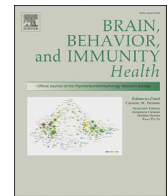


Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

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journal homepage: [www.editorialmanager.com/bbih/default.aspx](http://www.editorialmanager.com/bbih/default.aspx)

## Mindfulness interventions for offsetting health risk following early life stress: Promising directions

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## ARTICLE INFO

## Keywords:

Mindfulness  
Early life stress  
Inflammation  
Interventions  
Health disparities

## ABSTRACT

Early life stress (ELS), common to childhood maltreatment, socioeconomic disadvantage, and racial discrimination, is thought to create a proinflammatory phenotype that increases risk for poor health in adulthood. Systemic change is needed to address the root causes of ELS, but a substantial number of adults are already at increased health risk by virtue of ELS exposure. Interventions that target stress pathways have the potential to interrupt the trajectory from ELS to inflammatory disease risk in adulthood. Mindfulness-based interventions (MBIs), which train acceptance toward present-moment experience, have shown promise for reducing stress and improving a variety of stress-sensitive health outcomes. Although MBIs have primarily been conducted in more advantaged populations, evidence suggests that they may be uniquely effective for improving mental health and health-related quality of life among those with a history of ELS. Whether these effects extend to physical health remains unknown. To shed light on this question, I review evidence that MBIs influence inflammatory markers in at-risk samples, explore the promise of MBIs for improving stress-related health outcomes in diverse at-risk populations, and describe adaptations to MBIs that may increase their acceptability and efficacy in populations exposed to ELS. This prior work sets the stage for well-controlled RCTs to evaluate whether MBIs influence stress and inflammatory pathways among those exposed to ELS and for pragmatic and implementation trials focused on disseminating MBIs to reach these at-risk populations. Overall, the evidence assembled here shows the potential of MBIs for offsetting physical health risk related to ELS.

Disparities in health related to race, socioeconomic background, and childhood maltreatment are some of the most intractable public health problems faced today. Early life stress (ELS) accompanies childhood maltreatment (e.g., abuse, neglect, household dysfunction), socioeconomic disadvantage, and racial discrimination and is thought to contribute to their associations with inflammation and health risk (Baumeister et al., 2016; Cuevas et al., 2020; Fagundes et al., 2013; Jakubowski et al., 2018; Muscatell et al., 2020; Sternthal et al., 2011; Wegman and Stetler, 2009; Williams et al., 1997). Although these stressors are experienced across the lifespan, when experienced in childhood, chronic stress may trigger behavioral and biological adaptations that persist in adulthood (Gunnar and Quevedo, 2007; Miller et al., 2011; Shonkoff et al., 2009). Radical systemic change is needed to address the root causes of health inequity, including systemic factors (e.g., policy, culture) and unequal access to resources (e.g., health services, healthy food, education) (National Academies of Sci, 2017), but even if equity is achieved for future generations, a significant number of adults will still be at risk for poor health by virtue of ELS exposure. Interventions that target the stress common to each of these risk factors

may help to interrupt the trajectory from ELS to elevated inflammation and poor health in adulthood (Reiss et al., 2019).

Mindfulness-based interventions (MBIs), which train acceptance toward present-moment experience, have shown promise for reducing stress, reducing markers of inflammation in some samples, and improving a variety of stress-sensitive health outcomes (Creswell et al., 2019). I propose that MBIs may be uniquely effective for targeting biological stress processes and inflammatory pathways in populations exposed to ELS and are thus worth evaluating for their potential to offset health risk. This paper begins by situating ELS in the context of health risk, with inflammatory mechanisms linking several forms of ELS with multiple chronic diseases. It then focuses on MBIs: I review the evidence that MBIs influence inflammatory markers, explore the promise of MBIs for improving health outcomes in diverse at-risk populations, and describe how adaptations to MBIs may increase their acceptability and efficacy in populations with a history of ELS. Throughout, I suggest important directions for future research with consideration to NIH and NCCIH recommendations for intervention development, testing, and dissemination (NCCIH, 2021; Onken et al., 2014). For the purposes of

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<https://doi.org/10.1016/j.bbih.2021.100338>

Received 14 May 2021; Received in revised form 19 August 2021; Accepted 24 August 2021

Available online 26 August 2021

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this review, I define childhood maltreatment, low childhood socioeconomic status (SES), and early life racial discrimination as potent early life stressors, but since few MBI studies have focused on ELS populations, I also consider adulthood SES and racial minority status as risk factors that may associate with ELS exposure.

## 1. Chronic early life stress, inflammation, and health risk

Chronic stress exposure—when ongoing demands exceed the ability to cope (Lazarus and Folkman, 1984)—is widely accepted to associate with poor health in part through inflammatory processes that contribute to the pathophysiology of many chronic diseases and predict risk for mortality (Libby, 2002; Reuben et al., 2002). Although chronic stress in adulthood is linked with health risk (e.g., caregiving stress (Kiecolt-Glaser et al., 1991)), chronic stress that occurs in early life may become biologically embedded in ways that amplify the effects of adulthood stress (Kiecolt-Glaser et al., 2011). Indeed, a threatening early life social environment (e.g., exposure to trauma, violence, discrimination) has been associated with epigenetic modifications, including changes to DNA methylation of genes that regulate HPA axis and inflammatory stress responding (Janusek et al., 2017; Jiang et al., 2019; Turecki and Meaney, 2016). These adaptations to ELS are thought to contribute to a proinflammatory phenotype in childhood that influences lifelong health (Baumeister et al., 2016; Miller et al., 2011), situating ELS as one of the most critical public health problems faced today.

Although promising interventions have been developed to reduce ELS and its biological imprint during childhood (e.g., family-oriented interventions (Miller et al., 2014)), the majority of people reach adulthood with no such intervention, rendering a substantial portion of adults at risk for chronic disease. Yet there are currently no evidence-based interventions to offset this health risk in adulthood (Reiss et al., 2019). MBIs have been shown to reduce neural, biological, and subjective stress reactivity among stressed adults (Hoge et al., 2013; Lindsay et al., 2018; Taren et al., 2015), and thus may be promising for targeting health risk associated with ELS.

## 2. What are MBIs?

Widely used MBIs include (a) the 8-week Mindfulness-Based Stress Reduction (MBSR) program (Kabat-Zinn, 1982), which involves weekly group classes and daily home practice, (b) variants of MBSR developed for specific populations (e.g., Mindfulness-Based Cognitive Therapy [MBCT] for depression (Teasdale et al., 2000)), (c) abbreviated MBIs (Schumer et al., 2018), and (d) intensive MBI retreats (King et al., 2019). Common to these MBIs is training in monitoring present-moment sensory experiences (e.g., thoughts, emotions, body sensations, sounds) with an orientation of acceptance and equanimity (Bishop et al., 2004). Acceptance has emerged as a critical emotion regulation mechanism underlying the effects of MBIs on reducing stress (Lindsay et al., 2018) and we therefore consider it a key element for improving health outcomes (Lindsay and Creswell, 2017, 2019). Rather than trying to avoid or alter difficult and stressful experiences, practicing an attitude of acceptance involves welcoming and allowing all momentary experiences—even stressful ones—to arise and pass freely.

Acceptance training may be particularly useful for adults with a history of ELS. In the MBI tradition, acceptance is not a passive acquiescence toward external circumstances (e.g., abuse, discrimination), but rather an acknowledgement and welcoming of internal momentary experiences (e.g., emotions, sensations, thoughts) that allows space to consider how to respond to stressors. Indeed, equanimity allows for ‘the pain of injustice [to be] held in our hearts while the mind is still, steady, and clear’ (King, 2020), which, as discussed later, may engender compassion and prosocial actions that target structural issues at the root of ELS. Experiential acceptance contrasts with avoidance-based coping strategies that are commonly used to manage ELS but have been linked with detrimental consequences for health (Appleton et al., 2013). We have

shown in two dismantling trials that acceptance is a key component of MBIs for targeting stress perceptions and biology (Lindsay et al., 2018; Chin et al., 2019a). Moreover, MBIs have been uniquely effective for reducing mental health symptoms among adults with a history of childhood maltreatment (Earley et al., 2014; Joss et al., 2019; Kimbrough et al., 2010; Kuyken et al., 2015; Ma and Teasdale, 2004; Williams et al., 2014; for a review, see Joss and Teicher, 2021) and experiential acceptance is thought to underlie improvements (Thompson et al., 2011; Janusek et al., 2021). Whether these effects extend to markers of physical health remains unknown.

Further, the majority of MBIs have been conducted in more advantaged populations. A review of 69 MBI RCTs conducted in the United States reported an oversampling of white, higher SES women: ¾ of participants were white, 70% were women, and participants’ educational attainment and income were higher than US averages (Waldron et al., 2018). Thus, whether MBIs are acceptable and salubrious in populations underrepresented in research is a critical question (Chin et al., 2019b). Importantly, lower SES and racial minority status are associated with elevated inflammation and poorer health in part through stress exposure that often begins in childhood (Williams et al., 1997). As such, developing and evaluating culturally-informed, accessible MBIs for diverse populations exposed to ELS is a critical research direction.

To develop a translational science of MBIs that benefits public health—and those exposed to ELS specifically—it is important to conduct research in ELS populations across a continuum of stages as outlined by NIH and NCCIH (NCCIH, 2021; Onken et al., 2014). Stages include basic mechanistic research demonstrating that MBIs target stress and inflammatory pathways (Stage 0), culturally-informed intervention adaptation and standardization (Stage IA), feasibility and pilot studies focused on recruitment and adherence (Stage IB); efficacy studies assessing long-term inflammatory and health outcomes (Stages II and III), real-world effectiveness studies in healthcare and community settings (Stage IV), and dissemination and implementation studies (Stage V). To date, the majority of MBI research has focused on applying MBIs in new populations (Stage IA and IB) and evaluating efficacy (Stage II), with few pragmatic trials examining effectiveness or implementation in real-world settings (Stages IV and V) (Dimidjian and Segal, 2015). Below I describe progress and future directions for MBI research to address ELS-related health risk.

## 3. Do MBIs impact inflammatory mechanisms underlying health risk?

A pressing basic science question is whether MBIs influence inflammatory mechanisms thought to link ELS with disease risk. Early MBI trials showed promise for improving stress-sensitive disease outcomes and inflammatory processes theorized to underlie these effects (Creswell and Lindsay, 2014). Specifically, initial RCTs suggested that MBIs reduce circulating levels of CRP (Creswell et al., 2012; Malarkey et al., 2013) and neurogenic inflammatory responses to acute stress (Rosenkranz et al., 2013), but provided less consistent evidence that they reduce IL-6 or other proinflammatory markers (for reviews, see (Black and Slavich, 2016; Bower and Irwin, 2016; Morgan et al., 2014)). More recent RCTs show consistent effects of MBIs on upstream proinflammatory gene expression (Black et al., 2019) but not circulating inflammatory markers (Creswell et al., 2019). Further, it is unclear whether MBI-related changes in inflammatory markers translate to changes in clinical disease outcomes (Jedel et al., 2014).

Inconsistent associations of MBIs with markers of inflammation raise the possibility that some individuals benefit more than others (e.g., those with high stress burden, compromised immune status, and/or risk for inflammatory disease (Morgan et al., 2014)). For example, mood disorders are bidirectionally associated with elevated markers of inflammation (Miller and Raison, 2016), and a recent meta-analysis supported MBI-related reductions in inflammatory markers among individuals with depression and anxiety (Sanada et al., 2020; also see Hoge et al.,

2018; Walsh et al., 2016). Positive effects of MBIs on inflammatory markers have also been observed in other at-risk samples: in lonely, obese, or cognitively impaired older adults (Creswell et al., 2012; Ng et al., 2020; Smith et al., 2018), stressed adults (Creswell et al., 2016), inflammatory disease patients (irritable bowel disease (González-Moreo et al., 2020); glaucoma (Dada et al., 2018; Gagrani et al., 2018)), and breast cancer patients (Janusek et al., 2019; Kenne Sarenmalm et al., 2017; Lengacher et al., 2012).

Yet not all evidence is consistent with the idea that MBIs improve markers of inflammation in at-risk samples. Indeed, effects of MBIs on inflammatory markers do not always replicate in efficacy trials (e.g., obesity (Daubenmier et al., 2016); breast cancer (Lengacher et al., 2019)), and well-controlled trials have found null or nonsignificant effects in other at-risk samples (e.g., HIV (Hecht et al., 2018); rheumatoid arthritis (Zautra et al., 2008); cardiac patients (Nijjar et al., 2019)).

Might there be reliable conditions under which MBIs impact inflammatory processes? Sensitivity analyses reported in several trials provide clues. Mindfulness practice time (class attendance; home practice) has been associated with improvements in IL-6 (Bower et al., 2015; McClintock et al., 2019), including among women who experienced childhood trauma (Gallegos et al., 2015). MBI adherence is influenced by myriad factors, including higher enjoyment or perceived benefit and/or fewer barriers to participation. Promisingly, MBIs have been adapted to increase acceptability and adherence across diverse samples; these adaptations, reviewed below, have potential to boost overall MBI efficacy. Other trials find effects of MBIs on inflammatory markers in higher-risk subgroups, including those with higher pre-trial inflammation (Puhmann et al., 2019; also see Malarkey et al., 2013) and those with multiple risk factors (high stress plus obesity or older age Lindsay et al., 2019; Villalba et al., 2019).

Overall, data from pilot and efficacy trials and post hoc analyses identify individuals who may be most likely to benefit from MBIs: those with heightened systemic inflammation or risk thereof, particularly at the intersection of psychosocial risk (e.g., high stress, loneliness, mood disorders) and biological risk (e.g., high BMI, older age, inflammatory disease). Given the association of ELS with many of these risk factors, MBIs—especially those adapted to encourage adherence in Stage I research—are worth evaluating at Stage 0/II for their potential to alter inflammatory processes among adults exposed to ELS.

#### 4. Do MBIs have potential for offsetting health risk associated with ELS?

Despite evidence that MBIs may impact inflammatory markers in at-risk populations, much of the research to date has neglected individuals at greatest health risk, including those exposed to ELS (Waldron et al., 2018). However, indirect and exploratory evidence suggests that MBIs hold promise for offsetting health risk related to ELS.

A growing body of evidence suggests that MBIs are uniquely effective for improving mental health among those with a history of childhood maltreatment (for a review, see (Joss and Teicher, 2021)) and initial evidence shows improvements in mental health, health behaviors, and health-related quality of life among low-income and racially diverse participants following MBIs (for reviews, see (Chin et al., 2019b; Burnett-Zeigler et al., 2016a; Spears, 2019)). Indirectly, there is evidence that MBIs target stress pathways that may underlie risk for inflammation and chronic disease among those exposed to ELS (Fagundes and Way, 2014). For example, whereas ELS has been associated with reduced prefrontal and amygdala regulation (Kim et al., 2013), we have shown that mindfulness training increases prefrontal regulation and reduces amygdala reactivity (Taren et al., 2015, 2017; Creswell et al., 2016). ELS dysregulates HPA (Carpenter et al., 2007, 2009, 2011), autonomic (Pascoe and Smart Richman, 2009), and inflammatory (Lockwood et al., 2018) stress reactivity whereas we and others have shown that mindfulness training normalizes these physiological responses (Lindsay et al., 2018; Hoge et al., 2018). ELS is associated with increased stress

sensitivity (Glaser et al., 2006; Wichers et al., 2009) whereas mindfulness training reduces subjective stress (Khoury et al., 2015). However, whether MBIs similarly alter stress mechanisms among those exposed to ELS remains unknown, posing an important question for Stage 0 basic research.

To date, few studies have tested the effects of MBIs on biomarkers of physical health in ELS samples. One pilot trial explored the effect of MBSR on inflammatory markers in a sample of 42 women exposed to childhood trauma (Gallegos et al., 2015). Class attendance associated with reductions in IL-6, again highlighting the importance of optimizing MBI acceptability in ELS populations in Stage I research. In a sample of lonely older adults, we found that only lower SES and racial minority subgroups showed increased immune cell sensitivity to the anti-inflammatory effects of glucocorticoids following MBSR (Lindsay et al., 2021). These exploratory findings are consistent with the idea that MBIs may be most beneficial among those at greater health risk: here, participants with current stress burden and a greater likelihood of ELS.

Although promising, Stage 0/II RCTs are needed to evaluate whether MBIs can influence stress and inflammatory pathways that contribute to ELS-related health risk. Many basic science questions remain. Do MBIs target neural, biological, and subjective stress pathways and inflammatory mechanisms that may influence disease trajectories among adults exposed to ELS? Do they target stress processes specific to ELS (e.g., race-related stress; trauma symptoms)? If so, are MBIs more effective for interrupting the trajectory from ELS to disease risk in younger adulthood, or might they halt stress-sensitive disease progression across the life-span? Is current stress necessary for MBI efficacy, or might MBIs reprogram stress responding regardless of current stress exposure? Certainly, from a health risk perspective, adults with a history of ELS stand to benefit most from MBIs if they are effective in targeting stress pathways that were dysregulated in childhood. Establishing these biological mechanisms (along with feasibility; Stage I) will pave way for efficacy, effectiveness, and implementation research (Stages II-V).

#### 5. Are MBIs acceptable for people exposed to ELS?

There are hints that MBIs may improve stress-sensitive health markers related to ELS, but are MBIs acceptable for people exposed to ELS? MBIs show promise for improving mental health symptoms and health-related quality of life in culturally diverse, low-income, and vulnerable samples, but there is much work to be done (Chin et al., 2019b). MBI RCTs in at-risk samples are sparse, and many studies report poor MBI adherence. Promisingly, a growing body of Stage I research has evaluated the feasibility and acceptability of MBIs in at-risk samples, including adults with a history of childhood maltreatment, racial and ethnic minority samples, and lower SES samples (Joss and Teicher, 2021; Burnett-Zeigler et al., 2016a). Across trials, similar themes have emerged to inform MBI adaptations that address barriers to participation. Of note, it is important to involve clinicians experienced with specific ELS populations and/or community stakeholders in adapting MBIs at Stage IA to maximize acceptability and, ultimately, widespread implementation (Watson-Singleton et al., 2021).

Common barriers to MBI participation include time commitment and views of participation as a chore, childcare needs, transportation issues, doubts about expected benefits, and perceptions of incompatibility between religious, cultural, or personal values and mind-body philosophy (Burnett-Zeigler et al., 2016a). To overcome these obstacles, many feasibility studies have shortened class sessions and/or offered classes in familiar community settings (e.g., church, group home, community center), which fosters comfort and group cohesion and minimizes transportation issues (Palta et al., 2012; Woods-Giscombé et al., 2019). To further enhance acceptability and meaning, many feasibility studies have found ways to introduce mindfulness within specific cultural contexts (Waldron et al., 2018; Proulx et al., 2018), including connecting mindfulness practices with familiar religious practices (e.g., Christian centering prayer as a way of 'listening to God' (Bourgeault, 2004;

Woods-Giscombé and Gaylord, 2014)), offering MBIs in Spanish (Roth and Robbins, 2004), and adapting potentially triggering language (e.g., relabeling “homework” as “daily practice” to remove school-related connotations among lower SES participants (Vallejo and Amaro, 2009)).

Other issues that arise among vulnerable populations include hesitancy to share personal experiences in group classes and trauma-related distress while focusing attention inward (Dutton et al., 2013). Yet the social context is often transformative; in recognizing shared experiences, participants develop compassion and acceptance toward their own experiences (Bermudez et al., 2013). Adaptations to address triggers related to past trauma include offering eyes-open practice options, providing alternative attention anchors (e.g., sounds in the environment), and emphasizing the choice to approach or pull back from difficult experiences (Gallegos et al., 2015; Vallejo and Amaro, 2009). In effect, exposing oneself to previously avoided sensations and emotions with an attitude of gentle acceptance may be therapeutic (Kimbrough et al., 2010). Importantly, ELS may associate with greater risk for developing mental health symptoms during MBIs (Goldberg et al., 2021); the Meditation Safety Toolbox provides guidance for monitoring adverse events to enhance MBI safety (Britton, 2021).

Remote online MBIs may hold promise for addressing certain barriers to participation and implementation; they are more accessible and scalable than group-based MBIs and reduce the demand for experienced instructors (Dimidjian and Segal, 2015). However, questions remain about acceptability and adherence that impact public health relevance. Remote MBIs typically omit the social connection, shared experience, and instructor support that may be particularly important for vulnerable populations (Bermudez et al., 2013). Although high adherence has been observed in some remote MBI trials (Lindsay et al., 2018), both Stage I feasibility and Stage IV pragmatic trials are needed in ELS populations to test whether remote MBIs are abandoned before mindfulness skills are developed (Flett et al., 2020; Linardon and Fuller-Tyszkiewicz, 2020). Stage I trials might develop and test hybrid models that combine remote MBIs with community support to encourage adherence. Stage V implementation trials are also warranted to test the adoption of remote MBIs integrated into primary care, where disadvantaged populations are most likely to receive psychological treatment (Burnett-Zeigler et al., 2016b). Finally, Stage IV cost effectiveness trials may be possible in a primary care setting, comparing the costs of delivering remote MBIs to estimated costs associated with ELS-related disease burden (Kuyken et al., 2015).

Naturalistically, vulnerable populations are less likely engage in mindfulness practices, particularly lower SES and Hispanic adults (Olano et al., 2015). Yet feasibility and acceptability trials show that MBIs can be modified to address barriers commonly experienced in at-risk populations. There is also great potential for infusing mindfulness practices into tailored interventions developed in partnership with community members to address their specific needs (i.e., community-based participatory research (Teeters and Dimidjian, 2019)). Indeed, to implement sustainable MBIs within communities (Stage V), collaboration with community advisors allows for researchers to learn about the community's existing strengths, develop culturally-relevant MBI adaptations, and develop longstanding relationships built on trust (Proulx et al., 2018).

Of course, MBIs are one of many approaches that may be useful for targeting risk factors linking ELS with later life health. And more broadly, larger structural changes are needed to reduce the incidence of chronic stress in childhood. Although MBIs may be of benefit for those exposed to ELS, the onus of achieving health equity cannot be placed solely on individuals impacted by structural inequities. Yet mindfulness and contemplative practices may be useful in spurring systemic change. Community-engaged mindfulness—using mindfulness practices to facilitate community discussions that inform local policy—holds promise for encouraging social justice (Magee et al., 2016). More spontaneously, by cultivating awareness of personal and interpersonal suffering and insight about our shared humanity, widespread adoption of mindfulness and other contemplative practices may foster prosocial action (Berry et al., 2020; Donald et al., 2019) that begins to chip away at the structural

norms that give rise to ELS. It may be possible to observe this spread of mindfulness implementation through communities using MBI apps and social network tracking (Fowler and Christakis, 2008).

## 6. Conclusions

Preliminary evidence points to the potential efficacy of MBIs for targeting stress pathways linking ELS with inflammatory disease risk. There are many opportunities for research in this area. Feasibility and acceptability trials have adapted MBIs to increase accessibility and adherence in at-risk populations (e.g., shorter classes, culturally relevant practices, remote interventions); now, well-controlled RCTs are needed to evaluate the potential of MBIs for improving biological stress pathways and inflammatory mechanisms in ELS samples and, if efficacious, pragmatic and implementation trials are needed to integrate MBIs in community and healthcare settings to reach those exposed to ELS. Overall, many approaches at multiple levels—individual, family, community, environmental, institutional—are needed to address health disparities stemming from biological adaptations to ELS exposure (Woods-Giscombé and Black, 2010). MBIs may be useful for offsetting health risk and reducing the burden of disease among some individuals with a history of ELS.

## Declaration of competing interest

The author reports no conflicts of interest.

## Acknowledgements

I thank Karen Jakubowski, Brianna Natale, Anna Marsland, and Janine Dutcher for their thoughtful feedback on an earlier version of this manuscript.

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Emily Lindsay is a Research Assistant Professor in the Department of Psychology at the University of Pittsburgh. She received her PhD in social and health psychology at Carnegie Mellon University and completed postdoctoral training in psychoneuroimmunology at University of Pittsburgh. She conducts theoretically-driven research to test psychological and biological pathways explaining how mindfulness practices influence stress, well-being, and markers of physical health. She developed Monitor and Acceptance Theory (MAT) to describe how the core components of mindfulness—attention monitoring and acceptance—contribute to cognitive, affective, and health outcomes. Her experimental dismantling work testing this theory shows that acceptance training is a critical component of mindfulness interventions for improving biological stress reactivity, positive emotion, and social relationship outcomes. Her recent NIH-funded work explores biological pathways that may explain how mindfulness training impacts physical health in at-risk populations, showing that mindfulness interventions may reduce glucocorticoid resistance and improve innate immunocompetence among lonely older adults. In her upcoming NIH-funded work, she will test questions posed in this paper related to the feasibility, acceptability, and efficacy of MBIs for improving stress and inflammatory markers among diverse at-risk adults with a history of ELS. Her long-term hope is to contribute to effective intervention implementation that helps to offset health risk stemming from ELS.