NATIONAL SCIENTIFIC COUNCIL ON THE DEVELOPING CHILD

Connecting the Brain to the Rest of the Body: Early Childhood Development and Lifelong Health Are Deeply Intertwined

WORKING PAPER 15

Center on the Developing Child HARVARD UNIVERSITY

NATIONAL SCIENTIFIC COUNCIL ON THE DEVELOPING CHILD

This paper is dedicated to Bruce S. McEwen, Ph.D. (1938-2020)

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***** *Dr. Bruce McEwen contributed in many ways to the drafting of this paper before his untimely death in January 2020. We greatly miss him as a person and as a world-leading expert whose wide-ranging knowledge and gentle humor were so appreciated by the members of the National Scientific Council and all of his many admirers and students.*

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The National Scientific Council on the Developing Child, housed at the Center on the Developing Child at Harvard University, is a multidisciplinary collaboration designed to bring the science of early childhood and early brain development to bear on public decision-making. Established in 2003, the Council is committed to an evidence-based approach to building broad-based public will that transcends political partisanship and recognizes the complementary responsibilities of family, community, workplace, and government to promote the well-being of all young children. For more information, go to www.developingchild.net.

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The Issue: Health and Learning Are Interrelated in the Body but Separated in Policy

A growing understanding of how responsive relationships and language-rich experiences for young children help build a strong foundation for later success in school has driven increased investment and sparked innovation in early learning around the world. The rapidly advancing frontiers of 21st-century biological sciences now provide compelling evidence that the foundations of lifelong *health* are also built early, with increasing evidence of the importance of the prenatal period and first few years after birth.[1] The science is clear on two points:

1. What happens during this period can have substantial effects on both short- and long-term outcomes in learning, behavior, and both physical and mental health.
2. All of these domains are remarkably interdependent and the potential for learning is inexorably linked to the quality of physical and mental health.

A child who is living in an environment with supportive relationships and consistent routines is more likely to develop well-functioning biological systems, including brain circuits, that promote positive development and lifelong health. Children who feel threatened or unsafe may develop physiological responses and coping behaviors that are attuned to the harsh conditions they are experiencing at the time,[2] at the long-term expense of physical and mental well-being, self-regulation, and effective learning.[3] Policymakers, leaders of human services systems, intervention developers, and practitioners can all use this knowledge to create innovative solutions to reduce disparities in preventable diseases and premature deaths and lower the high costs of health care for chronic illnesses that have their origins in early childhood adversity.[4,5] Moreover, these costs are likely to grow unless society's investment in promoting health and preventing disease moves "upstream" to address the sources of these problems in early childhood.

Nearly all aspects of early development and later health are affected by interactions among experiences, genes, age, and the environments in which young children live. These interactions influence every biological system in the body, with especially powerful effects in the earliest years.[6,7] Systems relating to brain development, heart and lung function, digestion, energy production, fighting infection, and physical growth are all interconnected and influence each other's development and function. Each system "reads" the environment, prepares to respond, and shares that information with the others. Each system then "signals back" to the others through feedback loops that are already functioning at birth.[8] As an example, higher rates of infection in early childhood can increase the level of anxiety at later ages[9], which can then compromise school performance. Children living in conditions of threat and deprivation may emerge as adults with a greater risk for multiple forms of cardiometabolic disease. In short, the environments we create and the experiences we provide for young children and their families affect not just the developing brain, but also many other physiological systems, from cardiovascular function and immune responsiveness to metabolic regulation. All of these systems are responsible for our lifelong

The environments we create and the experiences we provide for young children and their families affect not just the developing brain, but also many other physiological systems.

health and well-being.

The brain and all other organs and systems in the body are like a team of highly skilled athletes, each with a specialized capability that complements the others and all of whom are dedicated to a common goal. The members of a well-functioning team read each other's actions, adjust their own actions according to what happens around them, and continuously learn from each other. Over time, biological systems in the body mature into a finely tuned unit and respond as one to a multitude of challenges. As their shared experiences or environments change, these systems must adjust, just as players in each position must respond. Each performance builds on what came before and, while adjustments are always possible, it is more difficult—and more costly—to change strategies, patterns, and habits later than to build a well-functioning and efficient team from the beginning. And just as every team is different in how the players respond and adjust to their environment, so is every child. The core concepts of development apply to every individual, but how these systems adapt and interact can vary, and these differences are essential for developing effective prevention and intervention strategies based on 21st-century science.

The policy and practice implications of this knowledge are striking: *Strategic investments in young children and the adults who care for them affect long-term physical and mental health as much as they affect early learning.* When access to essential resources and supportive relationships is secure, the building blocks of both resilience (e.g., self-regulation and adaptive skills) and wellness (e.g., well-regulated stress response systems) are strengthened.[10] When hardships or threats are extreme or persistent, particularly in the context of intergenerational poverty and/or systemic racism[11], multiple biological systems can be disrupted. The "downstream" results of these disruptions are poor educational achievement, lower economic productivity, higher rates of crime, and increased heath care costs.[12,13,14,15]

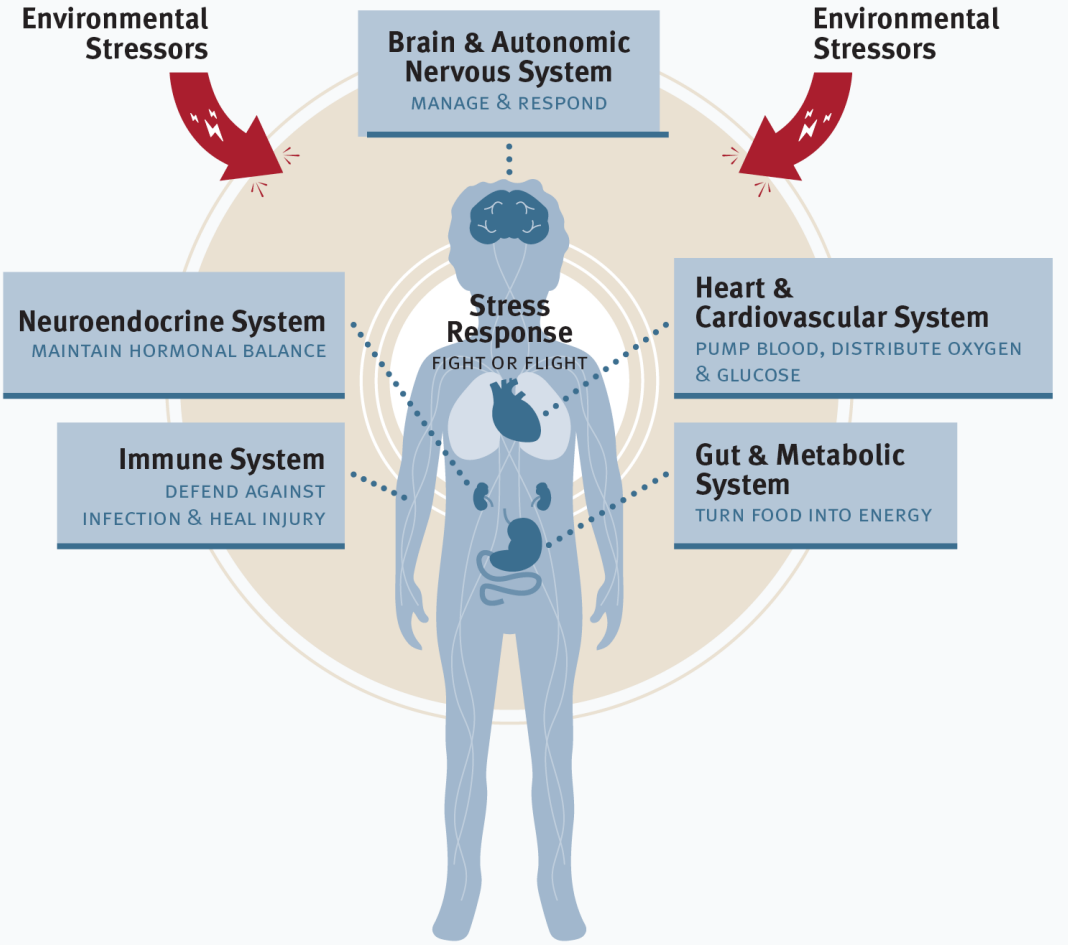
What 21st-Century Science Is Teaching Us

All biological systems in the body interact with each other and adapt to the contexts in which a child is developing—for better or for worse—and adaptations in one system can influence adaptations in others. Think about how all the systems in a young child's body must function in a highly coordinated way to respond to challenging conditions. The initial biological response is the same whether the experience is a short-lived, normative experience, like the first day in a child care center, or the ongoing trauma of recurrent physical abuse—it's the duration, severity, and timing of the experience (along with the availability of supportive relationships) that determine whether the response is ultimately harmful or growth-promoting.[16] In both situations, the body's stress systems respond by coordinating multiple interactive components: (1) the autonomic nervous system increases heart rate and breathing so the cardiovascular system can pump more oxygen-rich blood to the brain and muscles to drive the "fight or flight" response; (2) the immune system is activated to fight against the possibility of open wounds and infection; (3) metabolic systems are tuned up to generate more energy to fuel the body's cells, tissues, and organs; (4) the neuroendocrine system maintains the delicate balance of hormones that regulate many dimensions of the body's adaptation to what it senses in the environment.

This integrated response to threat is a vivid example of team players working toward a common purpose: All of these systems are robustly interconnected and together help the body adapt to the environment around it. The brain receives signals from each system, which influence how it works (and can even alter its chemistry and architecture), and then sends signals *back* to other organs. For example, multiple studies show that physical exercise

Biological Systems Interact With Each Other and the Environment

When external threats trigger the body's stress response, multiple systems spring into action like a team of highly skilled athletes, each with a specialized capability that complements the others. Systems relating to brain activity, heart and lung function, digestion, energy production, and fighting infection are all interconnected and influence each other's development.



promotes cardiovascular health and *also* stimulates the processes that lead to new neural connections and increased blood flow in the brain that improve memory and mood.[17,18,19,20,21] Diabetes is associated with problems in sugar metabolism that can affect tiny blood vessels in the eyes and kidneys that may lead to impaired vision and kidney malfunction. These same metabolic disruptions can also produce changes in brain architecture that may lead to impaired mood and memory, as well as increased risk for later dementia.[22,23] These are just a few of many examples that illustrate the connections between the brain and the rest of the body.

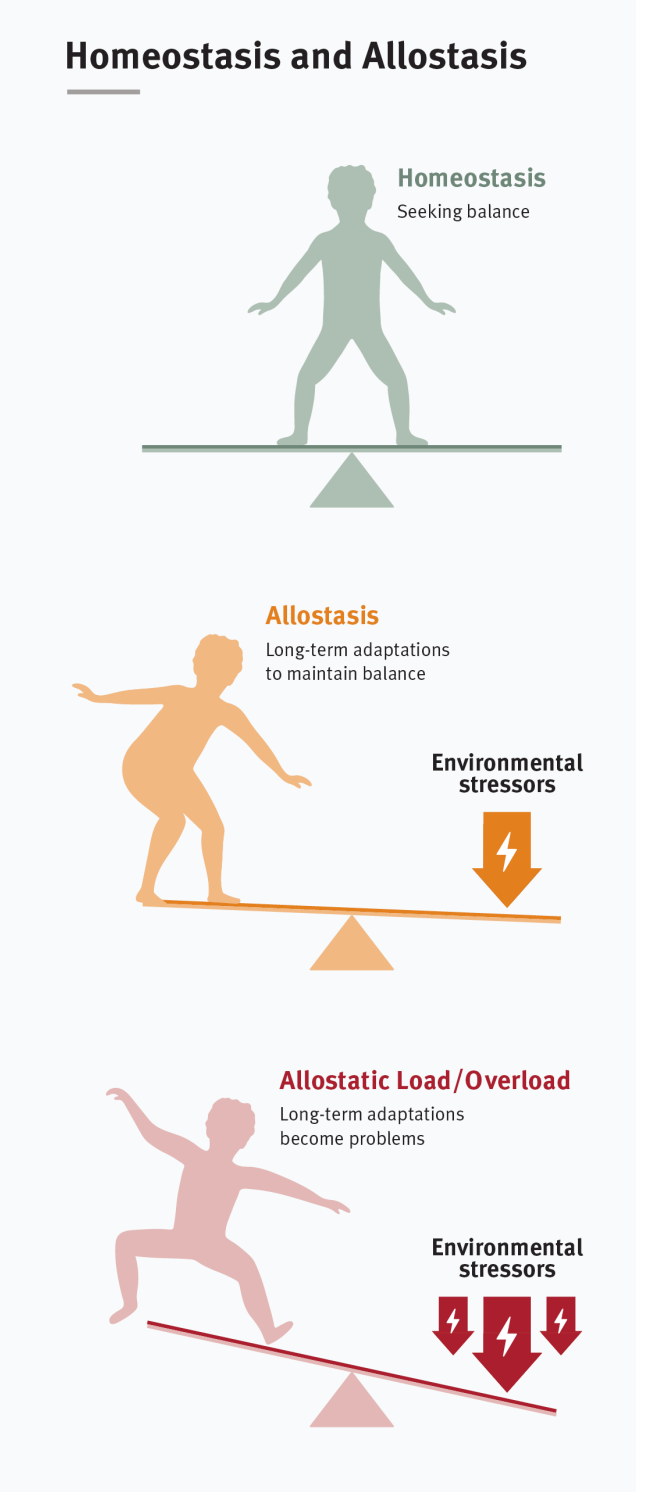
Our bodies are designed to maintain a healthy physiological balance and to restore

it when it's disrupted. The continuous interactions and responsive feedback among multiple systems are designed to seek and sustain that balance within a relatively narrow range of operation, a process that scientists call *homeostasis*. Normal body temperature, for example, is programmed to remain at around 98 degrees Fahrenheit, and too much variation on either side triggers multiple physiological responses to restore a normal range (e.g., sweating decreases body temperature and shivering increases it).

Excessive and persistent adversity early in life can overload biological systems and lead to long-term consequences. Mobilizing the body's responses to threat diverts energy away from growth and healthy development. For a child experiencing "time out" for a temper tantrum, the challenge will pass, balance is restored, and biology can return to the business of building a healthy brain and body. Not so for a child experiencing the persistent threat of maltreatment, as continuing activation of the stress response will compromise the body's investment in growth.

The process of the body adapting to manage threats, such as increased blood pressure as a response to stress, is what scientists call *allostasis*. If a threat or hardship is too intense or prolonged, it results in *allostatic load* or *overload*.[24] As with any overloaded system, allostatic load can lead to breakdowns (i.e., physiological and behavioral changes that can undermine both physical and mental health). Elevated blood pressure, for example, is initially part of the stress response that gets needed blood, nutrients, and oxygen to all cells in the body, but if it is too high for too long it damages arteries, which can lead to a heart attack or stroke.

If the body receives indications that the environment is generally predictable and presents manageable challenges, a child can develop a well-regulated stress response system more readily. If, however, the brain perceives excessive, frequent, or persistent threat, it learns to expect adversity and develops a "shorter fuse" for activating physiological responses throughout the body.[25] These adaptations can lead to costs as well as benefits—they are health-protecting in acute, short-term situations but can become health-damaging if activated at too high a level for



too long.[26,27,28] Such tradeoffs often occur when the body adapts to one environment (e.g., a threatening one) but later needs to adjust to different conditions (e.g., a neutral situation).

Consider, for example, children developing under conditions of poverty, where dedicated parents and other caregivers are burdened by the challenges of making ends meet. These challenges are often embedded in structural inequities such as residential segregation, food deserts, and limited employment opportunities. Nutritious food may not be readily available, stable housing may not be assured, and constant economic worries and unpredictability may impose continuous distractions on daily adult/child interactions, which activate multiple components of the stress response. Some children may develop behaviors that help them adapt to and cope with these conditions of scarcity or fear (e.g., binge eating whenever possible), yet these short-term adaptations can become problematic later in life.

For children who are not living under conditions of chronic hardship, activation of stress response systems that are brief and intermittent, followed by a return to balance, leads to healthy adaptations that build resilience—just as a fire drill prepares children for an emergency but then restores order after a short time. In contrast, if stress responses remain activated at high levels for long periods, this can have a significant wear-and-tear effect on the brain and other biological systems. In other words, if children were disrupted by urgent fire drills nonstop for days, weeks, or months, they would be worn down over time and less likely to respond effectively to a true emergency. In the body, this cumulative burden can lead to both short- and long-term consequences that may include maladaptive behaviors (e.g., difficulties with impulse control, addictions), a "weathering" effect that accelerates the aging process, chronic illness in adulthood, and a shortened lifespan.[29]

A growing body of evidence from both the biological and social sciences builds on this concept of chronic wear and tear. Beyond the cumulative effects of chronic adversity more generally, this research provides a compelling framework for exploring how well-documented racial disparities in health, independent of socioeconomic status, may be rooted in the effects of both individual and systemic racism on early childhood development.[30] At an individual level, multiple studies have documented how the stresses of everyday discrimination on parents or other caregivers can affect caregiving behaviors and adult mental health, and by extension child development.[31,32,33] At an institutional level, researchers are investigating how structural inequities and discriminatory laws affect the context in which families of color raise children. Unequal access to high quality education and health services, economic opportunities, and wealth accumulation, compounded by racial disparities in the child welfare and criminal justice systems, provide multiple examples of how the legacy of racism in policies and systems has created conditions that disproportionately undermine the health and development of children and families of color.[34]

How Early Adversity Affects Developing Biological Systems

When stress responses are activated frequently, intensively, and persistently during early childhood, the systems involved can become permanently calibrated to activate more easily and may not turn off as readily as they should.[35,36,37] From a biological perspective, this is essential for survival. If the world is a dangerous place, the internal systems designed to protect us need to develop in a way that anticipates frequent threats. Yet over time, these repeated activations lead to greater risk for stress-associated diseases well into the adult years—conditions such as cardiovascular disease, obesity, type 2 diabetes, respiratory and immunological disorders, and a range of mental health problems.[38,39] That's the trade-off of adapting to significant early adversity.

What might be happening in a young

child's environment that could transform an adaptation that is advantageous in the short term into an unhealthy, chronic stress activation with long-term consequences? Among the possible answers:

- the socioeconomic hardships of poverty;
- the material and psychosocial burdens of intergenerational racism or other forms of institutionalized discrimination;
- the psychological threats of maltreatment and community violence;
- the interpersonal challenges of maternal depression and parental addictions;
- the physiological disruptions of air pollution and environmental toxicants;
- the metabolic consequences of inadequate or excessive nutrition;
- the developmental burdens of chronic disease or disability.

Any of these stressors—particularly when perpetuated by recurrent triggers and/or systemic barriers to effective prevention, reduction, or mitigation—can contribute to an environment that may persistently and intensely activate a developing child's stress response systems.[40]

Poor health outcomes are not inevitable, but they are more likely if we do not adequately support children and families experiencing persistent hardships or challenges.

Physiological systems typically work most effectively when they operate within a well-regulated range—and significant deviations beyond either end of that range can lead to problems in physical and mental health. For example, an immune system that doesn't react at a sufficiently high level will be unable to fight off serious infection, but one that is hyperreactive could flood the body with disease-causing inflammation. When highly stressful experiences persist, biological dysregulations can result in either direction. The brain, for example, might become overly primed to trigger fight-or-flight responses when threats are relatively low, while the neuroendocrine system that elevates cortisol levels might become blunted and respond less vigorously after it has been activated repeatedly for a long time. These paradoxically lower cortisol levels are often seen as a result of chronic abuse and neglect.[41] Although the exact causal mechanisms have not been identified, this diminished cortisol activation has been associated with an increase in body fat[42], social and behavioral problems in maltreated children[43], and high levels of depressive symptoms in women with low income.[44] When effective treatment is provided, these systems can regain their responsivity.[45,46]

Finally, it is essential to remember that there are many opportunities to build resilience in the face of significant adversity—beginning in early childhood and continuing throughout life—by providing supportive relationships in predictable environments, reducing sources of significant stress, and building a toolkit of adaptive skills. Poor health outcomes are *not* inevitable, but they are more likely if we do not adequately support children and families experiencing persistent hardships or challenges.

Below are descriptions of how significant adversity affects three biological systems—three members of the stress-response team that also includes the lungs, the endocrine system, and the gut microbiome (i.e., bacteria that live in the intestines), among others—which illustrate how they are all interrelated with each other as well as with other systems.

Effects of excessive early adversity on the developing brain: The foundations of brain architecture are built during the prenatal, infant, and toddler periods and shaped by *experiences*, interacting with *genes*, in an *environment of relationships* over *time*.[47,48] During these periods of rapid development, the brain is as adaptable and flexible as it will ever be. This means that the brain's developing circuits are also highly sensitive to the disruptive effects of elevated stress activation, which releases a flood of hormones, immune responses, and neurotransmitters (the chemicals that send signals from one brain cell to another). Three brain systems are particularly susceptible: (1) emotion regulation systems, which include the amygdala, where circuitry for processing fear and threat develops early in life; (2) memory systems,

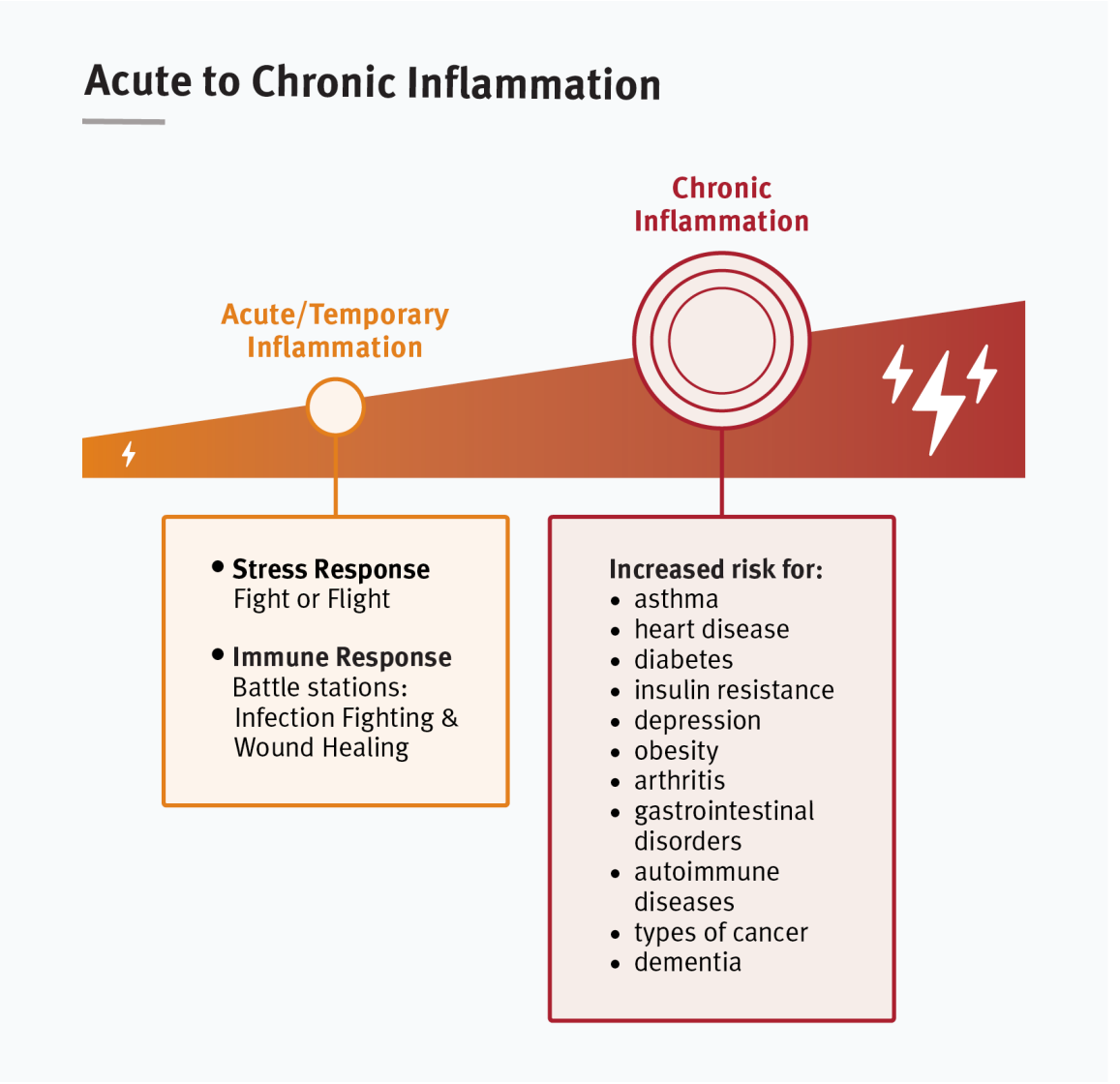
which include the hippocampus, where circuitry for memory and simple learning (e.g., remembering the location of an object) begins early and continues into later childhood;[49] and (3) executive function systems, which include the prefrontal cortex and other brain regions, where circuitry for focused attention, impulse control, and higher level cognitive skills develops well into the adult years.[50,51,52,53,54,55] These executive systems also help moderate stress responses (by regulating other brain regions) as well as the immune response to threat (by influencing the amount of inflammation that is mobilized to protect the body). Inflammation is one of the core features of the fight or flight response, as it prepares the body for potential wound healing and protection from infection, and the brain influences when and how much it is needed.[56,57]

Brief stress-system activation is protective in a dangerous environment, as it prepares the body and brain to respond to an acute threat. But these systems need to recover and return to balance after the source of the stress is eliminated or reduced. If they do not—if the stressors are severe, long-lasting, or there is a lack of supportive relationships to help children calm these responses—they can result in a brain that is "stuck" in a state of high alert. Over time, this can have harmful wear-and-tear effects. The earlier in life this kind of frequent, unmoderated response to adversity occurs, the greater the risk for stress-related health problems that will be more resistant to treatment well into the adult years. Recent research also has found that significant adversity before birth or in early infancy can build a brain that is more susceptible to harm from repeated stressors later in life.[58,59] Remediation may be possible at any age, but outcomes are better and easier to achieve when interventions are provided earlier—and promoting the healthy development of biological systems from the beginning is better, and more cost-effective, than trying to fix them later.[60]

Effects of excessive early adversity on the developing immune system: The immune system defends the body against infection and a variety of toxic substances. One of the most important components of the immune system's response is inflammation, a physiological function that attacks invading bacteria or viruses, clears out the tissue destruction they cause, and begins the repair process. *Acute* stress (triggered by experiencing or witnessing a brief but traumatic event) activates an inflammatory response by causing immune cells to "go to their battle stations." Our bodies need this physiological mobilization for survival. *Chronic* stress (experienced over a prolonged period of time in a threatening environment) can cause persistent inflammation. This prolonged state of alert puts powerful inflammatory substances used to kill microbes in constant contact with body organs, which can eventually damage them. At the same time, a constant state of activation also weakens the immune system, making it less efficient in its fight against microbes.[61] This double hit makes children living in adverse environments more susceptible to recurrent infection and more prone to develop chronic inflammatory conditions that may last for a lifetime[62], including heart disease, diabetes, depression, arthritis, gastrointestinal disorders, autoimmune disorders, multiple types of cancer, and dementia, among many others.

Remediation may be possible at any age, but outcomes are better and easier to achieve when interventions are provided earlier—and promoting the healthy development of biological systems from the beginning is better, and more cost-effective, than trying to fix them later.

Asthma provides an illustrative example of the consequences of too much inflammation in childhood. Household stress, exposure to auto exhaust and other forms of pollution, tobacco smoke, allergens, and a wide variety of viruses can all contribute to an increased inflammatory response in the lungs—especially in children who carry genes that make them more susceptible to developing asthma.[63,64] This recurrent inflammation, in turn, can stimulate reactions that make the bronchial



muscles twitchy and overreactive to usually innocuous triggers. As a consequence, the airways become too narrow, making it more difficult to breathe, and the child has asthma attacks that require medical intervention. Over time, chronic inflammation and overreaction in the small airways can cause structural changes in the lungs that increase the risk of developing chronic lung disease in the adult years.[65] Bottom line: If challenging *experiences* (e.g., exposure to stress, pollutants, or allergens) prompt a significant *immune response* (i.e., inflammation) early in life, and that response stays activated for too long, it can lead to greater risk for lifelong illness.

As one of the most common chronic illnesses in children, asthma illustrates the powerful influence of gene-environment interaction on physical health. Research shows that this condition is more frequent and more severe in children living in families with low income, children exposed to poor housing conditions, and children of color, regardless of income, whose families report experiencing discrimination.[66] These findings illustrate the extent to which structural inequities that affect the environments in which families raise children can undermine the foundations of health and well-being in the early years of life.[67]

Another example of how a child's immune system becomes finely tuned by experiences or environmental exposures comes from recent studies on the bacteria and viruses that normally live in our intestines (what scientists refer to as the "gut microbiome"). Beginning in the late phases of pregnancy, the fetus prepares

to adapt to an outside environment that is packed with a wide variety of microorganisms (or microbes). After birth, the many different ways in which newborns are held, fed, and cared for affect which bacteria and viruses become inhabitants in their bodies. The nature of these microbes is influenced by differences between vaginal and Caesarian deliveries, breast- and bottle-feeding, the type and quality of ingested nutrients, and the physical environment in which caregiving is provided. For example, children who live on farms beginning in early infancy are exposed to a diversity of bacteria and viruses that stimulate adaptive immune responses that result in much lower rates of allergies and asthma as they get older, compared with young children living in rural areas with non-farming families.[68,69]

Living in a wide variety of socially nurturing environments, with multiple interactions among caregivers, siblings, pets, and other human beings, allows an infant to acquire a robust and diverse microbiome. In contrast, lack of physical interaction with a variety of other people or obsessive cleanliness can lead to a microbiome that is not sufficiently varied. This results in an immune system that encounters fewer opportunities to distinguish biological "friend" from "foe" and to regulate immune responses in organs even far away from the gut itself, and may therefore respond excessively to usually innocuous viruses and allergens in early life.

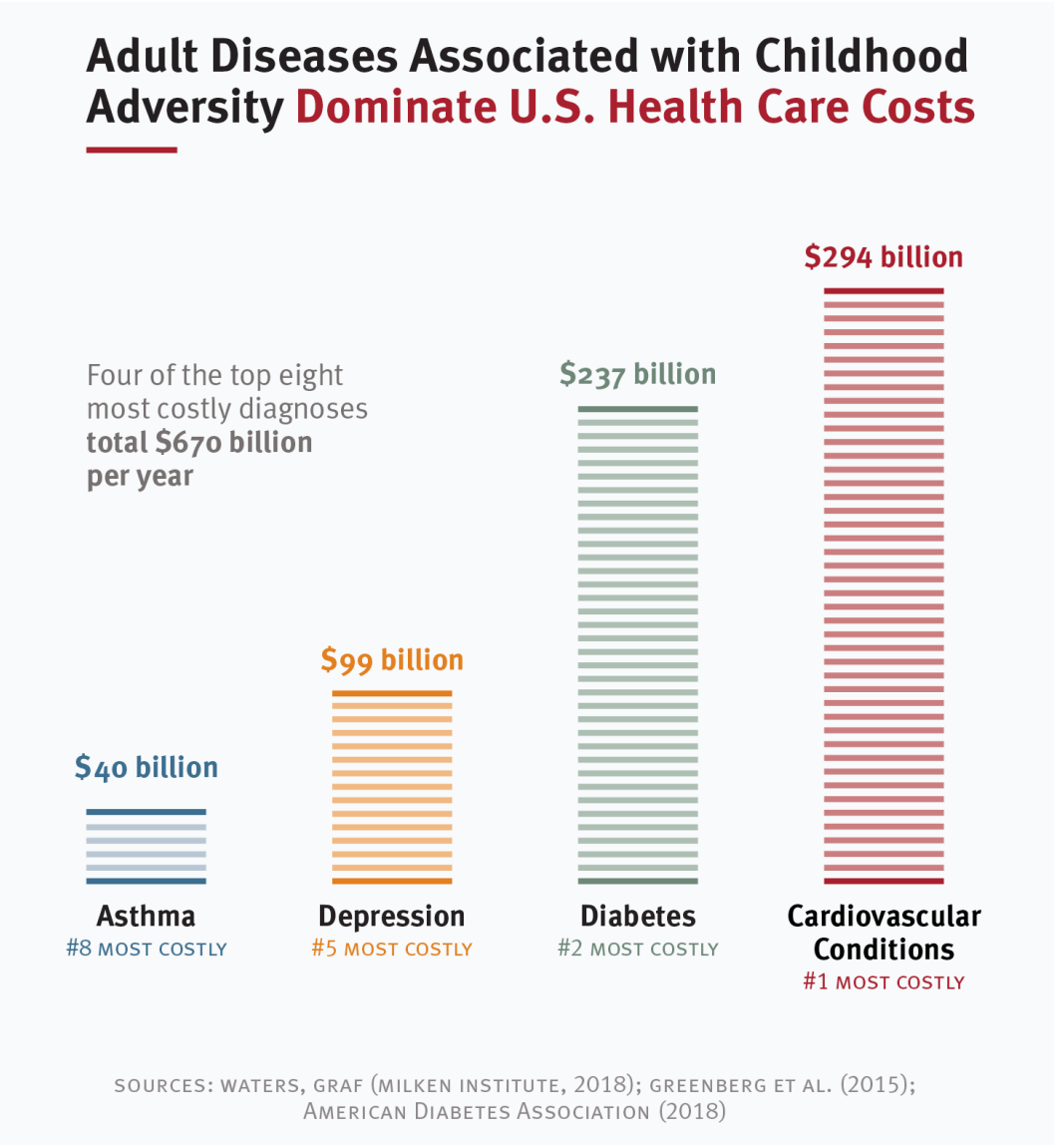
Effects of excessive early adversity on developing cardiometabolic systems: This network produces, distributes, and/or regulates the physiological fuel (e.g., oxygen and glucose) cells need throughout the body via the circulating blood stream. When the stress response is activated, this system springs into action (e.g., elevated heart rate, blood pressure, and blood glucose level) to provide increased energy to respond to threat while it ramps down other systems (e.g., digestion) that are relatively less essential in an acute situation. The impact of poor nutrition on cardiovascular health is well-documented.[70] Obesity and elevated blood pressure are also more prevalent in children experiencing the stresses of poverty, racism, unsupportive caregiving, overstimulation from excessive noise and overcrowding, and sedentary behavior from living in a violent neighborhood with no safe space for playing outdoors.[71,72,73,74] There is also growing evidence that inflammation is an important contributor to that increased risk, and the combination of stress and inflammation is especially threatening to health and well-being over time. For example, excessive amounts of stress hormones such as cortisol, combined with chronic inflammation, can result in insulin resistance—a physiological disruption that can lead to metabolic syndrome, obesity, diabetes, and cardiovascular disease, as well as brain changes and cognitive impairment.[75,76,77]

Addressing the early childhood stressors that lead to chronic, lifelong inflammation might dramatically reduce the need for costly treatments for a wide range of multiple health conditions, including cardiovascular disease.

In 2018, the American Heart Association issued a Scientific Statement that cited substantial evidence documenting an association between childhood and adolescent adversity and adult cardiometabolic disorders (e.g., obesity, hypertension, type 2 diabetes, and cardiovascular disease). Based on that growing knowledge base, the Statement asserted the following: "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."[78,79] In other words, addressing the early childhood stressors that lead to chronic, lifelong inflammation might dramatically reduce the need for costly treatments for a wide range of multiple health conditions, including cardiovascular disease.

Common Illnesses in Adults Have Roots in Early Childhood Adversity

Three chronic health impairments in the United States—cardiovascular disease, diabetes, and depression—together account for more than $600 billion in *direct* health care expenditures annually (above and beyond their indirect costs, such as lost productivity).[80,81,82] According to the Centers for Disease Control and Prevention, heart disease and stroke alone kill more than 859,000 people in the United States every year (accounting for one-third of all deaths and an even higher percentage in communities of color) and are also estimated to account for $131 billion annually in lost economic productivity. More than 30 million people have diabetes (a disproportionate number of whom are people of color) and another 84 million adults have a condition called prediabetes, up to 70% of whom will eventually develop diabetes.[83,84] All mental health and substance abuse disorders together constitute the most expensive category of chronic conditions, with depression alone incurring $99 billion in health care costs annually.[85] Beyond their financial cost, these



conditions also have enormous impacts on the quality of life of individuals, families, and communities.

The prevalence of cardiovascular disease, diabetes, and depression in adults is associated with higher rates of adverse experiences in childhood—and advances in biology are beginning to explain *how* and *why* that happens. Although they may appear to be unrelated on the surface, all three share a common association with elevated inflammation, which, as described above, can be influenced by recurrent hardships or threats in early childhood. These conditions are far from the only ones that could be listed, but they are among the most common and most costly of many possible examples that all point in the same direction: Efforts to prevent many chronic illnesses in adults need to begin in the early childhood years.

Cardiovascular disease: This diverse category of disorders includes medical conditions that involve narrowed or blocked blood vessels that can lead to sudden death or compromised life due to hypertension, chest pains (angina), a heart attack, or a stroke. The process that causes this narrowing or blockage is called *atherosclerosis*, which can begin early in life. This process involves a buildup of fatty deposits (called plaques) that thicken and stiffen artery walls, which can then lead to decreased blood flow to the heart muscle and brain, as well as to other body tissues.

As with any medical condition, understanding the underlying causes of cardiovascular disease can lead to effective prevention and treatments. Chronic inflammation, which as we've seen has its roots in early childhood, accelerates atherosclerosis by disrupting the walls of arteries and making them more likely to be sites for plaque formation and build-up. Although still an area of extensive scientific research, a biomarker of inflammation called C-reactive protein is measured by some physicians as another way to screen for cardiac risk. These findings make a strong case that detecting and reducing chronic inflammation, starting in early childhood, may be as important as lowering cholesterol for preventing a heart attack.

Nutritional factors during pregnancy and early infancy have been associated with heart disease later in adulthood.

Other underlying causal factors also point toward early childhood origins. Most of the public is aware that the risk of a heart attack or stroke is increased by an unhealthy diet (i.e., high in fats, salt, and sugar), lack of exercise, excess weight, and smoking. Many people also understand that high levels of "bad" cholesterol in the blood can increase the formation of plaques and thus accelerate atherosclerosis—and that poorly controlled high blood pressure can result in hardening and thickening of the arteries, which can then obstruct blood flow.[86] Less well known is the extent to which nutritional factors during pregnancy and early infancy have been associated with heart disease later in adulthood.[147] Although more research is needed to fully explain the causal mechanisms underlying this association, one compelling hypothesis[87] points to conditions of food scarcity during pregnancy leading to

WHY EARLY MATTERS: CARDIOVASCULAR DISORDERS

Heart disease is the leading cause of death for men, women, and most racial and ethnic groups in the United States.[132] Toxic stress in childhood is frequently associated with elevated inflammation[133] and atherosclerosis (which decreases blood flow to the heart in adults). Although scientists are still learning *how* the immune system's response to adversity in the early childhood period influences the development of cardiovascular disease in adults, there is enough evidence now to test the hypothesis that reducing early adversity could lead to breakthrough reductions in adult cardiovascular disease.

➢ *The U.S. spent $294 billion on direct health care costs and at least $137 billion in lost productivity for cardiovascular conditions in 2018.*[134]

altered fetal growth (e.g., low birth weight) and a metabolic system "programmed" for relatively excessive food intake in early childhood, leading to greater risk for type 2 diabetes and heart disease later in life.

Diabetes: This diagnosis includes several subtypes of chronic disease, all of which result in high levels of blood glucose (sugar) that persist over time. Glucose provides the main source of energy for cells in most body tissues. Insulin, a hormone made by the pancreas, controls the process by which glucose gets into most of those cells. Insulin, in a sense, "opens the doors" to allow glucose to enter into cells. If the pancreas doesn't produce enough insulin, or if the insulin is not opening those cell doors effectively, glucose stays in the blood and its level rises. When high levels of blood sugar are detected, it means that cells throughout the body are not getting enough of the glucose they need to function well.

WHY EARLY MATTERS: DIABETES

Extensive evidence indicates that disturbances in a pregnant woman's metabolic systems can "program" greater risk in the fetus for later development of type 2 diabetes and excess body fat.[135] These prenatal influences include insufficient protein and calories in the mother's diet—or *too many* calories—as well as hormones that affect developing systems that will regulate body weight and energy in the baby after birth. Studies of children born to mothers who were pregnant during times of famine found higher rates of obesity, insulin resistance, and diabetes than in children born in the same area a year or two earlier.[136,137,138] Substantial research findings also demonstrate sensitive periods in early infancy for long term effects of *overnutrition* (having more calories or nutrients than are needed for healthy growth) on the risk for later obesity and diabetes.[139,140,141]

- *The U.S. spent $237 billion in direct medical costs and lost $90 billion in reduced productivity due to diabetes in 2017.*[142]

In type 1 diabetes, which has a strong genetic component, the pancreas produces little or no insulin. In type 2 diabetes, which accounts for about 90% of diabetes diagnoses and is associated more strongly with environmental influences, insulin is produced but it doesn't work as well as it should.[88,89] This results in a condition called *insulin resistance,* in which the insulin is less able to "open the doors" and glucose stays in the bloodstream. The relation between insulin resistance and elevated inflammation is well-documented, although the nature of the association is not yet fully clear.[90]

The body's main source of glucose comes from what we eat and drink. Nutritious food that is accessible and affordable is an important protective factor against persistently elevated blood sugar and excessive intake of "junk food" increases the risk of disease. Activation of the stress response increases glucose levels in the blood in order to generate more energy to fuel the "fight or flight" response, which prepares our muscles and brain to deal with a sudden threat. But when the stress response persists over time, especially during the early developmental years, prolonged glucose elevation can trigger a cascade of events culminating in insulin resistance, metabolic syndrome, obesity, and eventually a diagnosis of type 2 diabetes.[91,92] Over the full life course, chronically elevated blood sugar can lead to greater risk of cardiovascular disease, kidney disorders, neurological impairments, and vision problems. Persistent insulin resistance, which can affect the brain, is also a risk factor for cognitive impairments, depression, and Alzheimer's disease.[93]

Depression: Clinical depression (also known as major depressive disorder or MDD) is one of the most common mental disorders in the United States and around the world. In the U.S., more than 7% of all adults and 13% of adolescents experienced at least one major depressive episode in 2017.[94] Individuals with diagnosed depression experience a range of symptoms that affect how they feel, think, and manage everyday tasks. Extensive evidence indicates that MDD is caused by a combination of genetic, biological, environmental, and psychological factors that interact in a variety of ways.[95] The following are some of the facts about MDD that

are well-documented by scientific evidence:

- Adults who experienced serious trauma in childhood are at greater risk (indicating that experiences are an important factor).[96,97,98]
- It occurs with greater frequency in some families more than others (indicating that genes also play a role).[99,100,101]
- It is twice as common in women as in men (although the reason is not known, some animal studies have found sex differences in adult behaviors following early life adversity, including more depressive-like patterns in females in contrast to more aggressive behaviors in males).[102,103,104]
- It is more common in urban populations than in rural areas (indicating that social and physical environments may also contribute).[105]
- Acute episodes are reported more commonly in whites in contrast to higher rates of chronic depression in communities of color.[106]
- Approximately one in seven pregnant and postpartum women nationwide are affected by mood and anxiety disorders, and 40-60 percent of low-income women report such maternal depressive symptoms.[107]
- Studies of diverse samples of pregnant and postpartum women have found minimal effects of screening on ameliorating depressive symptoms or increasing use of behavioral health care.[108]

WHY EARLY MATTERS: DEPRESSION

The prevalence of depressive disorders is markedly increased among people who face adversities related to poverty, homelessness, and exposure to violence.[143,144] Although researchers do not yet fully understand the relative impacts of the age at which the adversity was experienced, the duration of the adverse conditions, or the cumulative build-up of stress over time, recent research has identified *significant adversity in the first three years after birth* as a potential critical period associated with greater risk for clinical depression in adulthood.[145]

➢ *The U.S. spent $99 billion on direct health care costs and $112 billion on indirect costs for MDD in 2010.*[146]

There is extensive evidence that clinical depression, like cardiovascular disease and diabetes, is associated with increased inflammatory activation and insulin resistance.[109,110] Although many questions remain about whether this link reflects a cause or an effect, these associations are well-documented and underscore the importance of learning more about the relations among early life adversity, persistent inflammation, insulin resistance, and impairments in both mental and physical health throughout the adult years.

Facts About Health That Are Often Misunderstood

The experiences we have early in life are at least as important for the biological foundations of physical and mental health as the lifestyle choices we make as adults. Critical or sensitive periods provide unmatched opportunities for both positive and negative influences on developing biological systems. Above and beyond well-known impacts on early brain development, increasing evidence is also pointing to the importance of the prenatal period and first few years after birth for the development of core immune functions, metabolic regulation, and other physiological systems that can affect long-term well-being.[111,112,113] Without dismissing the influence of adult lifestyle (including nutrition, exercise, and sleep) on physical health, early adversity can increase the risk for many of the most common chronic diseases that appear later in life and that incur substantial costs to society.

Health-promoting environments early in life are critically important for building a strong foundation, but it's never too late to reduce risk. Although effective interventions can produce improvements in health and behavior

throughout life, the ability of the brain and other biological systems to adapt and change generally decreases as we age.[114] The brain can compensate for early disruptions at later stages, but full "reversals" are rare.[115] Stated simply, life is a continuous "one-way street"—what happens at each stage, including events before conception and during pregnancy, has consequences for what follows. Changing course is possible, but the changes we make later in life must contend with foundations that were laid down in the early years.

Expanding access to health care and decreasing utilization of unnecessary services are not the same as producing documented effects on child health. Although access and delivery of appropriate services are clearly important goals, direct measures of health status are needed to assess physical and mental well-being, identify problems that require intervention, and quantify the effects of services received. Since the launch of Head Start in 1965, programs have been mandated to promote health and address unmet medical needs by ensuring that all children receive pediatric examinations, immunizations, dental care, and assessments of nutrition, growth, vision, hearing, and speech.[116] Over more than half a century, the most common metric used to assess health impacts has been the *delivery of health-related services,* often supplemented by data on cost savings from decreased emergency room visits and hospitalizations. The need for greater attention to direct measures of *child health outcomes* (e.g., rates of common diseases) as well as *indicators of health risk* (e.g., biomarkers of excessive stress activation) is clear.

Future Directions for Policy and Practice

The effects of significant adversity on brain functions associated with early learning, social and emotional development, and kindergarten readiness are well-documented.[117] This knowledge has influenced policy objectives, program design, allocation of resources, and expected returns on investment in the early childhood period for decades.[118] The rapidly moving frontiers of the biomedical sciences now underscore the compelling need for an expanded mindset, informed by a deeper understanding of how early adversity can disrupt multiple biological systems in addition to the brain, with serious consequences for long-term physical and mental health.[119]

This new mindset views investment in the early years as a necessary priority for strengthening the foundations of both health and learning across the lifespan by addressing the common origins of disparities in each. The implications of this rapidly advancing scientific knowledge for a new era in early childhood policy and practice point to the need for: (1) implementing practical strategies for promoting health and preventing disease; as well as (2) overcoming longstanding barriers to change.

Implementing Practical Strategies

Advances in science should be informing the design, testing, iteration, and eventual scaling of innovative intervention strategies to protect the developing brain and other biological systems from the disruptive effects of early adversity. Above and beyond assuring enriched learning experiences for children and information on child development for parents and other caregivers, the biology of adversity and resilience points to three science-based principles[120] that should be used to inform more effective policies and programs across all sectors to strengthen the early childhood foundations of lifelong health.

- ***Support responsive relationships.*** Reliable "serve and return"[121] interactions between young children and the adults who care for them help to reduce the physiological disruptions of excessive

stress activation and protect developing biological systems, especially in the earliest years. Examples of policies or programs that align with this principle include: (1) giving parents and other primary caregivers the time needed to build the foundations of nurturing relationships with their children (e.g., paid family leave after the birth or adoption of a child); (2) minimizing disruptions of stable, adult-child relationships in child care centers (e.g., reducing staff turnover by providing competitive compensation through wages and benefits, as well as requiring reasonable adult-to-child ratios); (3) providing relationship-focused coaching for primary caregivers when needed; (4) focusing on the need to support continuing contact between children and parents who are separated in the child welfare system or when a parent is incarcerated (both of which are associated with longstanding racial disparities); and (5) protecting family cohesion in the design and implementation of immigration policies, both for newly arriving refugees where the risk of detention and parent-child separation is high, and for mixed-status families where the fear of separation is constant.

- ***Reduce sources of stress***. Policies and programs that lessen economic and psychosocial burdens on families with young children pay off in two ways. First, they reduce chronic activation of stress systems in both adults and children. Second, they enhance adult capacity for providing responsive caregiving that facilitates healthy child development. Examples include policies and practices that: (1) bolster safety-net policies that address income, nutrition, housing, and medical insurance needs; (2) eliminate punitive or unnecessary administrative regulations (e.g., streamlined eligibility processes for needed services); (3) address community and intimate partner violence; and (4) reduce systemic and economic racism[122] (e.g., fair hiring and lending practices, housing and home ownership programs, community policing initiatives, and efforts to reduce implicit bias[123]).
- ***Strengthen core life skills.*** In order to provide a well-regulated caregiving environment in both the family and community context, adults must be able to set and meet goals, manage their own behavior and emotions, establish daily routines for eating and sleeping, and facilitate social-emotional development and skill-building in children. Well-matched programs can help both children and adults build and apply these skills (known as executive function and self-regulation) through modeling, coaching, and practice (thereby providing a strengths-based approach similar to the way elite athletes rely on coaching and practice to continuously improve their already well-honed skills). Recognizing that stress can compromise *anyone's* ability to use the skills that they have can help programs offer supportive, scaffolding techniques, rather than threats of punishment, when existing efforts are not working well.[124]

This new mindset views investment in the early years as a necessary priority for strengthening the foundations of both health and learning across the lifespan by addressing the common origins of disparities in each.

Primary health care offers a science-based delivery channel for reaching the largest number of children at the earliest possible ages in a non-stigmatizing context. Team-based care provided through culturally and linguistically responsive, trusted relationships offers a promising model for individualized approaches to building resilience and preventing, reducing, or mitigating the consequences of early adversity. Reducing disparities in child health outcomes at a population level, however, will require a substantial shift in professional training, current practice, and payment systems to address the following challenges:[125]

- Pressures on physicians that demand brief interactions and high-volume service delivery undermine the ability to build supportive relationships—and more time is needed for families facing adversity. Credible evidence of improved child outcomes (see below) will strengthen the case for adequate funding, and engaging expertise in value-based reimbursement policies will be essential to secure the sustainability of that funding.
- Persistently low rates of routine developmental screening during well-child visits have been extremely difficult to improve, despite decades of task force recommendations, explicit mandates, and continuing education programs.[126] The emerging availability of biological and behavioral indicators of excessive stress activation and resilience in young children could present game-changing opportunities to generate more actionable and empowering information for both clinicians and parents/caregivers.
- Evaluations of "evidence-based" interventions linked to pediatric practice during the first three years after birth have demonstrated positive impacts on self-reported parenting behaviors but few *replicable* effects on child outcomes.[127] Direct measurement of key indicators of child health and development (including stress effects and resilience as well as common medical problems) will enhance clinical management and help secure payment for effective services.
- Limited progress in strengthening science-based content on early childhood development (including its underlying biology) and cultural context in pediatric residency programs, as well as in training of other health professions, indicates that a "top down" strategy to transform primary care practice will not be easy to achieve. In contrast, science-informed innovation in well-resourced, community-based laboratories could provide a potentially powerful, "bottom up" strategy to eventual impact at scale.
- Promising elements of this latter strategy include incorporating child development expertise within innovative team models (e.g., HealthySteps[128]), engaging team members who reflect the cultural and linguistic characteristics of the community, using rigorously validated measures to assess child outcomes directly, and embedding primary health care more seamlessly within community-based systems of services across sectors (e.g., Help Me Grow[129]).

Overcoming Longstanding Barriers

There is an urgent need for more effective strategies to support the health and development of young children by confronting poverty, racism, violence, housing instability, food insecurity, and other sources of chronic adversity that impose significant stresses on families. Public attention to these social determinants of health is increasing, but simply naming the problem, identifying "high-risk" children and families, and making referrals to services has not resulted in substantial or replicable impacts.

- The longstanding designation of *race* as a risk factor for disparities in health outcomes diverts critical attention away from systemic *racism* and its deep historical roots as a pernicious cause of stress-related disease.[130] Viewed through an equity lens, services and programs must move beyond a sole focus on children and families to an intentional, "upstream" focus on changing macro-level policies that systematically threaten the health and well-being of families of color.
- Evidence-based interventions that build resilience in children and caregivers facing adversity can lead to better *individual outcomes* at a program level, but achieving greater *impact at scale* will require increased efforts to confront structural inequities—such as unequal access to opportunities in education, health care, and wealth creation—at a societal level. Science alone is unable to address this challenge. But science-informed thinking combined with on-the-ground expertise and the lived experiences of families

raising young children under a wide variety of conditions (many of whom are typically marginalized) can be a powerful catalyst of new strategies at both levels.

All policies and delivery systems serving young children and families across sectors (including but not limited to medical care and early care and education) can and must measure their success by improved child outcomes in both health and learning.

Persistent attempts to increase access to services, reduce their fragmentation, build integrated delivery systems, and secure sustainable funding remain important objectives. But these efforts will not produce greater impacts until the measurement of their success moves beyond serving more children and enhancing interagency collaboration and begins to focus more explicitly on key child outcomes.

- Assessing child well-being and determining service needs by focusing exclusively on demographic risk factors (e.g., income, race, ethnicity, parent education) or number of adverse childhood experiences (e.g., ACE scores) can result in inappropriate labelling and unnecessary services for children and families who are doing well ("false positives") as well as missed opportunities to provide vital services for those who would benefit from them ("false negatives").
- More informed allocation of resources would be enhanced by supplementing social determinants of health with *individual-level* data on carefully selected indicators of child and family well-being—first to determine both assets and concerns, next to match specific services to identified needs, and then to find out who is benefiting from those services (which should prompt targeted scaling) and who is not (which should catalyze a search for alternative strategies).

Final Reflections in a COVID-19 World

Disparities in health outcomes related to socioeconomic inequalities impose substantial human and financial costs on all societies around the world.[131] Significant racial and ethnic differences in hospitalizations and deaths from COVID-19 in the United States have increased attention to this persistent inequity and much initial discussion has focused on conditions that make it more likely that people of color will be exposed to the virus. These include disproportionate employment in "essential" services without adequate protection from infection, residing in tight quarters, and hourly-wage jobs without paid sick leave or the ability to work at home. Inequalities in access to high-quality health care and higher rates of unequal treatment in the health care system have also been highlighted.

A different yet critically important question is why some people who are exposed to COVID-19 are more likely to have serious complications and less likely to survive. The exceptionally high risk of pre-existing medical conditions—including cardiovascular disease, diabetes, respiratory illnesses, and obesity at the top of the list—underscores the importance of the science reviewed in this Working Paper. Health-threatening conditions early in life (including poor nutrition, exposure to pollutants, and high levels of family stress associated with poverty, racism, and other forms of economic or social marginalization) can have disruptive effects on developing immune and metabolic systems, including excessive inflammation, that lead to a variety of health impairments well into the adult years. The implications for greater returns on innovative, science-informed investments in the early childhood period are clear and compelling. The brain is indeed connected to the rest of the body—and early childhood policy in the 21st-century must focus on the overwhelming evidence that early experiences affect the foundations of *both* educational achievement *and* lifelong physical and mental health.

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