distinct such that prestige is associated with better control behaviors within the home and lower exposure to smoke, whereas resources are associated with a more advantageous profile of immune regulation. The degree to which specificity across different forms of adversity exists in other neurobiological pathways involved in the adversity-health association remains a critical question for the field. Moreover, it is often not feasible to ask the types of detailed questions required for distinguishing adverse experiences, particularly in epidemiological samples. One article in this issue, however, provides an excellent example of combining detailed assessment with a population-based approach. Baldwin et al. (5) demonstrate in a large representative twin birth cohort that childhood bullying, especially when chronic, predicts adolescent overweight, adjusting for a broad range of potential confounds including other adversities such as maltreatment and genetic and fetal liability for overweight. Such sophisticated prospective study designs are required to evaluate the degree to which the mechanisms linking heterogeneous forms of adversity with physical health are general versus specific across experiences.

In addition to exposure types, greater attention to specificity in examining mechanistic pathways is needed. The investigation of Loucks et al. (9) on epigenetic mechanisms linking adversity with adult body mass index revealed that childhood SES was associated with adulthood DNA methylation in adipose tissue, but not in blood leukocytes, providing important data for the tissue-specificity debate within the field of social epigenetics and pointing, more broadly, to the importance of investigating specific disease-relevant systems and tissues when examining other neurobiological pathways. Again, the work of Chen et al. (7) provides an illustrative example by demonstrating that different dimensions of SES had distinct associations with particular markers of immune regulation in response to specific environmental and corticosteroid triggers but not others. This type of approach has the potential to identify the specific neurobiological mechanisms most relevant for specific exposures, which may ultimately generate innovative targets for early intervention.

Greater specificity would also be useful in the domain of emotional mechanisms, which reflect neurobiological and cognitive processes but are often measured with self-report instruments in the adversity-health literature. Given that many forms of adversity influence emotional development, more research is needed on the *affective* mechanisms linking early adversity and health using novel neuroimaging methodologies. This issue is particularly salient for the field of psychosomatic medicine given that in the Great Debate of 2001, the primary question under consideration was whether emotional processes or stress have direct physiological effects on physical health and whether interventions to improve emotional functioning also improve medical outcomes (19). Atypical patterns of emotional processing are a key mechanism linking early-life adversity with psychopathology (20) but have been investigated less frequently in relation to physical health outcomes.

Although several studies in this issue demonstrate the critical role of mental health in linking adversity to physical health, greater specificity in the measurement of affective mechanisms is needed. Given that many forms of early adversity are associated with deficits in emotional awareness and ability to report on feelings and emotions (21,22), there is a particular need for future studies to go beyond simple self-reports of affective symptoms in investigating emotional mechanisms linking early adversity with physical health. Advances in functional neuroimaging have provided useful tools for measuring emotional reactivity and regulation, as well other emotional processes. Yet, despite extensive work in the area of adversity and mental health, surprisingly little research has incorporated affective neuroscience measures into the study of mechanisms linking adversity with physical health. This represents an important next step for the field.

A final issue with regard to specificity involves health outcomes. In particular, mental and physical health outcomes are rarely considered simultaneously, precluding progress in identifying mechanisms that are shared across disparate health outcomes and those that are domain specific. This is surprising, in light of research demonstrating associations between atypical patterns of regulation of physiological stress response systems and both physical and mental health problems (23). A recent epidemiological study examining the associations of a wide range of early-life adversities with both mental and physical health outcomes provides evidence for shared pathways of social support and behavioral factors but also for specificity in the links between particular experiences and specific health outcomes (24). Evaluating the degree to which specific neurobiological, affective, and psychosocial pathways contribute to diverse health outcomes is a critical next step for the field, as innovations in intervention require greater knowledge about shared pathways that could be targeted to prevent a host of adverse health outcomes as well as unique pathways that have relevance to particular outcomes.

ARE THERE SENSITIVE PERIODS FOR EXPOSURE, AND DOES IT DEPEND ON THE SYSTEM OF INTEREST?

A fundamental principle regarding the effects of experience on neurobiological development is that timing matters. Although neural plasticity persists across the life course, extensive evidence documents that plasticity is heightened during developmental windows in which the nervous system is particularly responsive to certain inputs from the environment. These windows are referred to as critical or sensitive periods (25). Although sensitive periods have been identified with regard to the impact of experience on the development of sensory systems, the degree to which such periods exist within the peripheral nervous system and in other regulatory systems is largely unknown. A recent study, however, documented that psychosocial deprivation early in life exerted pronounced effects on the development of the hypothalamic-pituitary-adrenal (HPA) axis, but only during a sensitive period during the first 2 years of life (26). Determining whether such periods exist in other systems is critical not only for understanding when and how adversity will have the most potent influences on neurobiological development but also for targeting interventions during periods of heightened plasticity. Relatedly, multiple cascading sensitive periods that unfold over development have been observed in some domains (e.g.,language development) (for discussion, see 27) but have yet to be examined in most pathways underlying adversity-health associations. Identifying periods of particular susceptibility to the social environment represents a critical area for future research.

Research on sensitive periods and health is relatively consistent in documenting that exposures occurring very early in development may have more pronounced effects on development than those that occur later. Building upon extant animal literature, Thomfohr-Madsen et al. (4) highlight the possibility that exposures during a mother's own childhood can affect her child's risk for developing airway disease, through intergenerational transmission of the effects of adversity. An additional article in this issue found that exposure to maternal depression during the prenatal period, but not during preconception, is most relevant for offspring cortisol regulation (10). The burgeoning fields considering prenatal programming, intergenerational transmission of effects of the social environment, and sensitive periods of development are poised to provide important insights about the etiology of disease and opportunities for successful intervention.

DOES ALTERED DEVELOPMENT AFTER ADVERSITY REFLECT ADAPTATION OR DYSFUNCTION?

It is important to consider that humans are designed to adapt to a broad range of environments to promote survival and ensure reproductive success. Many outcomes of adversity described as dysfunction or dysregulation actually reflect adaptations that are advantageous in an adverse environment, at least in the short-term, despite having pernicious long-term consequences (23,28). For example, metabolic changes that allow a neonate to respond adaptively to undernutrition in utero may contribute to enhanced risk for obesity and cardiovascular disease in a calorie-rich environment later in life (29). In addition, some argue that environmentally shaped enhanced physiological reactivity is not only a risk factor for poor health in risky environments but can promote health and well-being in more advantageous environments (for reviews, see 30 or 31), or that

accelerated development provoked by adversity exposure is adaptive evolutionarily by increasing chances for survival and reproduction despite links with earlier onset of disease (32). Complexities in interpreting variation in biological functioning are further exemplified by evidence that associations between adversity and physiological indicators of stress regulation are sometimes nonlinear and vary by race/ethnicity (e.g., 33). The associations of adversity with early-onset pain conditions (6) and heightened central sensitization, a potential mechanism underlying enhanced pain (14), provide additional examples of adaptations that may confer benefits in an adverse environment in the short term but result in morbidity and disability in the long-term. In our quest to understand mechanisms, it is critical to attend to the potential benefits conferred by neurobiological and psychosocial adaptations to adverse environments, use caution with labels such as "maladaptive" and "dysfunctional," and integrate theories and evidence from the multitude of relevant perspectives on developmental variation following adversity.

WHERE DO WE GO FROM HERE?

The articles in this special issue provide a broad illustration of the immense progress in studying mechanisms for the effects of early-life adversity on health across the life course. Yet, much remains to be accomplished in charting these pathways. Despite increasingly large literature in this area, more large-scale research is needed that contains rich prospective measurements of early exposures, biological and behavioral mechanisms, brain structure and function, as well as multiple aspects of physical health. Many articles studied precursors to disease (e.g., adiposity, cardiometabolic measures, and immune processes) or endophenotypes thought to predict variability in health and disease outcomes (e.g., DNA methylation and telomere length) rather than disease outcomes. Additional studies are needed to determine the extent to which the biological embedding is enduring over time and whether such effects mediate broader health consequences.

Another significant challenge for this body of research is to incorporate rigorous methods that can identify causal effects while still capturing the complexity of adverse social experiences (34). To date, experimental evidence for the health effects of adversity have come from animal studies or from naturalistic experiments in humans (e.g., famines, natural disasters, and sudden economic shifts). Although their sample size was small, Schneper et al. (11) used random assignment of primates to parenting environments, increasing confidence in the causal nature of the effects on adult telomere length. Experimental manipulation of adversity exposure involves ethical complexities for both animal and human research, and a promising future direction for the field is to examine mechanisms of adversity in the context of randomized preventive interventions. Developmental processes that are altered by intervention and that confer protection against negative health outcomes can be inferred to be causal risk factors for those outcomes (35). Intervention designs are powerful tools that have yet to be widely used for shedding light on mechanisms linking early-life adversity to health. Given the consistent evidence in this issue documenting mental health symptoms as a mechanism linking adversity with physical health outcomes (2–4,8), intervention designs could be used to determine whether reducing psychological distress and/or treating psychopathology in populations exposed to adversity also confers physical health benefits.

The special issue specifically emphasizes mechanisms, but consideration of moderators at multiple levels of influence that confer resilience to physical health problems following adversity exposure is equally important. For example, Hagan et al. (1) demonstrate that individual differences in autonomic reactivity moderate the association of SES with child physical health impairment and suggest that better parent-child relationships protect children in low-SES families from poor physical health. Identifying modifiable factors that buffer children from the health consequences of adversity may stimulate innovation in preventing the health consequences of adversity by identifying novel targets for early intervention.

Leveraging basic research to develop more effective interventions for children exposed to adversity is the penultimate goal of the research presented in the issue. Although eradicating early-life adversity would likely produce substantial improvements in population health, this is unlikely to occur without substantial policy change (36). In the meantime, identifying mechanisms and protective factors is a particularly useful contribution of basic research in this area because it can contribute to greater knowledge of whether, and how, the negative health consequences of early-life adversity can be reversed or prevented. Relatively little is known currently about how to most effectively target the neurobiological mechanisms highlighted in this issue, although the effects of psychosocial interventions on neurobiological systems are being studied increasingly and the early evidence for such effects is promising (e.g. 37). The articles in this special issue stimulate progress in this domain because they provide additional foundation for understanding the mechanisms linking early-life adversity to health. These research findings can be used to generate novel strategies for preventing disease across the life course in individuals who are disproportionately vulnerable to adverse health outcomes.

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