



Toxic Stress and the Development of Young Children

Supporting the Frontiers of Innovation

SUMMARY

Scientists have uncovered increasing evidence of a link between adversity in childhood—associated with abuse, neglect, exposure to violence, and/or the stresses of poverty—and various indicators of biological disruption. These biomarkers,¹ as they are known, include elevated blood pressure, heart rate, circulating levels of stress hormones, and increased inflammation, among others. The evidence is building that “toxic stress” in childhood undermines healthy development and brain function and increases the risk of cardiovascular disease, diabetes, depression, and other chronic disorders later in life.

As a result of this growing knowledge, researchers and practitioners in early childhood development have become increasingly focused on the need for more effective strategies to mitigate the adverse biological impacts of excessive stress on young children.

Researchers at the [Center on the Developing Child at Harvard University](#) studied knowledge about biomarkers of stress in children and assessed their potential as a tool to measure the effectiveness of new interventions. From July 2010 through June 2013, they produced 10 journal articles documenting their work. See the [Bibliography](#).

Key Findings

Key findings reported in journal articles, as noted, include:

- “Studies show that cortisol activity can be altered by psychosocial interventions ... and suggest it may be possible to repair regulatory systems following childhood adversity.” However, the researchers also noted “there was remarkable inconsistency with regard to how the interventions influenced cortisol,” which is a hormone released by the adrenal gland in response to stress. ([“Interventions to Improve Cortisol Regulation in Children: A Systematic Review”](#)²)

¹ A biomarker is a measurable biological characteristic, such as blood pressure, cholesterol, or hormone level, that can be used to assess physiological function, health status, disease risk, or effect of a treatment.

² Slopen N, McLaughlin KA and Shonkoff JP. “Interventions to Improve Cortisol Regulation in Children: A Systematic Review.” *Pediatrics*. Published online, January 13, 2014. Abstract available [online](#).

- “Although childhood adversity was not consistently related” to markers of inflammation and other indicators of immune activation, “a trend towards positive findings was observed.” (“[Childhood Adversity and Immune and Inflammatory Biomarkers Associated With Cardiovascular Risk in Youth: A Systematic Review](#)”³)
- “Socioeconomic disadvantage was consistently associated with greater central adiposity” [ratio of waist circumference to height]. However, the available studies did not provide a clear association between childhood stressors and other cardiometabolic risk factors. (“[Socioeconomic and Other Social Stressors and Biomarkers of Cardiometabolic Risk in Youth: A Systematic Review of Less Studied Risk Factors](#)”⁴)

Funding

The Robert Wood Johnson Foundation (RWJF) supported this project with a \$300,000 grant.⁵ Eight other funders provided more than \$20 million to fund the Frontiers of Innovation through the Center on the Developing Child. (See the [Appendix](#) for a list of other funders.)

CONTEXT

Researchers in neuroscience, molecular biology, and epigenetics have uncovered multiple correlations among adverse childhood experiences—often associated with neglect, abuse, exposure to violence, and/or the stresses of poverty—and biomarkers of health risk.

While learning to cope with adversity is a normal part of growing up, toxic stress occurs when a child experiences excessive or prolonged activation of stress response systems in the face of ongoing hardship without the buffering protection of supportive adults. These physiological disruptions—including increases in blood pressure, heart rate, levels of stress hormones, and inflammation—can harm multiple biological systems, including the brain. This increases the risk of long-term impairments in both physical and mental health, such as heart disease, diabetes, and depression, according to a 2009 article in the *Journal of the American Medical Association*.⁶

³ Slopen N, Koenen KC and Kubzansky LD. “Childhood Adversity and Immune and Inflammatory Biomarkers Associated With Cardiovascular Risk in Youth: A Systematic Review.” *Brain, Behavior and Immunity*. 26(2): 239–250, 2012. Abstract available [online](#).

⁴ Slopen N, Goodman E, Koenen KC and Kubzansky LD. “Socioeconomic and Other Social Stressors and Biomarkers of Cardiometabolic Risk in Youth: A Systematic Review of Less Studied Risk Factors.” *PLoS ONE*. 8(7): 1–12, 2012. Available [online](#).

⁵ ID# 67751 (July 1, 2010 through June 30, 2013)

⁶ Shonkoff JP, Boyce WT and McEwen BS. “Neuroscience, Molecular Biology, and the Childhood Roots of Health Disparities: Building a New Framework for Health Promotion and Disease Prevention.” *Journal of the American Medical Association*, 301(21): 2252–2259, 2009. Abstract available [online](#).

“Toxic stress is a concept that describes what is happening inside the body in the face of significant adversity... Its wear and tear effects can disrupt the development of multiple maturing organs and regulatory systems that lead to lifelong consequences in learning, behavior, and health,” explains Jack P. Shonkoff, MD, professor of child health and development at Harvard University and director of the Center on the Developing Child.

Most early childhood programs—including child care, early education, and Head Start—focus primarily on providing enriched learning experiences to prepare young children to succeed in school. These programs pay relatively limited attention to health issues, and when they do, they tend to concentrate primarily on immunizations, sensory screening tests, dental care, and the prompt diagnosis and treatment of childhood illnesses.

Strategies for Buffering Stress

Shonkoff founded the Center on the Developing Child at Harvard University in 2006 to promote the healthy development of all children, and particularly those from disadvantaged backgrounds, by “closing the gap between what we know from science and what we do in our policies and practices,” he says.

“Our work is driven by a deep conviction that we can’t keep doing the same old things,” explains Shonkoff, who chaired an Institute of Medicine committee that in 2000 produced a report, *From Neurons to Neighborhoods: The Science of Early Childhood Development*.⁷ “We’re not saying that existing programs don’t make a difference, because many do produce important benefits, but it’s clear that current best practices are not enough for most young children who are experiencing toxic stress.”

For example, Shonkoff said, vulnerable young children might benefit more from programs that “build their parents’ capacity to buffer them from significant adversity and help build their coping skills, beyond efforts to enhance their language development.”

An example of such an intervention, developed by the Oregon Social Learning Center in Eugene, targeted young children in foster care. Caregivers were encouraged to reinforce positive behaviors and set limits for their children, and the children received behavioral therapy and participated in a playgroup that promoted positive socialization. Children who received the intervention showed improvements in stress hormone regulation and attachment-related behaviors as well as fewer behavior problems compared to children in a control group that did not receive the intervention.⁸

⁷ Shonkoff J and Phillips D (eds.). *From Neurons to Neighborhoods: The Science of Early Childhood Development*. Washington: Institute of Medicine, 2000. Available [online](#).

⁸ Fisher PA, Stoolmiller M, Gunnar MR and Berraston BO. “Effects of a Therapeutic Intervention for Foster Preschoolers on Diurnal Cortisol Activity.” *Psychoneuroendocrinology*, 32(8–10): 892–905. Available [online](#).

RWJF's Interest in This Area

RWJF has long supported efforts to reduce disparities in health outcomes, including efforts to improve and protect the physical and mental health of low-income children.

One of its major long-term efforts started in 1979 with support for the work of David Olds, PhD, and what is now called the *Nurse-Family Partnership*. The demonstration project, which began in Elmira, N.Y., used registered nurses to take preventive health services into the homes of young, low-income pregnant women and first-time mothers. Randomized controlled trials conducted in Elmira and subsequently Memphis, Tenn., and Denver showed the home visits yielded positive health and developmental outcomes for children and mothers. The program is going to scale nationally. In March 2010, the Affordable Care Act included \$1.5 billion in funding over five years for the Maternal, Infant, and Early Childhood Home Visiting Program, modeled on the *Nurse-Family Partnership*. At the close of 2010, enrollment was 21,438 mothers across the country. See the [Program Results Report](#) and a [Special Report](#) on Olds' and his work.

Another example is the Robert Wood Johnson Foundation Commission to Build a Healthier America, which, in 2006, began to identify ways—beyond health care—to improve the health of all Americans. In its landmark 2009 report,⁹ the commission noted the link between high-quality health care, education, and other services in early childhood and a reduced risk of becoming unhealthy over a lifetime.

RWJF reconvened the commission in 2013 to provide recommendations on how to increase opportunities for low-income Americans to make healthier decisions, with a specific focus on early childhood and healthy communities.

“Although we have seen progress since the commission issued its recommendations in 2009, we still have a long way to go before America achieves its full health potential,” says RWJF President and CEO Risa Lavizzo-Mourey, MD, MBA. “We know what works: giving children a healthy start with quality child care and early childhood development programs, and building healthy communities where everyone has an opportunity to make healthy choices. That is why RWJF is reconvening the commission, to concentrate on these two critical areas.”

THE PROJECT

From July 2010 through June 2013, the project team produced 10 journal articles that have advanced the knowledge base on how toxic stress affects biological systems in

⁹ Robert Wood Johnson Foundation Commission to Build a Healthier America. *Beyond Health Care: New Directions to a Healthier America*. Princeton, NJ: Robert Wood Johnson Foundation, 2009. Available on rwjf.org.

young children and “what we know about the utility of specific biomarkers of stress for identifying children at risk as well as measuring physiological responses to intervention,” says Shonkoff.

Natalie Slopen, ScD, then a post-doctoral fellow at the Center on the Developing Child,¹⁰ researched and wrote the articles in collaboration with the other investigators.¹¹

The findings presented in the articles have been used to guide the work of the Frontiers of Innovation—a community of researchers, practitioners, policy-makers, philanthropists, and experts in systems change—since its launch by the Center on the Developing Child in May 2011. The goal of Frontiers of Innovation is to drive science-based innovation in policy and practice to achieve breakthrough outcomes for children facing adversity.

Research Design

Originally, the project team had planned to produce a single review paper to examine potential biomarkers of toxic stress, followed by empirical studies to build on the findings. However, their early investigation of the scientific literature indicated that the existing research included “a lot of work that was very different in nuanced ways, and that required multiple systematic review articles,” says Slopen.

As a result, Slopen and co-authors completed three systematic reviews of existing studies that examined:

- The relationship between childhood exposure to adverse experiences and levels of inflammation and other markers of immune system activation, which are associated with an increased risk of cardiovascular disease later in life
- The effectiveness of interventions to promote the healthy regulation of cortisol, a stress hormone, in children
- The association between socioeconomic disadvantage and other stressors and cardiometabolic risk factors in youth, including cholesterol and other lipids, glucose levels, insulin resistance, waist circumference, and waist-to-hip ratio

These reviews helped to elucidate knowledge, identified areas where scientific evidence is lacking or inconsistent, and influenced the focus of seven empirical studies.

For these analyses, researchers used data from large, longitudinal studies of children and adolescents, including the following:

¹⁰ As of November 2013, Slopen was assistant professor, Department of Internal Medicine, Howard University College of Medicine, Washington.

¹¹ As of November 2013, six articles (plus a letter) had been published, two were “in press,” and two were under review by journals.

- Avon Longitudinal Study of Parents and Children (ALSPAC), a study of children born to mothers who lived in Avon County, England, while pregnant¹²
- National Longitudinal Study on Adolescent Health (Add Health), an ongoing study of U.S. students in 7th through 12th grade¹³
- Bucharest Early Intervention Project, a randomized controlled trial of foster care as an intervention for children abandoned close to the time of birth, which includes data on 136 children who were placed in institutional settings in Bucharest, Romania¹⁴

FINDINGS

The findings of the team’s work—which were detailed in journal articles and reports submitted to RWJF, as indicated with each finding—include the following:

Reviews of Previous Research

- **“Although childhood adversity was not consistently related” to markers of inflammation and other indicators of immune activation “a trend towards positive findings was observed.”** Based on an analysis of 20 studies, the researchers concluded that the link between childhood adversity and potential markers of risk for cardiovascular disease “is an avenue of research that is worth continuing to investigate.” (“[Childhood Adversity and Immune and Inflammatory Biomarkers Associated With Cardiovascular Risk in Youth: A Systematic Review](#)”¹⁵)
- **“Studies show that cortisol activity can be altered by psychosocial interventions ... and suggest it may be possible to repair regulatory systems following childhood adversity.”** However, the researchers also noted that “there was remarkable inconsistency with regard to how the interventions influenced cortisol.” They evaluated 19 articles to draw their conclusions. (“[Interventions to Improve Cortisol Regulation in Children: A Systematic Review](#)”¹⁶)
- **“Socioeconomic disadvantage was consistently associated with greater central adiposity.”** Based on a review of 37 publications, the researchers concluded that the available studies do not provide a clear association between childhood stressors and other cardiometabolic risk factors. (“[Socioeconomic and Other Social Stressors and](#)

¹² For more information, see ALSPAC’s website at: www.bristol.ac.uk/alspac.

¹³ For more information, see the project’s website at: www.cpc.unc.edu/projects/addhealth.

¹⁴ For more information, see the project’s website at: www.bucharestearlyinterventionproject.org.

¹⁵ Slopen N, Koenen KC and Kubzansky LD. “Childhood Adversity and Immune and Inflammatory Biomarkers Associated With Cardiovascular Risk in Youth: A Systematic Review.” *Brain, Behavior, and Immunity*, 26(2): 239–250, 2011. Abstract available [online](#).

¹⁶ Slopen N, McLaughlin KA and Shonkoff JP. “Interventions to Improve Cortisol Regulation in Children: A Systematic Review.” *Pediatrics*. Published online January 13, 2014. Abstract available [online](#).

Empirical Studies

Key findings from the team’s published empirical studies include the following:

- **Adverse events among children ages 6 to 8, and cumulative adversity from birth to eight, were associated with elevated levels of two inflammatory biomarkers by age 10.** These two biomarkers—C-reactive protein and interleukin-6, both proteins in the blood—have been associated with elevated risk of cardiovascular disease in other studies. The researchers also found that adversity in early childhood predicted increased levels of C-reactive protein at age 15. (“[Childhood Adversity and Inflammatory Processes in Youth: A Prospective Study](#)”¹⁸⁾
- **Behavior problems at age 8 were associated with elevated levels of C-reactive protein and elevated interleukin-6 at age 10.** “Our findings suggest that inflammation may be a pathway through which childhood behavior problems increase later risk for chronic diseases in adulthood,” the authors wrote. (“[Internalizing and Externalizing Behaviors Predict Elevated Inflammatory Markers in Childhood](#)”¹⁹⁾
- **Childhood adversity may have “a persistent influence on immune responses to latent infection in adulthood.”** For example, researchers found an association between “lower parental occupational status and some categories of lower education” and elevated levels of Epstein-Barr virus antibodies. They also found that individuals exposed to physical abuse at a very young age (3 to 5) had elevated antibodies compared to those whose first abuse came during adolescence. (“[Childhood Adversity and Cell-Mediated Immunity in Young Adulthood: Does Type and Timing Matter?](#)”²⁰⁾
- **Biomarkers of heightened risk for cardiovascular disease among gay and bisexual men “may emerge at a relatively young age.”** Young gay and bisexual men had elevated blood pressure, C-reactive protein levels, and pulse rates, compared to heterosexual men. The authors did not find comparable associations among

¹⁷ Slopen N, Goodman E, Koenen KC and Kubzansky LD. “Socioeconomic and Other Social Stressors and Biomarkers of Cardiometabolic Risk in Youth: A Systematic Review of Less Studied Risk Factors.” *PLoS ONE*, 8(7): 1–12, 2012. Available [online](#).

¹⁸ Slopen N, Kubzansky LD, McLaughlin KA and Koenen KC. “Childhood Adversity and Inflammatory Processes in Youth: A Prospective Study.” *Psychoneuroendocrinology*, 38(2): 188–200. Abstract available [online](#).

¹⁹ Slopen N, Kubzansky LD and Koenen KC. “Internalizing and Externalizing Behaviors Predict Elevated Elevated Inflammatory Markers in Childhood.” *Psychoneuroendocrinology* (in press).

²⁰ Slopen N, McLaughlin KA, Dunn EC and Koenen KC. “Childhood Adversity and Cell-Mediated Immunity in Young Adulthood: Does Type and Timing Matter?” *Brain, Behavior, and Immunity*, 28: 63–71, 2013. Available [online](#). See also: Slopen N, McLaughlin KA, Dunn EC and Koenen KC. “Reply to Letter Re: Childhood Adversity and Cell-Mediated Immunity in Young Adulthood.” *Brain, Behavior, and Immunity*, 34: 177–179, 2013. Abstract available [online](#).

women, except levels of C-reactive protein were lower among lesbian/bisexual women. (“[Sexual Orientation Disparities in Cardiovascular Biomarkers Among Young Adults](#)”²¹)

- **Children raised in institutions “had elevated symptoms of attention-deficit/hyperactivity disorder [ADHD], anxiety, depression, and disruptive behavior.”** The authors concluded that high levels of ADHD symptoms in this population “may be attributable, in part to abnormal patterns of neurodevelopment, as measured by event related potentials (i.e., a brain response to a specific stimulus), generated by these adverse rearing environments.” (“[Alterations in Neural Processing and Psychopathology in Children Reared in Institutions](#)”²²)

Limitations

The authors noted these limitations in their research:

- In the systematic reviews, the findings were limited by variation in the quality of the studies examined, such as those related to small sample sizes and short duration of follow up. The authors also note the potential bias toward publishing positive results, which can overemphasize the association between adversity and poor health.
- The findings of the empirical investigations, which analyzed data from earlier longitudinal studies of children and adolescents, were limited by missing data, as well as by the tendency of children from disadvantaged backgrounds to participate inconsistently in research over time.

Biomarkers: Not Ready for Prime Time

Although the project team had hoped to identify valid and reliable biomarkers to be able to measure the impacts of toxic stress on children and the degree of “physiological healing” produced by effective interventions, they learned that existing evidence was incomplete and inconsistent and therefore concluded that more research is necessary before they could make recommendations for broad application beyond research settings.

“I don’t think we can walk away from the work we have been able to do over the last few years feeling a tremendous amount of confidence that we know what to measure yet. Looking at the literature systematically, it tells us how to do research better, and what looks promising, and what doesn’t look promising,” Slopen says.

²¹ Hatzenbuehler ML, McLaughlin KA and Slopen N. “Sexual Orientation Disparities in Cardiovascular Biomarkers Among Young Adults.” *American Journal of Preventive Medicine*, 44(6): 612–621, 2013. Abstract available [online](#).

²² Slopen N, McLaughlin KA, Fox NA, Zeanah and Nelson CH. “Alterations in Neural Processing and Psychopathology in Children Reared in Institutions.” *JAMA Psychiatry*, 69(10): 1022–1030, 2012. Available [online](#).

Center Director Shonkoff adds, “Before we rush forward and spend a lot of time and money conducting more tests on large numbers of children who are already burdened by significant adversity in their lives, we ought to be as precise as possible about what we’re measuring, what the results are going to tell us, and what we will do with the findings.

“Aside from the problem of cost and inconvenience, there is the even greater danger of inappropriately labeling children based on findings that we don’t yet completely understand,” Shonkoff says.

Communications Results

The Center on the Developing Child hosted two invitation-only meetings to begin to explore this new area of investigation “to assure a strong community voice at the table before any further work is conducted under the auspices of the Frontiers of Innovation,” says Shonkoff:

- A meeting in April 2013 convened community representatives from Atlanta, New Haven, Ct.; Detroit, Seattle, and Palm Beach County, Fla., scientists, and clinicians to address issues related to the use of biomarkers in communities of color.
- A meeting in June 2013 convened a group of basic and applied scientists and clinicians who were unable to agree on a core list of biomarkers of toxic stress that is ready to be used in community settings at this time. “The lack of consensus on a recommended core battery of indicators underscored what we have been learning over the past three years,” Shonkoff wrote in a report to RWJF.

Both Shonkoff and Jane Isaacs Lowe, PhD, senior advisor for program development at RWJF, spoke about the relation between stress and health at the Massachusetts Institute of Technology’s Picower Institute Symposium on April 18, 2012.

See the [Bibliography](#) for the journal articles produced during this project.

AFTERWARD

The JPB Foundation awarded a planning grant to the Center on the Developing Child and the Center for Youth Wellness in San Francisco to create a multi-institutional Research Consortium on Toxic Stress and Health. The proposed consortium will support a collaborative effort among scientists and community-based clinicians to “deepen our understanding of the relations among adversity, biomarkers, and disease and to design and test new intervention strategies to mitigate the lifelong health impacts of toxic stress on children,” says Shonkoff.

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APPENDIX

Other Funders

The following funders have supported the Frontiers of Innovation to create innovation clusters within a network of programs, communities, and states/provinces across North America to design and test new interventions and policies to mitigate the adverse impacts of toxic stress on the health and development of young children.

Organization	Amount
Alliance For Early Success	\$1.2 million
Anonymous	\$1.2 million
Bezos Family Foundation	\$4.7 million
Bill & Melinda Gates Foundation	\$250,000
Buffett Early Childhood Fund	\$3.4 million
Casey Family Programs	\$1.8 million
Norlien Foundation	\$5 million
W.K. Kellogg Foundation	\$3 million

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