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TOXIC STRESS

MITIGATING CHILDHOOD ADVERSITY
THAT AFFECTS LIFELONG PHYSICAL
AND MENTAL HEALTH

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TOXIC STRESS MITIGATING CHILDHOOD ADVERSITY THAT AFFECTS LIFELONG PHYSICAL AND MENTAL HEALTH

Report of the PTSD and Toxic Stress
in Children Forum 2020

CONTENTS

- 04 Foreword
- 05 Section 1. Adversity in childhood is linked to mental and physical health throughout life
- 18 Section 2. Mitigating toxic stress in children affected by conflict and displacement
- 28 Section 3. Children's prolonged exposure to the toxic stress of war trauma in the Middle East
- 37 Section 4. Conclusion and recommendations
- 41 Acknowledgments
- 42 Article citations
- 43 References

FOREWORD

Over the past 50 years, we have made significant progress in improving the health and wellbeing of children across the globe. Despite this progress, countless children experience adversity and toxic stress, particularly those exposed to war, natural disasters, displacement, poverty and, more recently, the effects of the COVID-19 pandemic.

Adversity in childhood can lead to an array of behavioral, physical, and psychological issues across the life course. Children who experience toxic stress are at greater risk of a host of health problems in adulthood – from depression to cardiovascular disease and obesity. In addition to negatively affecting the health and wellbeing of individuals, increased prevalence of these conditions puts additional strain on healthcare systems.

All children deserve the chance to thrive in safe and supportive environments. It is imperative that governments, policymakers, non-governmental organizations, healthcare providers and the private sector work together to minimize the risk of toxic stress in childhood, and to intervene early when it occurs.

To complement our flagship [Forum Reports for 2020](#), WISH partnered with *The BMJ* to commission a collection of peer-reviewed articles (as well as this report, *Toxic Stress: mitigating childhood adversity that affects lifelong physical and mental health*, there is a further collection available [online](#)) exploring the key causes, and resulting effects, of toxic stress in children.

This report concludes with a number of recommendations to address these issues and promote the health and wellbeing of all children. We hope that these recommendations will guide researchers and policy-makers in tackling this critical issue.



A handwritten signature in black ink that reads "Nadine Harris".

Dr Nadine Burke Harris
Surgeon General of California



A handwritten signature in black ink that reads "Zulfiqar A Bhutta".

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SECTION 1. ADVERSITY IN CHILDHOOD IS LINKED TO MENTAL AND PHYSICAL HEALTH THROUGHOUT LIFE

Charles A Nelson, Zulfiqar A Bhutta, Nadine Burke Harris, Andrea Danese, Muthanna Samara

Today's children face enormous challenges, some unforeseen in previous generations, and the biological and psychological toll is yet to be fully quantified. Climate change, terrorism, and war are associated with displacement and trauma. Economic disparities cleave a chasm between the haves and have nots, and, in the US at least, gun violence has reached epidemic proportions. Children may grow up with a parent with untreated mental illness. Not least, a family member could contract COVID-19 or experience financial or psychological hardship associated with the pandemic.

The short- and long-term consequences of exposure to adversity in childhood are of great public health importance. Children are at heightened risk for stress-related health disorders, which in turn may affect adult physical and psychological health, and ultimately exert a great financial toll on our healthcare systems.

Growing evidence indicates that, in the first three years of life, a host of biological (for example, malnutrition, infectious disease) and psychosocial (such as maltreatment, witnessing violence, extreme poverty) hazards can affect a child's developmental trajectory and lead to increased risk of adverse physical and psychological health conditions. Such impacts can be observed across multiple systems, affecting cardiovascular, immune, metabolic, and brain health, and may extend far beyond childhood, affecting life course health.^{1,2,3} These effects may be mediated in various direct and indirect ways, presenting opportunities for mitigation and intervention strategies.

Defining toxic stress

It is important to distinguish between adverse events that happen to a child – 'stressors' – and the child's response to these events – the 'toxic stress response'.⁴

A consensus report published by the US National Academies of Sciences, Engineering, and Medicine (2019) defined the toxic stress response as:

Prolonged activation of the stress response systems that can disrupt the development of brain architecture and other organ systems and increase the risk for stress related disease and cognitive impairment, well into the adult years. The toxic stress response can occur when a child experiences strong, frequent, and/or prolonged adversity – such as physical or emotional abuse, chronic neglect, caregiver substance abuse or mental illness, exposure to violence, and/or the accumulated burdens of family economic hardship – without adequate adult support. Toxic stress is the maladaptive and chronically dysregulated stress response that occurs in relation to prolonged or severe early life adversity. For children, the result is disruption of the development of brain architecture and other organ systems and an increase in lifelong risk for physical and mental disorders.

What is childhood adversity?

A large number of adverse experiences (that is, toxic stressors) in childhood can trigger a toxic stress response.^{5,6,7} These range from the commonplace (such as parental divorce) to the horrific (for example, the 6-year-old ‘soldier’ ordered to shoot and kill his mother).⁸

Adversity can affect development in myriad ways and at different points in time, although early exposures that persist over time can lead to more lasting impacts. Moreover, adversity can become biologically embedded, increasing the likelihood of long-term change. Contextual factors are important.



The type of adversity

Not all adversities exert the same impact or trigger the same response; for example, being physically or sexually abused may have more serious consequences for child development than does parental divorce.^{9,10}



The duration of adversity

How long the adversity lasts can have an impact on development. However, it is often difficult to disentangle duration of adversity from the type of adversity (for example, children are often born into poverty, whereas maltreatment might begin later in a child's life).



Developmental status and critical period timing

The child's developmental status at the time he or she is exposed to adversity will influence the child's response, as will the timing of when these adversities occur.¹¹



The number of adversities and the interaction among them

The Adverse Childhood Experiences (ACE) study^{12,13} and subsequent body of ACE research provide compelling evidence that the risk of adverse health consequences increases as a function of the number of categories of adversities that adults were exposed to in childhood. Although this seems intuitive, it belies the fact that, when it comes to severe adversity (such as maltreatment), few children are exposed to only a single form of adversity at a single point in time. In addition, the effects of exposure to multiple adversities is likely more than additive. Thus, multiple forms of adversity may act in complex and synergistic ways over time to affect development.



Exacerbating factors

Children with recurrent morbidities, concurrent malnutrition, key micronutrient deficiencies, or exposure to environmental toxicants may be more sensitive to the adverse effects of other forms of toxic exposures.¹⁴



Supportive family environments

Children develop in an environment of relationships, and supportive relationships can buffer the response to toxic stress.^{15,16,17} Safe, stable, and nurturing relationships and environments are associated with reduced neuroendocrine, immunologic, metabolic, and genetic regulatory markers of toxic stress, as well as improved clinical outcomes of physical and mental health.^{18,19}



Pre-existing characteristics

Many of the adversities being considered are not distributed at random in the population. They may occur more commonly in children and families with pre-existing vulnerabilities linked to genetic or fetal influences that lead to cognitive deficits.^{20,21,22} Infants who are more vulnerable to adverse life events (for example, stigma) include: those born very early (for example, at 25 weeks' gestation) or very small (such as less than 1,500g); those born with substantial perinatal complications (such as

hypoxic-ischemic injury); infants exposed prenatally to high levels of alcohol; or those born with greater genetic liability to develop an intellectual or developmental disability (for example, fragile X syndrome) or impairments in social communication (such as autism).



Individual variation

Finally, children may have different physiological reactions to the same stressor. For example, Boyce has proposed that by virtue of temperament, some children (such as those who are particularly shy and behaviorally inhibited) are highly sensitive to their environments²³ and unless the environment accommodates such children, the risk of developing serious lifelong psychopathology is greatly increased; conversely, some children thrive under almost any conditions.

Figures 1 and 2 illustrate how duration and type of adversity interact with family environments and pre-existing characteristics to affect development (Figure 1), and how early adversity may become biologically embedded (Figure 2).

Figure 1. The interplay of adversities, context, and human development

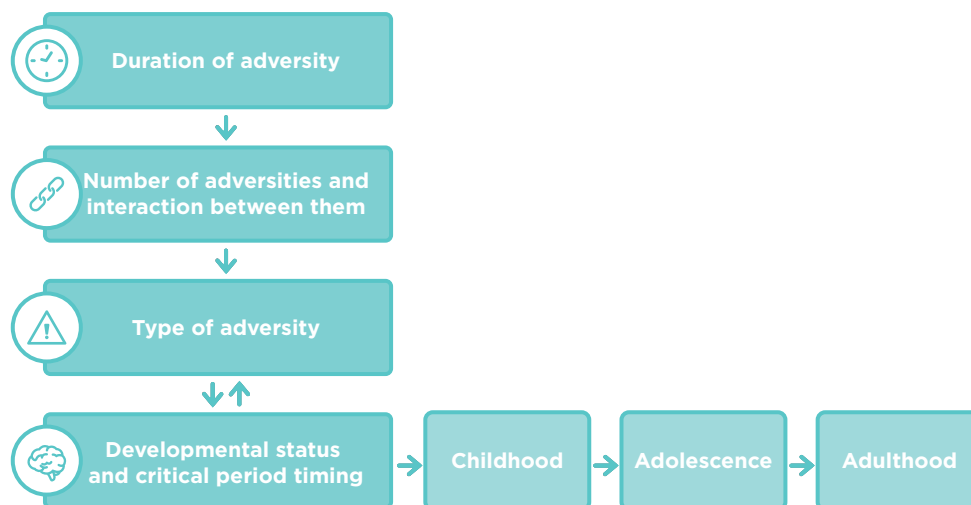
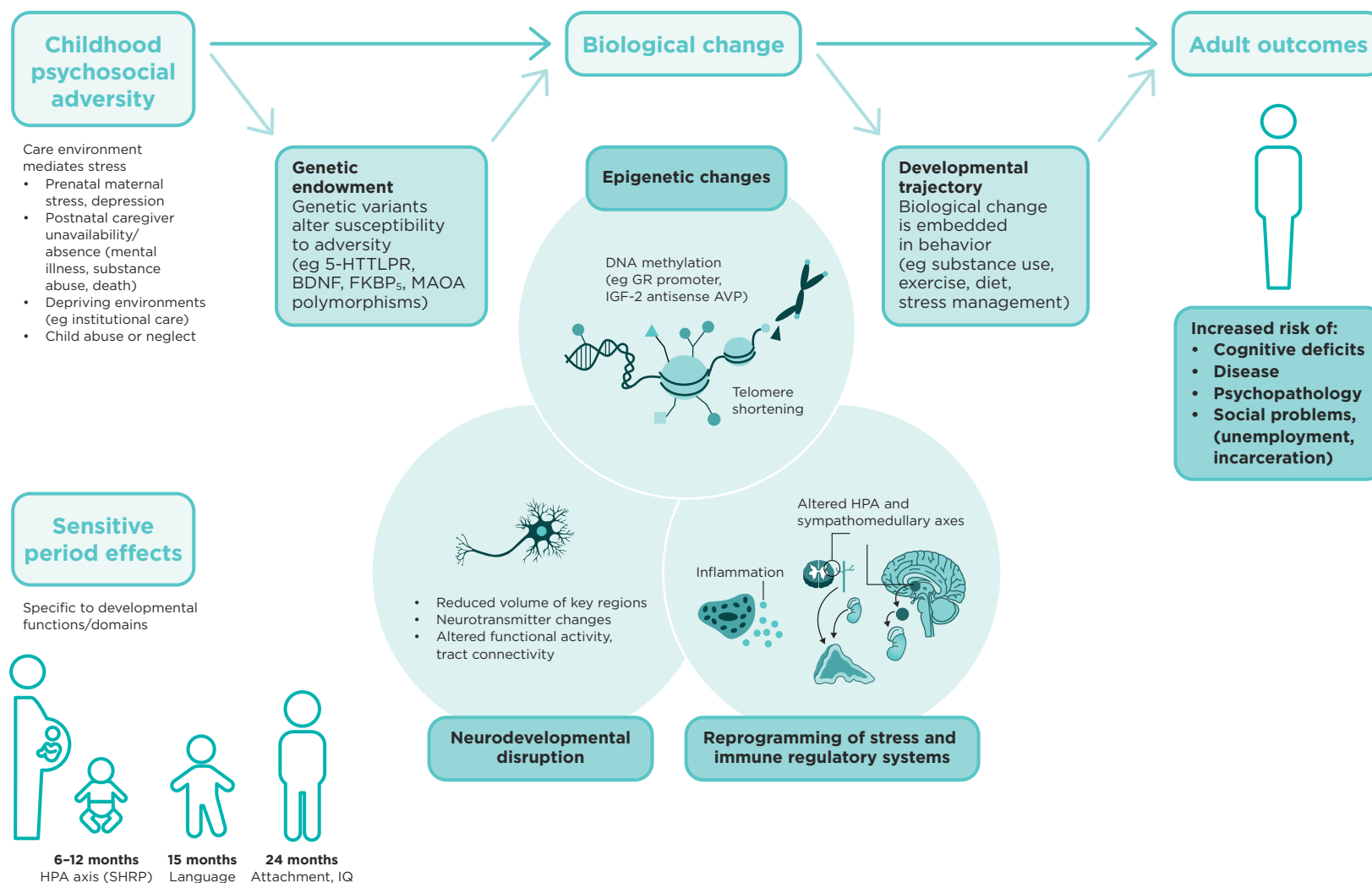


Figure 2. Some of the pathways that mediate exposure to early adversity and adult outcomes



Note: Exposure to adversity early in life interacts with a child's genetic endowment (for example, variations in genetic polymorphisms), which in turn leads to a host of biological changes across multiple levels. These changes, in turn, influence adult outcomes (adapted from Berens et al.²⁴ HPA axis (SHRP) = hypothalamic-pituitary-adrenal axis (stress hypo-responsive period).

Consequences of exposure to adversity

Behavioral consequences

Childhood exposure to adversity may result in a variety of behavioral and emotional problems²⁵ – for example, increased risk taking, aggressive behavior, involvement in violence (home, school, and neighborhood), and difficulties in relationships with others.^{26,27} Of great concern is the development of post-traumatic stress disorder (PTSD).^{28,29}

Children experiencing trauma (for example, witnessing the murder of a family member; or sexual assault) are also at elevated risk of several other psychiatric disorders, including depression, PTSD, conduct problems, substance abuse, self-harm, and suicidal thoughts and attempts.^{30,31} Some forms of physical and psychological abuse in early childhood can be associated with eating disorders and mental health issues, affecting typical development and education.

Neurobiological consequences

Many studies have identified structural and functional differences in brain development associated with environmental stressors, such as low socioeconomic status,³²⁻³⁶ physical abuse,³⁷ and caregiving neglect.^{38,39} For example, exposure to maternal stress in infancy has been associated with reduced brain activity, as inferred from electroencephalogram (EEG) testing,⁴⁰ and profound psychosocial deprivation has been associated with differences in overall brain volume, along with reductions in white and grey matter volume in several brain areas^{41,42} and reduced brain electrical activity.^{43,44} Differences in brain development have also been associated with decreases in several cognitive functions,⁴⁵ and particularly executive functions,⁴⁶ and distally, in educational achievement.⁴⁷

Physical consequences

Early exposure to adversities, especially poverty, is associated with linear growth failure and wasting, and has recently been shown to be associated with reduced brain volume⁴⁸ and altered functional connectivity.⁴⁹ Children exposed to higher psychological stress have been shown to have higher cortisol levels and greater risk of common diseases of childhood, including otitis media, viral infections, asthma, dermatitis, urticaria, intestinal infectious diseases, and urinary tract infections.⁵⁰

Childhood adversities have also been associated with greater risk of adult chronic conditions, including cardiovascular disease, stroke, cancer

(excluding skin cancer), asthma, chronic obstructive pulmonary disease, kidney disease, diabetes, overweight or obesity, and depression, as well as increased health risk behaviors.^{51,52}

Tables 1 and 2 show many of the physical and psychological harms observed among children and adults exposed to adversity early in life.

Table 1. ACE-associated health conditions in children

Symptom or health condition	For $\geq X$ ACEs (compared with 0)	Odds ratio
Asthma	4	1.7-2.8
Allergies	4	2.5
Dermatitis and eczema	3*	2.0
Urticaria	3*	2.2
Increased incidence of chronic disease, impaired management	3	2.3
Any unexplained somatic symptoms (eg, nausea/vomiting, dizziness, constipation, headaches)	3	9.3
Headaches	4	3.0
Enuresis, encopresis	-	-
Overweight, obesity	4	2.0
Failure to thrive, poor growth; psychosocial dwarfism	-	-
Poor dental health	4	2.8
Increased infections (viral, upper and lower respiratory tract infections and pneumonia, acute otitis media, urinary tract infections, conjunctivitis, intestinal)	3*	1.4-2.4
Later menarche (≥ 14 years)	2*	2.3
Sleep disturbances	5**	PR 3.1
Developmental delay	3	1.9
Learning and/or behavior problems	4	32.6
Repeating a year at school	4	2.8
Not completing homework	4	4.0
High school absenteeism	4	7.2
Graduating from high school	4	0.4
Aggression, physical fighting	For each additional ACE	1.9
Depression	4	3.9

Symptom or health condition	For $\geq X$ ACEs (compared with 0)	Odds ratio
Attention deficit hyperactivity disorder (ADHD)	4	5.0
Any of: ADHD, depression, anxiety, conduct/behavior disorder	3	4.5
Suicidal ideation	For each additional ACE	1.9
Suicide attempts	For each additional ACE	1.9-2.1
Self-harm	For each additional ACE	1.8
First use of alcohol at <14 years	4	6.2
First use of illicit drugs at <14 years	5	9.1
Early sexual debut (<15-17 years)	4	3.7
Teenage pregnancy	4	4.2

*Odds ratio represents at least one ACE, but also includes other adversities

**Prevalence ratio represents at least one ACE, but also includes other adversities

Table 2. ACE-associated health conditions in adults

Symptom or health condition	Odds ratio (excluding outliers)*
Cardiovascular disease (coronary artery disease, myocardial infarction, ischemic heart disease)	2.1
Tachycardia	≥ 1 ACE: 1.4
Stroke	2.0
Chronic obstructive pulmonary disease (emphysema, bronchitis)	3.1
Asthma	2.2
Diabetes	1.4
Obesity	2.1
Hepatitis or jaundice	2.4
Cancer, any	2.3
Arthritis, self-reported	3 ACEs, HR: 1.5 \geq ACE: 1.3
Memory impairment (all causes, including dementias)	4.9
Kidney disease	1.7
Headaches	≥ 5 ACEs: 2.1
Chronic pain, any (using trauma z-score)	1.2
Chronic back pain (using trauma z-score)	1.3

Symptom or health condition	Odds ratio (excluding outliers)*
Fibromyalgia	≥ 1 ACE: 1.8
Unexplained somatic symptoms, including somatic pain, headaches	2.0-2.7
Skeletal fracture	1.6-2.6
Physical disability requiring assistive equipment	1.8
Depression	4.7
Suicide attempts	37.5
Suicidal ideation	10.5
Sleep disturbance	1.6
Anxiety	3.7
Panic and anxiety	-
PTSD	4.5
Illicit drug use (any)	5.2
Injected drug, crack cocaine, or heroin use	10.2
Alcohol use	6.9
Cigarette or e-cigarette use	6.1
Cannabis use	11.0
Teen pregnancy	4.2
Sexually transmitted infections, lifetime	5.9
Violence, victimization (intimate partner violence, sexual assault)	7.5
Violence perpetration	8.1

*Odds ratios compare outcomes in individuals with >4 ACEs with those with 0 ACEs, except where specified.

What mediates the effects of adversity?

The link between exposure to adversity early in life and physical and psychological development are thought to be mediated through several direct and indirect pathways. We first talk about the effects on physical development, then turn our attention to psychological development.

Effects mediated directly may include: altering the regulation of stress-signaling pathways and immune system function;⁵³ changing brain structure and function;⁵⁴ and changing the expression of DNA and by accelerating cellular aging.^{55,56} For example, abuse or neglect might directly lead

to physical injury or undernutrition or malnutrition. Similarly, stress can directly lead to dysregulation of the hypothalamic–pituitary–adrenal axis and associated neuroendocrine-immune⁵⁷ as well as epigenetic effects.⁵⁸

Effects mediated indirectly might include changing the quality of the caregiving environment (for example, less responsive care)⁵⁹ or the surrounding distal environment (for example, neighborhood violence, which in turn will affect child development across several levels);⁶⁰ or building dysfunctional cognitions about the self and the world.^{61,62,63} The effects of food insecurity (leading to undernutrition or malnutrition) and unsafe or substandard housing (resulting in exposure to asthmagens or environmental toxicants such as lead) can cause social disparities in health.⁶⁴ Distal effects of adversity include the early adoption of health-damaging behaviors (such as smoking, or poor food choices) that later in life lead to diabetes, heart disease, and metabolic syndrome.⁶⁵

On the psychological side, early adversity can lead to the development of psychopathology early in life (for example, disruptive behavior) that later in life manifests in more severe forms (such as antisocial personality). Furthermore, it can lead to the development of dysfunctional cognition about self and others.⁶⁶ The interplay of these different mediation mechanisms remains largely unclear.

Modeling the effects of adversity must take into consideration the type of adversity, the duration and timing of the adversity, the synergistic effects of multiple forms of adversity with the child's genetic endowment (see [Figure 2](#)), and the social supports and interventions on which the child can depend (such as caregivers to whom the child is attached).

What can we do now?

If we wish for today's youth to inherit a world that is safe and conducive to healthy development, we must do all we can to create such a world. Even for children living in adverse circumstances, much can be done now to make a difference by preventing such disorders from developing and intervening once they have surfaced. For example, we can screen children experiencing adverse life events, and once screened refer such children to early intervention services, as California is doing (see [elsewhere in this collection](#)).

Intervention strategies have been developed to help children manage their toxic stress response^{67,68} and to help families cope with adversity. Many children are resilient, and physician–community partnerships can help foster resilience.⁶⁹

Recommendations for research

Much of the evidence has depended on the use of self-reporting, or parent-reported measures, which are relatively easy to score, can be scaled at population level, and can be used (with modification) across cultures. However, such measures are inherently subjective and prone to biases (such as recall bias). Other measures, such as official court or child protection records, provide a more objective assessment but often underestimate the prevalence of adversity.

Objective and subjective measures of childhood adversity identify largely non-overlapping groups of individuals⁷⁰ and, thus, may be associated with health outcomes through different pathways. Subjective experience that is particularly important for psychopathology, over and above objective experience.⁷¹

A challenge in examining the effects of adversity on development is how to compare children growing up in different cultures. For example, one study⁷² reported that a questionnaire on bullying used in different cultures and countries did not generalize well (that is, one culture's interpretation of bullying differed from another). Adversity and trauma should be considered in context, and investigators in different cultures may need to develop different assessments.

Research must move away from subjective evaluations of toxic stress (that is, self-reported or other report), and gain insight into the neural and biological mechanisms that mediate the toxic stress response. To do so, several investigators have started to develop more objective biomarker panels for screening for toxic stress that use markers of neurological, immunological, metabolic, and genetic regulatory derangements.^{73,74,75} As this work continues, issues to consider include how much better (for example, as predictors) such measures are than behavior, how early in life they can be used, and whether they are scalable.

The study of toxic stress and the toxic stress response needs to move away from correlational and cross-sectional studies and deploy designs that are amenable to drawing causal inference. This would include longitudinal studies and ideally studies that involve interventions. An advantage of the latter includes the ability to shed light on mechanism.

More attention also needs to be paid to individual differences. Different people respond differently to the same stressors. For example, only a minority of children who experience trauma or maltreatment go on to develop enduring psychiatric disorders; and some children develop physical health disorders such as asthma, whereas others will not.⁷⁶ In addition, individual differences exist in biological sensitivity to

stressors – for example, children identified as shy or inhibited early in life may be more vulnerable to stressors, and are more predisposed to anxiety as adults,⁷⁷ than children with more robust temperaments, and who are less fearful of novelty.^{78,79,80}

Recommendations for policy

Policy is only as good as the underpinning evidence, and these recommendations have sufficient evidence to support them.

Careful consideration should be given to implementing evidence-informed policies for optimizing health, nutrition, and early child development,⁸¹ which in turn can be expanded to include older children and adolescents. Although the first three years of life are generally emphasized, older children exhibit remarkable plasticity in molding their personalities and behaviors.^{82,83} Effective interventions exist to treat (and possibly prevent) psychopathology emerging after childhood trauma, but implementation needs to be scaled up.⁸⁴

Linking and optimizing preventive child health and education initiatives early in life are key to successful intervention.⁸⁵ It needs to be done at the appropriate level in the health and education systems. The development of the World Health Organization's (WHO's) Nurturing Care Framework⁸⁶ has been a welcome step in this direction, engaging platforms such as community health workers and pre-schools.⁸⁷

Community-based, school, and after-school based interventions can reduce the effects of traumatic events among children and adolescents living in adverse circumstances.^{88,89}

Public health strategies for primary, secondary and tertiary prevention of childhood maltreatment and adversity include both universal and targeted interventions, ranging from home visiting programs to parent training programs, routine screening for adversity, and cognitive behavioral therapy (CBT).^{90,91}

Key recommendations

- Researchers should consider both objective and subjective measures of childhood adversity.
- Researchers should broaden assessment of interventions beyond mental health measures to more regularly include health outcomes such as asthma, infection, inflammation, insulin resistance.
- Adversity and trauma should be considered in context, and investigators in different cultures may need to develop different assessments.
- Researchers should consider how much better (for example, as predictors) objective biomarker panels are than behavior, how early in life they can be used, and whether they are scalable.
- Researchers should move toward longitudinal studies and ideally studies that involve interventions.
- Researchers should pay more attention to individual differences.
- Governments should implement evidence-informed policies for optimizing health, nutrition, and early child development.
- Health and education systems should link and optimize preventive child health and education initiatives early in life at the appropriate level.
- Use community-based, school, and after-school interventions.
- Consider public health strategies for primary, secondary and tertiary prevention of childhood maltreatment and adversity.

SECTION 2. MITIGATING TOXIC STRESS IN CHILDREN AFFECTED BY CONFLICT AND DISPLACEMENT

Anushka Ataullahjan, Muthanna Samara, Theresa S Betancourt, Zulfiqar A Bhutta

Armed conflict and displacement pose a threat to the health and wellbeing of children. As the global community begins to recognize the cumulative effects of conflict and displacement related stressors, our attention has shifted to toxic stress and its short- and long-term health effects.⁹² Toxic stress, regarded as the result of prolonged activation of the stress response, can occur before birth and during childhood. It is known to contribute to epigenetic changes, with health and neurodevelopmental consequences.⁹³ However, various social factors and early and appropriate intervention can help mitigate the negative effects.⁹⁴

How conflict and displacement affect children

Over 415 million children were living in conflict-affected countries in 2018,⁹⁵ including 33 million displaced children (16 million refugees and asylum seekers, and 17 million internally displaced children).⁹⁶ Although all children are vulnerable to toxic stress, certain subgroups are particularly vulnerable because of their marginalization – for example, orphaned or unaccompanied children, girls, children with HIV infection, and children with developmental disorders or a disability. These groups may face additional stressors and have reduced access to services. The emergence of COVID-19 has also raised concerns about spread in conflict-affected populations, adding to the risk of toxic stress (see [Box 1](#)).

Conflict and displacement increase toxic stress in children through sudden and extreme trauma exposures such as violence and forced displacement (see [Figure 3](#)). Moreover, the frequency and severity of existing daily stressors such as family violence can increase in response to armed conflict.⁹⁷ Data on the number of children affected by conflict who are experiencing toxic stress globally are lacking, but regional studies indicate that it is pervasive. To illustrate, a study from Syria found that 71 percent of children experienced frequent bed-wetting and involuntary urination, which are common features of toxic stress.⁹⁸ Further research to accurately quantify the extent of toxic exposures faced by conflict-affected children is needed.⁹⁹

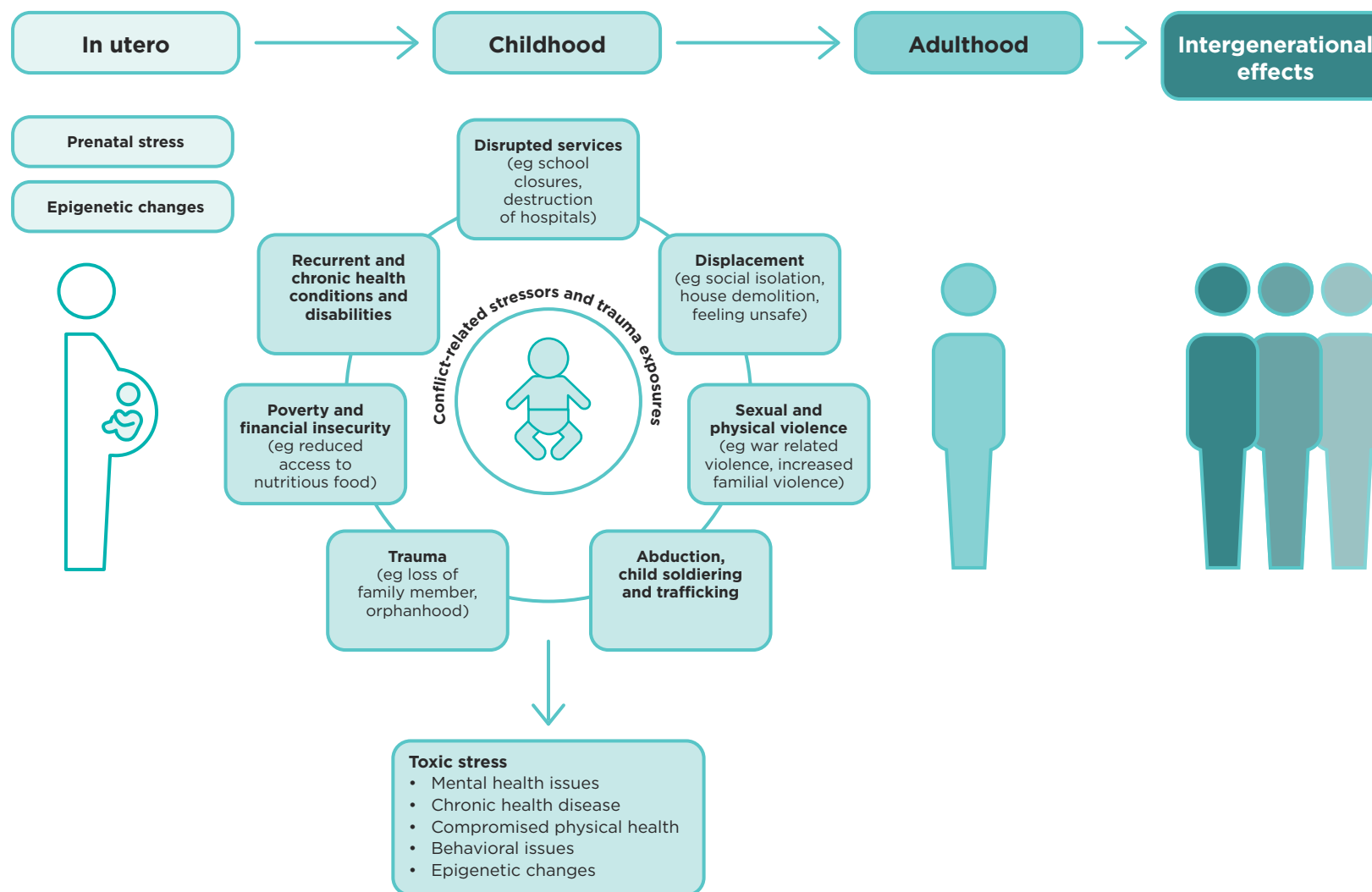
Box 1. COVID-19 in humanitarian settings

Conflict-affected populations are particularly vulnerable to COVID-19. Overcrowding and inadequate water and sanitation systems in refugee camps and informal settlements, coupled with previously existing illnesses, may increase the spread and severity of COVID-19. Moreover, resource and health system constraints may restrict access to adequate and appropriate care.^{100,101} Control measures such as physical distancing may be difficult, and may also increase economic precarity, intimate partner violence, and food insecurity in populations already vulnerable because of conflict or displacement.

There are concerns that the health needs of conflict-affected populations may be deprioritized by host governments. In refugee camps in Lesbos, Greece, for example, a lack of government support required grassroots mobilization by refugees to increase awareness, create masks, and improve sanitation in their camps.^{102,103} In addition, social isolation and distancing during quarantine are associated with different stressors such as fears, insomnia, anxiety, unfulfilled basic needs, interrupted medical care, and family problems, all of which are common triggers of mental illnesses and suicidal tendencies.^{104,105} We must also assume that refugees in host countries will be at greater risk of these problems since they are further socially isolated.

Although swift action is needed to control the transmission of COVID-19, it is important to ensure that these control measures are context sensitive. Community-based participatory methods can be used to establish youth and community advisory boards to help guide COVID-19 mitigation strategies to ensure that they are culturally appropriate and thus more effective.¹⁰⁶ Ensuring that the most vulnerable people are protected may require contextually appropriate measures such as isolation: at a household level with designated rooms for vulnerable family members; at street or extended family level, where community members swap houses and designate one home for high-risk members; or at neighborhood or sector level, where areas of settlements are designated for only vulnerable individuals.¹⁰⁷ The Inter-Agency Standing Committee has created guidelines for managing COVID-19 that recommend increasing awareness, strengthening health facilities, and strategic planning.¹⁰⁸

Figure 3. Conflict-related stressors and trauma exposures and their effect through the life course



Active conflict disrupts economic activity and food systems, pushing many families into poverty. Overhead bombing and artillery fire can damage health, water, and electricity infrastructure, thereby decreasing access to health services, increasing displacement, and physical injury.¹⁰⁹ The interruption of immunization schedules may cause outbreaks of previously uncommon infectious diseases, as was seen with polio in Syria in 2013.^{110,111}

Early and repeated exposure to violence can have lifelong effects, including propagating social norms tolerant of violence.¹¹² The United Nations Security Council's monitoring and reporting mechanism tracks data on six grave violations against children during armed conflict: killing and maiming; sexual violence; attacks against schools or hospitals; abduction; denial of humanitarian access; and recruitment by armed forces and groups.¹¹³ All of these grave violations contribute to toxic stress.

Most people affected by conflict are not externally displaced and continue to live in active conflict zones, while some are internally displaced.¹¹⁴ For those who are forcibly displaced, the process of displacement can introduce a range of adversities. Raids on homes, schools, and villages, as well as political oppression, characterize preflight insecurity. Many families remain internally displaced for extended periods, unable to access adequate health, educational, and social services. During displacement, children may be exposed to increased environmental, social, and physical hazards, including crowded and makeshift living conditions with poor access to water and sanitation. Diseases such as malaria, tuberculosis, and cholera are easily transmitted in these contexts.¹¹⁵

Forcibly displaced children and families are often exposed to extreme temperatures and novel disease vectors. The 'Lost Boys of Sudan' provide a good example of the physical hardships encountered by unaccompanied minors during displacement. While traveling thousands of miles, many lost their lives to armed militia, wild animals, malnutrition, and exposure to the elements.¹¹⁶ Young children, and girls in particular, may be targets of sexual violence as part of systematic militarized action, such as the genocidal rape seen in countries from the Balkans to the Great Lakes region in sub-Saharan Africa¹¹⁷ or exploitive exchanges by UN peacekeepers, as noted in several countries, including the Central African Republic, and Democratic Republic of Congo.^{118,119}

When resettling as refugees in host countries, children may experience stress related to social dislocation, isolation, and adjusting to an unfamiliar language and culture. Separation from family networks can disrupt children's access to traditional knowledge and protection systems.¹²⁰ Moreover, resettlement policies may further disadvantage asylum seekers by accommodating them in impoverished areas.¹²¹ Navigating a foreign legal

system can be challenging, particularly for orphaned or unaccompanied children.¹²² Disrupted educational systems and lack of economic opportunities may shift marriage practices, with families choosing to marry their daughters young, as has been seen among Syrian refugees in Lebanon.¹²³

After resettlement, children may exhibit disruptive behavior, disorientation, and cultural bereavement.¹²⁴ Refugee children report more functional impairment, physical health, psychosomatic, and peer problems.¹²⁵ Parenting can also be challenging, as many caregivers struggle with their own trauma and emotion dysregulation while learning the norms and practices of a new country.¹²⁶ Adjusting to an unfamiliar and, at times, unfriendly educational system is an additional challenge for children. Furthermore, the educational progress of some children may be affected by difficulties with concentration and learning.

Health effects

Despite a broad understanding of the myriad conflict and displacement related stressors experienced by children, the literature capturing the health effects of these stressors on children is limited. A recent Save the Children report on Syria found that 78 percent of children reported feeling extreme grief and sadness at some time. The report contends that toxic stress, coupled with prolonged exposure to war during children's key developmental stages, has the potential to become irreversible if appropriate action is not taken quickly.¹²⁷ Evidence from Sierra Leone has shown that lower levels of social stigma and higher community and familial acceptance of former child soldiers was associated with a more positive mental health trajectory and adult life outcomes.¹²⁸

Global evidence suggests that toxic stress continues to affect the health of future generations through epigenetic changes long after conflict has subsided.^{129,130} A small but growing body of literature has described the intergenerational effects of war, including low birth weight, developmental delays, chronic illness, mental health problems, and intergenerational violence.¹³¹ Children of parents with post-traumatic stress disorder (PTSD) after the 1994 Tutsi genocide in Rwanda showed higher secondary traumatization symptoms and lower resilience than children whose parents did not have PTSD.¹³² Additionally, new evidence suggests that our knowledge of the interplay between genetics and psychosocial symptoms is still limited. A recent study on male Syrian refugees who participated in a stress attunement intervention found a relation between MAOA genetic variants, which affect the concentrations of the neurotransmitters dopamine, norepinephrine, and serotonin. The MAOA-L variant was associated with sharper reductions of perceived psychosocial stress over time than the MAOA-H variant.¹³³

Research with general populations has established the effect of toxic stress on immunological responses.¹³⁴ With infectious diseases such as diarrhea, measles, malaria, and pneumonia and acute malnutrition causing the majority of child deaths in conflict,¹³⁵ the role of toxic stress in increasing susceptibility to these diseases requires further investigation. Research on how toxic stress may influence the development of chronic diseases later in life is also needed.

Mitigating strategies

Prevention

Removing the stressor of armed conflict and displacement is arguably the best and most effective strategy to mitigate the impact of toxic stress. Getting the necessary co-operation of a range of state and non-state groups will be difficult, but it is important to recognize the importance of peace and stability for the health of children. These rights are affirmed by WHO's Nurturing Care Framework, which ensures that children's rights are protected, and focuses on their healthy development.¹³⁶

Although halting armed conflict is the ultimate goal, additional safeguards can decrease the effect of conflict on children. The UN's monitoring and reporting mechanism has an important role in monitoring the conduct of state and non-state actors to reduce grave violations against children.¹³⁷ Similarly, funded community monitoring could help to ensure the safety and rights of conflict-affected children. Decreasing additional daily stressors by ensuring the basic human rights of families experiencing conflict and displacement through financial assistance, food, housing, education, employment, and healthcare can also benefit children.¹³⁸

As conflict-affected settings begin to develop and strengthen health systems, mental health and social services will be critical.¹³⁹ Increasing access to services requires improving refugees' mental health literacy and knowledge of services.¹⁴⁰

Improving parenting quality and caregiver support can encourage children to build resilience and strengthen protective factors that allow children to better manage stressors.¹⁴¹ Positive interactions with primary caregivers have an important protective role in reducing synaptic pruning (the process by which extra neurons and synaptic connections are eliminated to increase the efficiency of neuronal transmissions) during childhood.¹⁴² Furthermore, friendship quality and increased number of friends can protect refugee children from some behavioral and psychological problems.¹⁴³ In contexts of conflict, particularly protracted

conflict, we must expect to see intergenerational violence and trauma. By improving caregivers' capacity to provide a stable, nurturing relationship, and highlighting the role of fathers, the intergenerational effects of war can be mitigated.

Group and community programs

Since few mental health professionals are available in many war-affected settings, various studies have explored the use of group mental health treatments to expand access to care. These models often leverage the strengths inherent in collectivist cultures in war-affected regions.¹⁴⁴ As epidemics or pandemics such as COVID-19 further constrain resources and health worker capacity, task-shifting to community health workers can allow access to hard-to-reach populations in countries such as Somalia¹⁴⁵ and Yemen.¹⁴⁶

Community-based interventions are important in the short- and long-term rehabilitation of children experiencing toxic stress.¹⁴⁷ School-based programs can help overcome some of the barriers to access to care, and can improve educational outcomes.¹⁴⁸ Awareness of trauma also allows teachers to create a safe and stable environment for students to buffer their stress response. The trauma-informed approach focuses on nurturing relations and attachments, increasing ability to self-regulate, and cultivating students' developmental competencies.¹⁴⁹ Lay counselors delivering mental health interventions within schools can also improve psychosocial problems.¹⁵⁰ Furthermore, mentoring schemes and after-school clubs have helped refugee children overcome some of their behavioral and psychological difficulties.¹⁵¹ Additionally, evidence suggests that social protection services, such as cash transfers, can benefit child development by reducing the financial stress experienced by families.¹⁵²

Family-based therapies

A range of therapies targeting caregivers such as carer-child interaction therapy, child and caregiver psychotherapy, and stress reduction can help improve stress responses.¹⁵³ Research in Kosovo has highlighted the role of the family in improving children's response to adversity.^{154,155} One study found that mobilizing families to access community-based social support services for people with severe mental health illnesses led to increased family coping and quality of life.¹⁵⁶ Similarly, a study in Rwanda with vulnerable families found that home visits to promote early childhood development improved interactions, reduced violence, and created a more enriched home environment. The intervention also increased equitable decision-making and child dietary diversity.¹⁵⁷

The success of such interventions shows the interconnectedness of stressors and supports the Nurturing Care Framework approach, which focuses on the links between health, nutrition, safety, caregiving, and early education for childhood brain development. This multisectoral approach integrates health and nutrition interventions for children as a way to buffer stress response and decrease the impact of toxic stress.¹⁵⁸

Personal therapies

Several approaches aim to build resilience and mitigate the impact of the stress response. Mindfulness-based therapies have been shown to decrease psychological distress and anxiety and increase wellbeing. Biofeedback therapies focusing on decreasing heart and respiratory rates have also been shown to reduce toxic stress, as have other breathing techniques and guided imagery relaxation.¹⁵⁹ These techniques have been used successfully among children and adolescents in Gaza,¹⁶⁰ Sri Lanka,¹⁶¹ and Kosovo.¹⁶²

More traditional approaches such as trauma-focused psychotherapy and CBT can also ameliorate toxic stress and reduce PTSD symptoms.¹⁶³ Integrating trauma-informed treatment across systems of care is essential to ensure that conflict-affected and displaced children receive the care they need.¹⁶⁴ This will require strong collaboration between healthcare providers, development workers, the international community, and governmental and non-governmental organizations (NGOs). Implementation science can help to develop and test innovative strategies to expand reach and ensure the quality and sustained use of evidence-based interventions as conflict-affected regions move toward peace and development.¹⁶⁵

Next steps

Despite the growing evidence on toxic stress in children affected by conflict and displacement, gaps in our knowledge persist. A recent systematic review on the mental health of women, children and adolescents affected by conflict highlighted the need for interventions to be described in more detail in research papers. Moreover rigorous evaluation of success, failure, and effectiveness of interventions and strategies for widescale implementation in conflict-affected regions should be prioritized.¹⁶⁶ Most research has not included children affected by conflict and displacement, and knowledge of best practices for these contexts is limited (see [Box 2](#)). Existing interventions to reduce toxic stress in regions affected by conflict need to be adapted to take account of cultural context and values, vulnerable subgroups, and resource constraints in their design and delivery.

Box 2. Examples of the rehabilitation of children of conflict

Bosnia and Herzegovina

The 1992–95 war had severe long-term effects on the health and well-being of children and adolescents, with high rates of PTSD, anxiety, and depression.¹⁶⁷ A UNICEF-funded psychosocial program, delivered in over 32 secondary schools across the region, shows how appropriate and comprehensive intervention can reduce the rates of PTSD, depression, and grief symptoms among children through normalizing, validating, and processing traumatic experiences. The program also enhanced coping, tolerance, social skills, and problem-solving abilities.¹⁶⁸

Syria

Syrian refugee children have developed increased mental health problems, including PTSD and emotional dysregulation.¹⁶⁹ An eight-week humanitarian intervention program of structured activities for 12- to 18-year-olds was designed based on the profound stress attunement framework. The intervention reduced symptoms of insecurity, distress and perceived stress, depression, and anxiety and improved behavioral outcomes, but had no effect on prosocial behavior or symptoms of PTSD.¹⁷⁰

Sierra Leone

Community consultations have been used to adapt common elements of CBT and interpersonal therapy to create the Youth Readiness Intervention for War-Affected Youth.¹⁷¹ The intervention, which focused on increasing emotion regulation, interpersonal skills, and problem-solving, was delivered to youth aged 15- to 24-years-old by trained lay workers. A randomized control trial found that the intervention significantly improved emotion regulation skills, prosocial attitudes and behaviors, and social support, and reduced functional impairment. An eight-month follow-up found that participants were more likely to persist in school and had better attendance and academic performance than those who did not receive the intervention.¹⁷²

Appropriate action to reduce toxic stress requires a better understanding of the scope of the problem among children and families affected by conflict. Objective measures of toxic stress are essential, and biomarkers offer one such possibility. A recent study of adolescents affected by conflict showed that hair cortisol concentration can be used to assess response to interventions.¹⁷³ Further research on the use of biomarkers to track and measure stress responses is key to ameliorating toxic stress.

A broader understanding of toxic stress in children is particularly important during the COVID-19 pandemic, when measures to limit the spread of this disease may unintentionally increase exposure to multiple adversities through school closures, movement restrictions, and economic disruption. In India, for instance, where national lockdowns resulted in mass cross-country migrations, children risked separation from family members, economic insecurity, and violence.¹⁷⁴ The compounding effect of daily stressors and conflict and displacement related stressors encountered by children increases their vulnerability to toxic stress. As social and economic stressors take hold and families are forced into isolation, there has been a rise in family conflict and violence as well as increasing rates of mental health problems among children and their caregivers.¹⁷⁵

Research has indicated that low socioeconomic status, multiple types of violence, and low parental support aggravate the consequences of traumatic events on the development of mental health problems.^{176,177} Multisectoral approaches must engage the child, family, community, and, at times, humanitarian groups to prevent and ameliorate the impact of toxic stress among conflict-affected and displaced children, and strengthen sustainable systems of prevention and care. As the number of people affected by conflict and displacement continues to grow, action to decrease the long-term negative effects of toxic stress must be targeted and swift.

Key recommendations

- Research is needed to determine optimal strategies for sustained implementation of proved interventions to reduce toxic stress.
- Clinicians and pediatricians must work closely with other sectors to integrate trauma-informed treatment across systems of care.
- Response agencies and professionals working with conflict-affected and displaced children can mitigate the effects of daily stressors by ensuring access to food, housing, education, employment, financial assistance, and healthcare.
- Task-shifting and training of lay workers to deliver community-based programs can increase access to psychosocial support in marginalized and difficult-to-reach populations.

SECTION 3. CHILDREN'S PROLONGED EXPOSURE TO THE TOXIC STRESS OF WAR TRAUMA IN THE MIDDLE EAST

Muthanna Samara, Sara Hammuda, Panos Vostanis, Basel El-Khodary, Nader Al-Dewik

Violent political conflict has had a devastating effect on the physical and mental health of children in the Middle East (see Box 3).¹⁷⁸ Many have been killed or injured. Many have been displaced, including 2.5 million Syrian child refugees.¹⁷⁹ Conversely, Palestinian children under blockade in the Gaza Strip cannot escape, not even to relative safety.¹⁸⁰

Box 3. A century of political violence

The Middle East has seen several conflicts since the second world war: between Arab states and Israel, between 1948 and 1982; the Lebanese Civil War, from 1975 to 1990; wars in Iraq beginning in 1980, and with continuing unrest to the present day; the invasion of Kuwait in 1990; and the North Yemen Civil War, from 1962 to 1970. In late 2010, anti-government protests throughout the Middle East gave rise to the so-called Arab Spring. Subsequent Libyan, Syrian, and Yemeni civil wars have been violent and prolonged. In addition, Palestinians in the Gaza Strip have experienced three wars in the past 12 years and have been living under a blockade since 2007.

Yemen's dire situation has triggered the world's biggest food security emergency and the largest recorded cholera epidemic.¹⁸¹ Children in conflict settings may lack access to water, and experience bombing, loss of their home, and the injury or death of loved ones.^{182,183} Sexual exploitation and abduction can proliferate when rule of law collapses. The effects of poverty and destroyed healthcare and schools can persist long after violence has ceased.

The threat of harm intensifies exposure to psychological trauma.¹⁸⁴ Continuous exposure to trauma is associated with mental health problems including PTSD,¹⁸⁵ emotional dysregulation, depression, and suicidal thoughts or behaviors.¹⁸⁶

Toxic stress, when children experience strong, frequent, or prolonged adversity without adequate adult support,^{187,188,189} can disrupt development of the brain and other organs, and increase psychopathology as well as cognitive and emotional impairment.^{190,191} Effects are likely to

persist into adulthood, even after violence stops. Prompt identification and evidence-based treatment of serious psychopathology can help.¹⁹²

Children must be supported in healing from the effect of toxic stress to break the cycle of violence in which the next generation struggles to rebuild society after the trauma of war.¹⁹³ But a focus on the short-term effect of war means scant attention has been paid to longer-term mental health support. A cohesive effort is needed among policymakers, humanitarian agencies, and health services in the region to increase resilience and prevent escalation in mental and physical health problems, and to advocate for security and health.¹⁹⁴

Toxic stress and mental health

Children in armed conflict areas in the Middle East experience high rates of mental disorders, including PTSD, depression, anxiety, behavioral problems, and attention deficit hyperactivity disorder, as well as functional impairment.¹⁹⁵ Worldwide, as many as one in five children and adults affected by conflict may experience mental ill health, compared with a mean global prevalence of one in 14.¹⁹⁶

Children in conflict areas are also at increased risk of suicide ideation, enuresis, nightmares, hypervigilance, grief, separation anxiety disorder, phobia, stuttering, stereotypic movements, refusal to attend school, learning disabilities, conduct disorders, aggression, and feeding disorders in infancy or early childhood.

These conditions impair children's ability to engage in daily life, to focus and perform in school, to form relationships and attachments, and to feel safe.¹⁹⁷⁻²⁰⁴ Multiple exposures to violence cumulatively increase the risks.^{205,206,207}

Without early intervention, these mental health problems could continue into adulthood and to predict adverse outcomes. Untreated adults who experienced adverse childhood experiences may carry 12 times the risk for alcoholism, drug misuse, depression, and suicide attempts. They are also more likely to have physical health conditions, including heart disease, cancer, chronic lung or liver disease, and skeletal fractures.²⁰⁸

Young Kuwaiti adults' educational and occupational outcomes, for example, were adversely affected by exposure to war trauma a decade before.^{209,210,211} Boys with greater exposure were less likely to pursue further education and more likely to have PTSD, poor sleep quality, high body mass index, and poor self-reported health in adulthood.

Mediating factors in toxic environments

Children's risk of poor mental health is mediated by genetic, familial, societal and environmental factors, which influence their development in a toxic environment.^{212,213,214} Effects are subsequently transmitted through biological, psychological, familial, economic, and societal pathways.^{215,216,217} In war environments, good parenting, relationships with teachers, social networks, and healthcare systems are also affected by trauma and toxic stress, and may be less protective or even harmful.^{218,219}

Children with traumatized parents may be at increased risk of poor mental health outcomes, particularly without social support.^{220,221,222} Postwar trauma among Palestinian fathers,²²³ and arrest of Kuwaiti fathers during the war,^{224,225,226} were related to increased mental health problems, avoidance behaviors, and attachment insecurity among their offspring. Also, intergenerational transmission has been observed in increased rates of mental illness in the children of Holocaust survivors.²²⁷ Poverty that persists after violence stops affects children directly and indirectly through the parent-child relationship, aggravating toxic stress responses.^{228,229} In addition, parents worrying about daily survival can become less nurturing and more aggressive toward their children.^{230,231,232}

Mental health services in the Middle East

Health services in Middle Eastern countries are provided by governmental, commercial, and NGOs. Disruption to health services often continues, even after violence stops,²³³ while demand for healthcare remains high. The Libyan system operates far below the needs of the population, for example,²³⁴ including mental health services.²³⁵ Retention and recruitment of staff in war contexts is especially difficult, for reasons including disruption to education systems (see Boxes 4 and 5).²³⁶

Box 4. Maternity services in Palestine

Disruption to maternity services increases risks of health and birth complications. Delays caused by military checkpoints in Palestine, for example, were associated with more home births (8 percent in 1999 and 33 percent in 2002).^{237,238} Low birth weight and prematurity raise risks of long-term adverse outcomes among children, including mental health and behavioral problems, eating problems, lower IQ, and poorer educational outcomes.^{239,240}

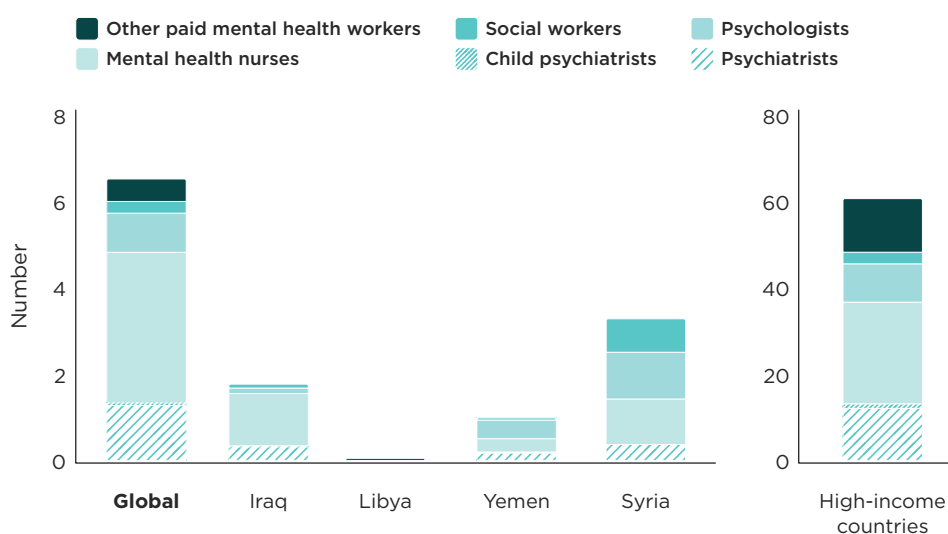
Box 5. Mental health services in Yemen

Rates of mental health problems are much higher in Yemen than other countries in conflict.²⁴¹ War, floods, epidemics, poverty and water shortages have damaged healthcare and education systems,^{242,243,244} and they lack practitioners.²⁴⁵ An intervention among general practitioners was found to improve their performance in the emergency management of acute medical problems.²⁴⁶ WHO's Mental Health Gap Action Programme subsequently trained health and community workers to increase access to mental health services,²⁴⁷ although these services have not been evaluated for use and effectiveness.

Although some national healthcare plans have started to recognize mental healthcare as essential (such as those in Iraq and Palestine),^{248,249} many Middle Eastern countries tend to lack mental health funding, resources, and workforce (see Figure 4).²⁵⁰ Psychosocial service providers face a lack of qualified, specialist staff, financial constraints, political conflict, and poor community awareness, a study of practitioners at refugee camps in the West Bank, Palestine, found.²⁵¹

Additionally, stigma means people are less likely to access that help even when services are offered. Further obstacles may include inadequate transport and complex referral processes. Patients may seek alternatives, such as faith healers, as seen in Iraq.²⁵²

Figure 4. Mental health workforce (rate per 100,000 population) in Middle Eastern countries



Note: Mental health workforce (rate per 100,000 population) in Middle Eastern countries with continuous conflict, compared with high-income countries and global rate (where value is zero this is equal to zero or not reported).²⁵³

Psychosocial interventions and service transformation

Limited service provision and reluctance to access services must be at the forefront when designing mental health interventions for children in areas affected by conflict. A growing body of research from the Middle East and elsewhere shows the complexity of such children's needs, influenced by the interplay of multiple risk and protective factors. Overwhelming needs and paucity of specialist resources indicate the importance of multimodal interventions that maximize current resources and community strengths.²⁵⁴

Evidence also shows the importance of tackling concurrent challenges that mental health services face in Middle Eastern cultures, such as: stigma;²⁵⁵ collective exposure to toxic stress of children, parents, communities, and professionals; limited contextualization and cultural adaptation of interventions; and constraints in infrastructure and staff competencies.²⁵⁶

First-level response interventions should aim to strengthen children's coping strategies and resilience, life skills, and symptom management. Several psychoeducation approaches (educating those seeking or receiving mental health services) and 'trauma-informed' programs (meaning that activities link to children's trauma exposure without intending for them to re-experience and re-process their experiences) have shown promising results.^{257,258,259} These can include body-mind interventions such as mindfulness that deal with physical and psychological presentations of distress (such as meditation, breathing techniques, guided imagery, and self-expression through words, drawings, and movement). Creative interventions emphasize interactive activities such as drama and music to help children build better relationships and improve resilience and wellbeing.²⁶⁰⁻²⁶⁴

Crucially, such programs bypass many challenges faced by mental health services in the Middle East because they are low cost and can be delivered by paraprofessionals (or community volunteers), peer educators, teachers, social care or NGOs, who nevertheless require training, supervision, and links with mental health services.²⁶⁵

First-level interventions are non-stigmatizing, as these can be provided to groups in schools, community, and religious centers. These contexts also solve access difficulties during conflicts and capitalize on feelings of belonging and comfort associated with their functions (especially religious forums). In Palestine, for example, school-based intervention, including

mind–body skills group programs²⁶⁶ and teaching recovery techniques^{267,268} showed success in decreasing various mental health problems among children and adolescents exposed to war trauma (see Box 6).

Box 6. A psychosocial school-based support program in the Gaza Strip, Palestine

Wars in Palestine²⁶⁹ exposed children to trauma and mental health problems.²⁷⁰ After the 2014 war, teachers, social workers, and counselors implemented psychosocial support programs in all schools in the Gaza Strip. Parents were actively involved. Cognitive behavioral techniques included group psychoeducation, discussion of past traumatic experiences, physical exercises, co-operative games and drama. PTSD, other emotional, and somatic symptoms, as well as cognitive functional impairment, significantly decreased after the intervention.²⁷¹

The second level of interventions can draw on contextualized frameworks such as trauma-focused CBT, narrative exposure, and child-centered therapy, and require skilled mental health professionals²⁷² who are lacking in Middle Eastern settings. These interventions should be offered to children whose symptoms continue after a resilience-building approach. Long-term investment in mental health will mean that more children can be targeted for intervention at this level. Ideally, parents should be involved, otherwise their own unresolved distress can adversely affect their children. Psychoeducation and parent-child dyadic developmental psychotherapy or trauma-focused CBT have been applied in war contexts (in Palestine, for example), but these should be adapted to the Middle Eastern culture and combined with social support.²⁷³ Co-ordination of services can offer adult mental health input.

Children, young people, and parents should actively be involved in the co-design and adaptation of interventions to ensure that they are engaging and culturally acceptable. Interventions and capacity-building should be framed in a stepped care service model (see Box 7).^{274,275}

Digital interventions and staff training can be delivered in conflict-affected areas using smartphones.^{276,277,278} These interventions have been shown to be efficient in assessing, screening, evaluating, and intervening among children, adults, and practitioners in Middle Eastern countries, where smartphone use is common.²⁷⁹ Digital tools are relatively low cost and can be easily integrated to both response levels (see Box 8).

Box 7. Psychotherapy treatment in the Gaza Strip and the West Bank, Palestine

The occurrence and treatment of psychiatric disorders in the Gaza Strip and the West Bank in Palestine were studied from 2005 to 2008. Patients aged one and older were clinically assessed by a psychologist or a psychiatrist (supervised by a senior psychologist or psychiatrist) through a local mental health and counseling health network. Psychological care, consisting of individual, family, group, or dyadic developmental psychotherapy,^{280,281} at home or in a consultation center, was provided to the patients diagnosed with PTSD, depression, or anxiety. The majority (79 percent) had reduced symptoms through psychotherapy, and around 30 percent required additional psychotropic medication.²⁸²

Box 8. Online cognitive behavioral therapy (CBT) intervention in Iraq

Technology can help treat mental health problems in unstable areas that lack healthcare practitioners.²⁸³ An online CBT approach was developed to treat PTSD and other emotional problems in adults in Iraq.^{284,285} Patients and trained therapists in Iraq, the Middle East, and Europe communicated through structured writing assignments submitted online. This form of intervention can improve symptoms of PTSD, anxiety, depressed mood, and grief across different cultures.^{286,287}

Recommendations for practice in the Middle East

Firstly, in the immediate term, short courses should be provided for primary care professionals so they can detect and treat mental illness and refer to specialist services. Longer term, undergraduate medical curriculums need increased emphasis on mental health and formal training for practicing medical practitioners.²⁸⁸

Secondly, mental health professionals should train paraprofessionals, teachers, social workers, and other community workers in first-level responses to strengthen children's coping strategies and resilience, and to recognize those who need specialist interventions. Ideally, these professionals would themselves receive mental health support.

Thirdly, mental health professionals should be trained and supervised to implement level-two interventions. Capacity-building should be tailored to community and specialist levels, and an interdisciplinary context is needed to promote joint working, networks, and efficient use of resources.²⁸⁹ The particular social, cultural, and religious contexts in the Middle East should be taken into account.

Finally, a long-term goal should be to upgrade and integrate mental health services across the health sector.

Recommendations for research in the Middle East

Research on child mental health, especially on interventions, has been underprioritized in Middle Eastern countries. Research examining specialist second-tier interventions targeting children most at need specific to Middle Eastern contexts is currently lacking.

Policymakers and researchers should prioritize assessing prevalence, needs, and mechanisms to establish the amount of psychosocial support needed and shape planning. Accurate data on mental health resources, use, and expenditure in conflict-affected Middle East settings are lacking. War-torn populations are usually hard to access and screen for mental health disorders. More data are needed to evaluate national mental health integration programs such as those established with WHO's support.

Traditional paper-based data collection is often difficult. Mobile phone data collection, access to services, and interventions have had positive effects, such as in screening Palestinian children to enable timely intervention for children with psychopathology.²⁹⁰

Mental health literacy campaigns could assuage the concerns about stigma that deter participation in studies.²⁹¹ Extending assessment to positive psychosocial functioning, coping strategies, and other indicators of resilience could also encourage participation.

Screening should use mixed methods to capture comprehensive psychosocial outcomes. Research tools and interventions may need cultural adaptation to Middle Eastern contexts, including language translation, piloting, culturally appropriate analogies, and focus group discussions with children, parents, teachers, and other stakeholders to co-design programs and tools that match communities' needs.^{292,293} Tools and interventions should be contextualized to marginalized groups, including women and girls, disabled people, and developmentally delayed children.

Finally, research findings in the Middle East are mostly based on cross-sectional studies, assessing mental health problems at one time. More longitudinal studies are needed, as they can assess the effects of prolonged trauma and toxic stress over time and generations.

Key recommendations

- Continuous and prolonged war trauma exposure in conflict areas in the Middle East affects children's development and mental health. Psychosocial interventions need to focus on building children's resilience and coping strategies and progress to more focused service provision for those who remain symptomatic.
- The development of mental health problems can be mediated by multiple stressors, including parenting, parental wellbeing, and economic hardship. These need to be taken into account when designing multimodal interventions.
- Instruments and interventions need to take into account the social, cultural, and religious contexts in the Middle East.
- Research and practice barriers in the Middle East such as stigma, limited transportation, costs, and mental health services should be considered.
- Middle Eastern countries that are affected by war and recurrent conflicts largely lack skilled mental health resources. Alternative plans could include training of paraprofessionals and frontline professionals on trauma-focused, resilience, and coping strategies and interventions.
- Use of mobile mental health resources and digital technologies could be maximized.
- The Middle East lacks planned, sufficient, and integrated mental health services. Policymakers should integrate the development of mental health services in healthcare system plans and policies.

SECTION 4. CONCLUSION AND RECOMMENDATIONS

We have a responsibility to ensure that children grow up in a world that is safe and conducive to healthy development. In order to succeed, we must address the root causes of toxic stress in children, and intervene as soon as possible to mitigate the harmful effects of these experiences.

Below, we outline a number of policy and research recommendations, which we hope will serve as a starting point for governments, researchers, healthcare providers, health professionals, and policymakers in achieving this goal and giving all children the chance for a healthier future.

Recommendations for research

1. Consider both objective and subjective measures of childhood adversity

Relying on self-reporting or parent-reported information may be convenient, but such measures are inherently subjective and prone to bias. Other measures, such as official court or child protection records, are an objective assessment but may underestimate the prevalence of adversity. Objective and subjective measures of childhood adversity tend to identify distinct groups²⁹⁴ and thus may be helpful in different ways – for example, subjective experience is particularly important for psychopathology.²⁹⁵

2. Include cultural context when assessing adversity and trauma

A challenge in examining the effects of adversity and trauma on development is how to compare children from different cultures: one culture may interpret bullying differently from another.²⁹⁶ When developing assessments, investigators should allow for social, cultural, and religious contexts.

3. Assess the role of biomarkers in evaluating toxic stress

Objective biomarkers for neurological, immunological, metabolic, and genetic regulatory changes may have a role in understanding the neural and biological mechanisms that mediate the toxic stress response.^{297,298,299} Issues to be assessed include whether biomarkers are better predictors than behavior, how early they can be used, and whether they are scalable.

4. Move toward the use of prospective study designs

Studies of toxic stress response tend to be limited by their cross-sectional design, which is unable to draw causal inferences. A move toward prospective follow-up or intervention studies will enable a better understanding of mechanisms of disease and possible solutions, for example, to determine optimal strategies for implementation of interventions proven to reduce toxic stress.

5. Pay more attention to differences between individuals

People respond differently, mentally and physically, to the same stressors. For example, only a minority of children who experience trauma or maltreatment develop enduring psychiatric illness; some children develop physical illness such as asthma, whereas others will not.³⁰⁰ Individual differences in biological sensitivity to stressors explain why children identified as shy or inhibited early in life may be more vulnerable to stressors than children with more robust temperaments.^{301,302,303}

6. Prioritize rigorous evaluation of interventions and strategies in conflict settings

Most research does not include children affected by conflict and displacement, and knowledge of best practices for these contexts is limited. A better understanding is required of the scope of the problem among children and families affected by conflict.

7. Understand the impact of COVID-19 on toxic stress in children

During the COVID-19 pandemic, measures to limit its spread may unintentionally increase exposure to multiple adversities through school closures, movement restrictions, and economic disruption. In India, where national lockdowns resulted in mass cross-country migrations, children risked separation from family members, economic insecurity, and violence.³⁰⁴

Recommendations for policy

1. Implement evidence-informed policies for health, nutrition, and early child development

Evidence-informed policies exist to optimize health, nutrition, and early child development,³⁰⁵ and should be implemented and scaled up to prevent

and treat the effects of childhood trauma.³⁰⁶ These can be expanded to include older children and adolescents. Although the primary focus is generally the first three years of life, the personalities and behaviors of older children are malleable.^{307,308}

2. Link and optimize child health and education initiatives

Clinicians and pediatricians must work closely with the education sector to integrate preventive and therapeutic interventions across systems of care. Doing this early in life is key to successful intervention,³⁰⁹ and needs to be done at the right time in the health and education systems. The development of the Nurturing Care Framework³¹⁰ is a welcome step in this direction, engaging stakeholders such as community health workers and pre-schools.³¹¹ Interventions across settings, such as community, school, and after-school care reduce the effects of traumatic events.^{312,313}

3. Adopt multisectoral, context-specific approaches, including in conflict settings

Engage children, families, communities, and humanitarian groups to prevent and ameliorate the impact of toxic stress. As the number of people affected by conflict and displacement grows, action to reduce the long-term effects of toxic stress must be targeted and swift. Existing interventions to reduce toxic stress in regions affected by conflict should be adapted to take account of cultural context and values, vulnerable subgroups, and resource constraints in their design and delivery.

4. Utilize public health strategies for primary, secondary, and tertiary prevention

Public health strategies include universal and targeted interventions, ranging from home visiting programs to parent training programs, routine screening for adversity, and CBT.^{314,315} The Middle East lacks planned, sufficient, and integrated mental health services. Policymakers should integrate mental health services building and development in the health-care system plans and policies.

5. Upskill the health and community workforce to identify and treat mental illness

Mental illness may be missed by health professionals. Primary care workers should be trained to detect and treat mental illness, and refer to specialist services. Longer term, undergraduate medical curriculums need increased emphasis on mental health.³¹⁶ Mental health professionals can

train paraprofessionals, teachers, social workers, and other community workers in first-level responses to strengthen children's coping strategies and resilience and to recognize those who need specialist interventions.

6. Embrace technology and health literacy

Mobile phone data collection, access to services, and interventions have had positive effects, such as in screening Palestinian children for timely intervention.³¹⁷ Mental health literacy campaigns can lessen the stigma that deters children from seeking care or participating in research.³¹⁸

7. Build capacity and integrate mental health services

Capacity-building is required at community and specialist levels. An interdisciplinary context is important to promote joint working, networks, and efficient use of resources.³¹⁹ Finally, a long-term goal should be to upgrade and integrate mental health services across the health sector.

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ARTICLE CITATIONS

Section 1

Nelson CA, Bhutta ZA, Burke Harris N, Danese A, Samara M. Adversity in childhood is linked to mental and physical health throughout life. BMJ 2020;371:m3048

Section 2

Atallahjan A, Samara M, Betancourt TS, Bhutta ZA. Mitigating toxic stress in children affected by conflict and displacement. BMJ 2020;371:m2876

Section 3

Samara M, Hammuda S, Vostanis P, El-Khodary B, Al-Dewik N. Children's prolonged exposure to the toxic stress of war trauma in the Middle East. BMJ 2020; 371:m3155

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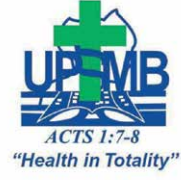


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