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Applications of psychoneuroimmunology models of toxic stress in prevention and intervention efforts across early development

Marin M. Kautz

Department of Psychology, Temple University Psychology, 1701 N. 13th St., Weiss Hall, Philadelphia, PA, 19122, United States

A B S T R A C T

Although evidence supporting psychoneuroimmunology (PNI) models of toxic stress have emerged over the past decade, the PNI field has struggled to integrate these important findings into real-world practical applications. There is great potential for these models to reduce the societal burden of childhood adversity by facilitating early detection and prevention with those children and adolescents at greatest risk for stress-related physical and psychological disorders. But further research is needed to validate and scale developmentally appropriate interventions with specific immune and endocrine mechanism-based targets that are developmentally sensitive. The allostatic load and additive PNI models of toxic stress exposure in youth are summarized. These models highlight the importance of integrating a standardized screening of environmental and interpersonal risk factors with stable and scalable cognitive and biological markers of risk. PNI models of toxic stress illustrate the need for intervention delivery as early as possible to prevent negative health outcomes in youth and comprehensive screening efforts would facilitate the deployment of community and family level interventions. This review discusses practical applications of toxic stress models that are currently under investigation, clarifies key obstacles, such as research gaps and scalability, and provides potential solutions, including cross-disciplinary partnerships.

1. The impact of childhood adversity on society

Childhood adversity (e.g., maltreatment, family discord, poverty) is a public health crisis (Edwards et al., 2003; Norman et al., 2012). Exposure to childhood adversity is associated with elevated risk for chronic diseases, impaired social, academic, and economic success, early mortality, and mental illness globally (Montez and Hayward, 2014). Adversity also predicts risk-taking behaviors in youth, including violence toward self and others and substance use (Hughes et al., 2017; Wadman et al., 2020). Despite a growing literature supporting the role of psychoneuroimmunology (PNI) systems in the biological embodiment of childhood adversity, the scientific community has struggled to translate and apply these models to clinical practice to protect youth in need. Early and effective intervention efforts at the level of PNI mechanisms may ameliorate these long-term health concerns before they persist (Benjet et al., 2010). The goal of this review is to highlight the practical applications of PNI models of toxic stress following childhood adversity exposure (see Fig. 1).

2. Embodiment of risk for psychological and physical health outcomes

PNI describes the communication of the brain, nervous, immune, and endocrine systems. Within these systems, the main components associated with childhood adversity are glucocorticoids, pro- and anti-inflammatory cytokines, and neurotransmitters (Danese and Lewis, 2017). When responding to both physical and psychological threats, the autonomic nervous system regulates the endocrine signaling of the hypothalamic-pituitary-adrenal (HPA) axis, which controls inflammatory macrophages and cytokine production through the anti-inflammatory effects of glucocorticoids following the release of adrenocorticotropic hormones from the pituitary gland (McEwen, 1998a; Sternberg, 2006). When exposed to an acute stressor, peripheral cytokines trigger a cascade by modulating neurotransmitter metabolism, HPA axis and vagal nerve activation, or directly crossing the blood-brain-barrier (Bennett et al., 2018; Sternberg, 2006). This cascade of biological responses prepares the body to respond to the stressor until it is no longer present (Silverman and Sternberg, 2012). When stressors are present chronically (i.e., over a prolonged period of time), this same functionally adaptive cascade begins to exhaust the body's resources leading to increased risk for

Fig. 1. Marin Kautz. Marin's research focuses on integrating innovative statistical techniques with markers of biological stress responsivity to better understand how early life adversity is linked to the development of mood disorders and self-injurious thoughts and behaviors among adolescents. Throughout her graduate career, she has examined how changes in neurobiological mechanisms following toxic stress exposure elevate youths' risk for self-harming. Her multimodal investigations support a model in which childhood toxic stress exposure alters cognition (e.g., stress perception and motivation), peripheral immune functioning, and neural activation and structure leading to increases risk for psychopathology during adolescence. Her current work focuses on understanding the risk factors immediately preceding suicidal thoughts and behaviors that disproportionately affect youth with a history of maltreatment, including increased inflammation following acute stress exposure. Her work aims to help establish a developmentally informed psychobiological theory of suicide that identifies modifiable risk factors. Ultimately this work can be used to develop mechanistically targeted interventions and facilitate the translation of psychoneuroimmunology models into clinical practice. Marin completed her undergraduate education at Barnard College of Columbia University, was a clinical research coordinator at the Depression and Anxiety Center at the Icahn School of Medicine at Mount Sinai, and joined Dr. Lauren Alloy's Mood and Cognition Laboratory in 2017 where she began her clinical psychology Ph.D. at Temple University. She is completing her clinical training at Temple University's Psychological Services Center and the Children's Hospital of Philadelphia's Safe Place Treatment and Support Program focusing on Dialectical Behavioral Therapy and Trauma-Focused Cognitive Behavioral Therapy for children and adolescents experiencing maltreatment and self-injurious behaviors. Her research has been supported by several awards and grants, including a National Science Foundation Graduate Research Fellowship and an American Psychological Foundation Visionary Grant. She is looking forward to starting a clinical internship in July 2022.

long-term negative health outcomes (McEwen and McEwen, 2017). Dysregulation of the HPA axis occurs when glucocorticoids fail to regulate inflammation, which may result from mutations or polymorphisms of the glucocorticoid receptors through epigenetic mechanisms following chronic stress exposure (Derijk et al., 2002; Bartlett et al., 2019).

Childhood adversity is a robust predictor of negative health outcomes related to PNI system dysregulation in children (see Fig. 2). For example, autoimmune and somatic issues commonly co-occur with an array of psychological symptoms in youth exposed to adversity (Oh et al., 2018). Low-grade (i.e., subclinical) immunologic dysfunctions have been associated with many psychological conditions, including anxiety, depression, and bipolar disorders (Barbosa et al., 2014; Capuron and Castanon, 2016; Kautz et al., 2020; Moriarity et al., 2020). Adversity has been associated with alterations in cognitive processes, including heightened threat sensitivity, blunted reward responsivity, and elevated emotional reactivity (McLaughlin et al., 2020; Teicher et al., 2016). Structural modifications in the brain following neurodegeneration caused by inflammatory mediators, such as pro-inflammatory cytokines, are theorized to account for the association between inflammatory dysregulation and cognitive and behavioral changes (Nusslock and Miller, 2016). Meta-analyses have found increased peripheral inflammation, C-reactive protein (CRP), interleukin- (IL-) 6, and tumor necrosis factor-alpha (TNF-α) in adults and adolescents with a history of childhood trauma in clinical and community samples (Baumeister et al., 2016). Childhood adversity has been confirmed as an independent predictor of inflammation, beyond the relationship between psychological symptoms and

elevated inflammatory biomarkers (Carpenter et al., 2010; Hartwell et al., 2013). These findings highlight the role of PNI systems in establishing vulnerability following childhood stress exposure, but several questions about the sequence, longevity, and potency of this relationship remain.

3. PNI models in children

3.1. Stress in childhood affects immune functioning in later development

A meta-analysis of eight studies identified a positive association between adversity and CRP in adolescence (Kuhlman et al., 2019). But how early in life can immune and endocrine system dysregulation be detected and how long does the dysregulation last? Although the longitudinal PNI literature in youth is still limited, initial research has demonstrated that the relationship between childhood chronic stress exposure and immune system dysregulation begins to emerge as early as age 3 (Entringer et al., 2020). When assessed longitudinally between ages 9 to 16, adolescents with more cumulative adversity had greater increases in CRP across this seven-year period (Copeland et al., 2014). This elevated inflammatory response appears to persist into young and middle adulthood, indicating the long-term impact of adversity on inflammatory responses across development (Copeland et al., 2014; Renna et al., 2021). It remains unclear how subsequent experiences of psychological stress exposure during adolescence and adulthood affect the neuroimmune system of those who already have experienced childhood adversity.

3.2. Cumulative stress exposure model

One proposed model to account for the negative health outcomes following chronic stress exposure as mediated by PNI systems is the cumulative stress exposure model, also known as the allostatic load model (McEwen, 1993). This model proposes that each stressor an individual experiences results in progressive and cumulative wear and tear in the stress response system regardless of prior experiences of stress exposure (McEwen, 1998b). Glucocorticoids, such as cortisol, are released following HPA axis activation and become toxic if high levels are sustained (Howell and Sanchez, 2011). Chronic exposure to high levels of cortisol have been linked to hypertension, diabetes, alterations in immune system responsivity, and alterations in brain regions associated with cognitive stress perception, such as the hippocampus and amygdala (Kolber et al., 2008; McEwen, 1998a; Sánchez et al., 2001). Demonstrating support for the cumulative nature of this biological degradation in youth, higher cumulative risk exposure prior to age 13 was associated with elevated markers of allostatic load at age 17 (Evans and Kim, 2012). The increase in number of adverse life events experienced from birth to age 9 also was associated with higher levels of inflammatory markers for female children (Flouri et al., 2020). Additionally, more frequent cumulative environmental risk factor exposure during childhood was associated in a dose-dependent manner with higher allostatic load in adolescence (Theall et al., 2012). Evidence has supported the embodiment of chronic stress in youth through the mechanisms described in the cumulative stress exposure model (Danese and McEwen, 2012; Guidi et al., 2021). However, this model does not account for earlier stress exposure's effect on subsequent cognitive and biological responses to perceived threats, and instead, focuses on progressive biological resource consumption across development (Howell and Sanchez, 2011).

3.3. Additive stress exposure model

A model that expands on the concept of allostatic load, but addresses some critical gaps, is the additive stress exposure model, also known as the developmental programming model or the reactive scope model. In this model, exposure to stress during particularly sensitive periods "program" biological systems to be primed for exaggerated responses when these systems are triggered in later development. In longitudinal
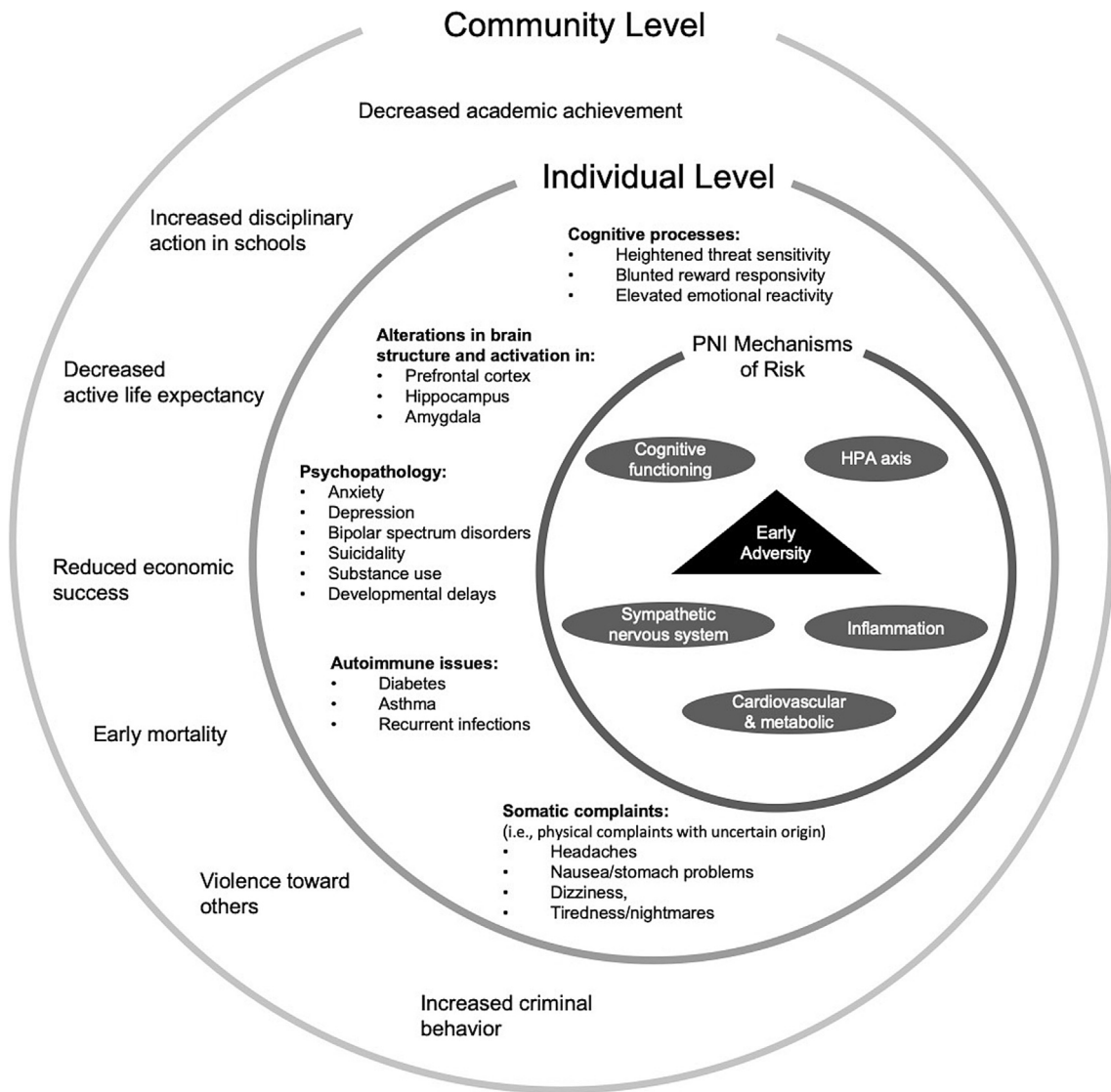
Fig. 2. The effects of adversity on physical and psychological health outcomes during childhood and adolescence through PNI-related mechanisms of risk (Danese and Lewis, 2017; Gherardi et al., 2020; McEwen and McEwen, 2017; Montez and Hayward, 2014; Oh et al., 2018; Teicher et al., 2016; Wadman et al., 2020).

adolescent samples, those raised in a harsh environment, who also experienced recent stressors over the last six months, had exaggerated immune responses to a bacterial challenge (Miller and Chen, 2010). Children with asthma who experienced chronic family stress during childhood and acute stressful events during the past three months had greater immune reactivity to an in-vitro stimulation (Marin et al., 2009). Additionally, adolescent females with a history of childhood adversity were found to have elevated IL-6 release following an in-vitro stimulation with a bacterial challenge (Ehrlich et al., 2016). These findings support the hypothesis that early stress exposure primes the immune system to exaggerate responses to subsequent stressors. These priming effects seem to persist into adulthood, as adults exposed to both childhood adversity and recent acute stressors experience higher levels of inflammatory markers (Carpenter et al., 2010; Gouin et al., 2012; Simons et al., 2019). This model illustrates the need for widespread community and individual level screening *and* intervention efforts to prevent exposure to toxic stress as early as possible because interventions delivered during childhood may have the greatest effect on decreasing risk for negative long-term outcomes.

Table 1

Cognitive and biological markers of risk to include in a comprehensive screening protocol of toxic stress.

Associated system:	Cognitive and biological markers of risk:
Cardiovascular and metabolic systems	Blood pressure, heart rate variability, blood glucose, insulin, blood lipids, body mass index (BMI), and waist circumference
HPA axis	Cortisol, dehydroepiandrosterone sulfate
Sympathetic nervous system	Epinephrine, norepinephrine, dopamine, and vagal reactivity
Inflammation	C-reactive protein, interleukin-6
Cognitive functioning	Learning, memory, and executive functioning (e.g., inhibition, set-shifting, and planning)

4. Screening for PNI markers of risk

Moving these PNI models beyond the academic sphere and into the lives of youth involves the integration of widespread tracking of environmental and interpersonal risk factors with the identification of stable and scalable cognitive and biological markers of risk. The standardized screening of risk would facilitate the deployment of traditional and technology-based therapeutic interventions to families. As shown in

Table 1, a comprehensive screening of PNI markers of risk should include markers associated with cardiovascular and metabolic diseases, HPA axis, sympathetic nervous system, inflammation, and cognitive functioning (Seeman et al., 2010). Screening for PNI markers of risk also should include a thorough assessment of objective prior and recent acute and chronic stressful life events and subjective levels of perceived stress exposure utilizing developmentally appropriate assessments. Finally, a comprehensive screening procedure should account for environmental exposure to immunotoxins, including traffic-related air pollution (Clougherty et al., 2007).

Annual health screenings of children already include several markers of risk, including brief screenings for psychological symptoms, autoimmune-related illnesses, and markers of cardiovascular diseases (Pediatrics, 2021). BMI, in particular, is regularly assessed at annual health screenings and is associated with cognitive impairment and immune dysregulation in adolescence (Mac Giollabhui et al., 2019). Although not currently assessed at screenings, toxic stress related changes in cognitive functioning should be assessed, including memory and executive functioning (Chen and Baram, 2016; Shields et al., 2017). Measures with low administrator burden that are language independent to reduce cultural biases are preferred, such as the International Guide for Monitoring Child Development and Cambridge Automated Neuropsychological Test and Battery (Ozturk Ertem et al., 2019; Syvaoja et al., 2015). Peripheral levels of CRP and cortisol also are recommended additional screening measures of immune and HPA axis functioning, as they have been identified as persistent markers of stress in early childhood (Entringer et al., 2020; Hunter et al., 2011; Slopen et al., 2013). They are commonly assessed on standard blood and salivary panels, which decreases the barriers of adding them to regularly performed screenings. Vagal reactivity also has been identified as a marker of sympathetic nervous system functioning and heightened biological reactivity to stress (Alkon et al., 2017; McLaughlin et al., 2014). Vagal tone and regulation can be assessed through non-invasive measures (e.g., respiratory sinus arrhythmia) utilizing basic medical equipment, such as an electrocardiogram. Ideally, a comprehensive screening procedure for PNI risk markers in youth would be supported by public health policies to integrate these procedures into behavioral and physical health settings, culminating in the calculation of a uniform index of allostatic load that could be generalizable and tracked longitudinally.

5. PNI based prevention and intervention efforts

5.1. Community level interventions

There are several levels at which public health initiatives can utilize PNI models of development to reduce the societal burden of childhood adversity (Burke Harris et al., 2017). The first level is the prevention of adverse events themselves. Recently, local and regional initiatives have introduced trauma-informed trainings for school employees and law enforcement officers to prevent subsequent exposure to adverse events (Chafouleas et al., 2021; Jones et al., 2017). Additionally, tailored parent trainings have been proposed, including using low-cost technologies like subsidized smartphone applications to widely distribute mindfulness practices and stress monitoring tools. Another approach currently being evaluated is the creation of local data dashboards to compile measures of child well-being and to create bidirectional communication between residents, policymakers, and advocate organizations to inform new initiatives (Jones et al., 2017). The additive stress exposure model highlights the importance of reducing stressor exposure as early as possible to lessen the effects of elevated low-grade inflammation on the neural architecture and cognitive functioning of youth. For successful engagement, any PNI-based interventions must educate community stakeholders on the cumulative impact chronic stress exposure has on children's health (Weems et al., 2021).

Support for the additive stress exposure model has demonstrated that early identification is key to preventing the onset of toxic stress, which is

the second level of potential community intervention. The two main barriers to early identification are inadequate screening of standard childhood adverse events (e.g., abuse, neglect, loss of loved one, bullying, etc.) and the struggle to monitor socially situated sources of adversity (Chafouleas et al., 2021). Socially situated sources of adversity for children include structural racism, immigration status, gender and sexual orientation identity discrimination. As a primary basis of socialization, schools may be best equipped to identify children experiencing socially situated sources of adversity and to reduce these stressors by questioning and challenging the larger societal norms that increase the experiences of adversity for youth with minority social identities (Gherardi et al., 2020). Classroom management procedures that emphasize physical and emotional safety, restorative discipline techniques, and opportunities for peer support among students or in their community can be integrated to reduce inequality and re-traumatization (Gherardi et al., 2020). Pediatrician offices are another setting in which comprehensive and standardized screening of adverse event exposure, as well as routine screening for biomarkers of toxic stress, may have the greatest opportunity for preventing the onset of cascading responses to toxic stress.

The third level is the treatment of the effects of a toxic stress response. Although most interventions will be delivered on an individual level, the distribution of warning signs for potential experiences of toxic stress in schools and pediatrician offices can empower families to seek information about treatment options, if necessary. The cumulative and additive stress exposure models both demonstrate that identifying the early onset of toxic stress response is beneficial for dampening the risk of negative health outcomes. These warning signs for children include cognitive difficulties (e.g., disorientation, poor concentration, memory difficulties), emotional and behavioral issues (e.g., difficulty sleeping or eating, increased anxiety, sadness, or aggression), and physical distress (e.g., fatigue, gastrointestinal distress, increased sweating, thirst, or headaches; Fava et al., 2019). Children rely on familial support to engage with and adhere to treatment recommendations, so practitioners must account for access to resources and experiences of intergenerational trauma during psychoeducation.

5.2. Individual level interventions

At an individual level, initial studies have shown that tailored diets may reduce the symptoms of toxic stress exposure at a downstream level (Alessi and Bennett, 2020). For example, individuals with high omega-6 to omega-3 ratios in their diets have been found to produce greater levels of proinflammatory cytokines during stressful life events (Kiecolt-Glaser et al., 2007; Maes et al., 2000). Additionally, diets high in refined carbohydrates and processed sugars have been associated with higher levels of CRP (Berk et al., 2013). Because processed food is often targeted toward children, this may be a critical area for prevention efforts. Additionally, certain micronutrients are immune system modulators; thus, single nutrient (e.g., vitamin D) and broad-based micronutrient (e.g., multivitamin) supplements may help to reduce the symptoms of toxic stress if properly regulated (Kaplan et al., 2015). Initial evidence from randomized control trials (RCTs) in adults have shown that the introduction of these supplements reduced symptoms of psychological distress (Rucklidge and Kaplan, 2013). Probiotic supplements also have been found to reduce symptoms of depression and CRP levels in a RCT (Akkasheh et al., 2016). Future research should focus on testing the effects of these tailored diets and supplements in reducing inflammatory dysregulation following stress exposure in children.

Initial work has found that nonsteroidal anti-inflammatory drugs (NSAIDs) modulate immune responses alone or in conjunction with other interventions. In adults, NSAIDs have been found to reduce symptoms of depression compared to a placebo, and NSAIDs requiring a prescription, like celecoxib, have been found to increase antidepressant efficacy over antidepressant treatment alone (Akhondzadeh et al., 2009; Kappelmann et al., 2018). Pharmacological interventions may help with reducing the symptoms of mental and physical illnesses, but they have not been shown

to prevent or reverse the effect of toxic stress exposure. Future research should examine whether child safe NSAIDs could be introduced during periods of high stress earlier in life to prevent the onset of psychological symptoms later in development.

Inflammation may be targeted indirectly by modifying the perception and appraisal processes that initiate psychological distress. Initial evidence has indicated that psychological interventions, such as cognitive restructuring, acceptance-based approaches, and meditation, reduce markers of inflammation (Black and Slavich, 2016; Creswell et al., 2016; Lopresti, 2017). Few studies have assessed the efficacy of these interventions in youth with a history of adversity, an important avenue of future research (Pace et al., 2013; Purewal Boparai et al., 2018). Altering the cognitive interpretation of events as stressful may be a key treatment target to reduce the neuroendocrine system dysregulation that mediates the pathway between stress perception and physiological arousal. Psychological interventions are hypothesized to reduce HPA axis activation and increase stress recovery, thereby interrupting the cycle of chronic immune system activation (Schakel et al., 2019). Cognitive coping strategies also have been associated with lower levels of IL-6 in children (Caserta et al., 2011). Initial evidence supports the feasibility of classroom and parent training interventions targeted at reducing the distress caused by toxic stress exposure (Woods-Jaeger et al., 2018b). Future research should identify what stress reduction techniques are most effective at reducing distress following exposure retrospectively and shifting the subjective perception of a stressor in real time. A nurturing environment, attention from caring adults, and coping skills are all protective factors for children that have shown potential for decreasing the biological impact of toxic stress exposure (Purewal Boparai et al., 2018). Future research should focus on cultivating these protective factors through psychological interventions at community and family levels (Woods-Jaeger et al., 2018a).

6. Current gaps, obstacles, and potential solutions

There is a need for the creation and validation of developmentally appropriate interventions with specific immune and endocrine mechanism-based targets that are sensitive to developmental timing. Individual and community level interventions must be developed to reduce the neurobiological symptoms of toxic stress, prevent future elevated biological reactivity, *and* reverse the effect of prior chronic stress exposure. This requires identifying the specific psychological, pharmacologic, and genetic factors involved in the etiology of children's stress perception and response systems (Heim et al., 2019). Future research should evaluate the feasibility of integrating a standardized comprehensive screening for PNI markers across healthcare settings. Transdisciplinary treatment teams focused on inter-individual care may be a core component of delivering effective interventions for toxic stress exposure and would be ideal settings to test the feasibility of such a screening protocol. Finally, the adoption of policy-level changes to reduce environmental stressors affecting population health, such as the establishment of a universal basic income and universal healthcare, will be a critical next step (Alessi and Bennett, 2020). PNI models could facilitate prevention and identification of youth at greatest risk for stress-related disorders, but further work is necessary to validate and scale these efforts.

Obstacles continue to exist in the execution of these recommendations, including the education of mental health care providers on basic biology, physiology, and fundamental immunological concepts, and the education of physical health care providers on the fundamental processes of stress perception and basic coping skills to help reduce distress following exposure (Kiecolt-Glaser, 2009). It is difficult at times to bridge the gap between what researchers in the field see as the next pressing questions to tackle versus the unknown areas that practitioners and entrepreneurs need clarified in order to effectively reach vulnerable populations. A primary solution will be early and continuous cross-discipline collaboration between biomedical and basic science colleagues with primary mental and physical healthcare providers, including pediatricians and school counselors. Gaining input from community stakeholders during the early phases of research design also will be necessary for the widespread adoption of any proposed screening or intervention efforts.

6.1. Conclusions

The goal of this review was to highlight the need for PNI model integration into practical and effective applications to decrease the societal burden of childhood adversity. With experiences of adversity recently rising 8.4% in the United States, bridging the gap between schools, primary healthcare settings, laboratories, and technology-based businesses is an urgent future direction (U.S. Department of Health and Human Services, 2020). When translating PNI models of development into practice, the focus on individual and family risk and protective factors needs to be expanded to include community, societal, and systems level intervention and prevention efforts (Jones et al., 2017).

Declaration of competing interest

The author has no conflicts of interest to declare.

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