Special Issue Article

The Future of Developmental Psychopathology: Honoring the Contributions of Dante Cicchetti

Programming the next generation of prenatal programming of stress research: A review and suggestions for the future of the field

Nicole R. Bush

Department of Psychiatry and Behavioral Sciences, Center for Health and Community, Department of Pediatrics, Division of Developmental Medicine, University of California, San Francisco, CA, USA

Abstract

In this article, I highlight core ideas, empirical findings, and advances in the study of how stress during pregnancy may prenatally program child neurodevelopmental, psychopathological, and health outcomes, emphasizing reviews, metanalyses, and recent contributions of conceptual and empirical work. The article offers a perspective on the history of this area of science, the underrecognized contributions of influential scholars from diverse fields of study, what we know from the evidence to date, the persistent challenges in sorting through what is left to learn, and suggestions for future research. I include sections focused on promoting resilience, pregnancy interventions that demonstrate positive effects across two generations, and the translational implications of the accruing data for practice and policy, highlighting opportunities for integrating across a range of fields and sectors. In the concluding sections, I discuss lessons learned from conducting this work and provide a closing summary of progress and future directions. The goal of this writing was to provide a viewpoint on some ways that emerging intergenerational transmission scholars might responsibly contribute to the future of the field of developmental psychopathology.

Keywords: intergenerational transmission; child psychopathology; DOHaD; prenatal programming; stress

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The perception that women's social and emotional experiences during pregnancy might affect the development of the child within her belly has been described across a range of ancient historical texts, and likely existed prior to recorded history. References to "prenatal programming" of child development, although not explicitly addressing the concept as understood in modern scientific terms, have appeared in ancient Hindu scriptures (Vedas; ~500 BCE), writings of Greek physician Hippocrates (4th century BCE; Ferreira, 1965), and in the wisdom shared from generation to generation by birthing people and those that care for them. Despite this long history, empirical study of the role of maternal experience on fetal development can be traced back less than a century (Sontag & Richards, 1938), and the topic was not truly considered by many in the fields of psychology or medicine until relatively recently. Despite comprehensive training in developmental psychopathology, and an emerging expertise in the manner in which social experiences "get under the skin" to affect development beginning early in life (Bush & Boyce, 2014; Bush et al., 2011; Hertzman, 1998), I was surprised when I first learned that this process began within the pregnancy period. Thinking with a developmental lens, and building upon my understanding of the growing experimental animal literature in

this space, the logic of pursuing this science to advance understanding of the etiology of child developmental outcomes was immediately clear. However, when I first proposed to conduct research in this area as a postdoctoral fellow, the pediatricians and child psychologists that I initially consulted with were unfamiliar with the concept, which was based in epidemiologic findings of birthweight associations with adult cardiovascular outcomes (Barker, 1990). Since then, research examining associations between prenatal maternal stress (and related factors such as depression, anxiety, and biological correlates of stress) and children's neuro-developmental outcomes has increased dramatically (see for review Monk et al., 2019; Van den Bergh et al., 2020). A search of publications in the PsycInfo database with "prenatal programming" in the title or abstract yields 422 articles that begin occurring in 1977, two-thirds of which have been published in the past decade. The construct is now a foundational driver for the science of two major U.S. child health research consortiums (https://www.nih.gov/research-training/environmental-influences-child-health-outcomes-echo-program and https://hbcdstudy.org/), and the topic now occupies keynote lectures across disciplines. The idea that stress in one generation can affect child health in the next, beginning in utero, has also graced mainstream media magazine covers. Prenatal programing has transitioned from a niche idea to a key construct of child health and development, and the future of developmental psychopathology should most certainly include expansion and evolution of this science.

State of the science

Studying adversity/stress exposures is a public health imperative

Beyond the value of understanding these phenomena because of their inherently interesting nature, what child psychology scholar wouldn't want to better understand all manners by which, and when, social factors affect our mental and developmental health? Deeper attention to the phenomena is necessary because of the disturbing prominence of social adversity during sensitive periods of development. A meta-analysis of 206 studies from 22 countries and more than half a million adults found that 60% reported at least one major adverse childhood experience, with 16% having 4 or more and high rates of exposure most common in individuals from low-income or minoritized racial and ethnic groups (Madigan et al., 2023). In the United States, more than half of women report a history of exposure to adversity during their childhoods, which includes physical, sexual, and emotional abuse, neglect, and household dysfunction (Frankenberger et al., 2015; Mersky & Janczewski, 2018). In pregnancy, women's rate of exposure to major adversities is also unfortunately high–according to the Centers for Disease Control and Prevention's Pregnancy Risk Assessment Monitoring System, in 2010, nearly three-quarters of pregnant women experienced at least one stressful life event in the year prior to their child's birth (Burns et al., 2015), such as a family member being hospitalized/dying, separation from a partner, and job loss. Interpersonal violence is also a key concern, with the World Health Organization estimating that one-third of women are subjected to intimate partner violence during their lifetime, with up to 13% facing intimate partner violence during pregnancy (Organization, 2021). Notably, women disproportionally experience these stressors – especially those from lower income families and communities of color (Conradt et al., 2020; Stockman et al., 2014). These high rates of exposure to violence and adversity during childhood and pregnancy reflect some of the principal antecedent threats to individual well-being and, as such, represent a pressing social issue nationally and globally. It is especially important to understand their additional deleterious health consequences on future generations.

Developmental origins of health and disease

A range of frameworks exist for examining the intergenerational impact of maternal stress exposures on offspring health. The most well-known is the concept of Developmental Origins of Health and Disease (DOHaD; Barker, 2007), which posits that maternal factors during pregnancy, including experiences of stress, can have long-term implications for her child's health. Since its origins in studies of nutritional deficiencies during pregnancy (Barker, 1990), the theory has expanded to include understanding of the various maternal-placental-fetal biological pathways through which social experiences can affect offspring development (see for reviews Entringer et al., 2015; Monk et al., 2019; Van den Bergh et al., 2020). This work draws from evolutionary biology and developmental plasticity frameworks (Ellis & Del Giudice, 2014; Gluckman et al., 2011; Pluess & Belsky, 2011) wherein environmental conditions are understood to have shaped an organism's survival, such as differences in the availability of safety from predators, shelter, nutrient rich foods, and other challenges that might impact an organism's bodily integrity, functioning, and reproductive fitness. Stress biology is considered to be a primary mediator of the effects of these conditions, and cross-species research has demonstrated that biological markers of stress activation (evidence is predominantly from study of glucocorticoids),

are transmitted from the mother to the fetus throughout pregnancy in a manner that directly or indirectly can impact the development of offspring bodily structures and physiological systems (Glover et al., 2018; Howland et al., 2017; Monk et al., 2019). Thus, maternal prenatal stress was identified as an important aspect of the intrauterine environment with the capacity to influence a broad range of offspring developmental outcomes. The fetal period, with its exceptionally rapid pace of development, provides a particularly sensitive window for intrauterine inputs, such as maternal circulating stress hormones and immunologic activity. This sensitivity is key to survival outside the womb, as it allows tailoring and adaptation to changing inputs (Entringer et al., 2015) in a manner that can have positive and negative implications for development and health across the lifecourse (Davis & Narayan, 2020).

Evidence for maternal stress during pregnancy

A robust body of rapidly accumulating empirical evidence now demonstrates the myriad ways in which maternal prenatal stressors or experiences of distress are associated with variability in offspring outcomes. It has been found to associate with variability in fetal and infant stress responses across multiple levels of biological and behavioral functioning (see for review DiPietro, 2004; Entringer et al., 2015; Monk et al., 2019). The evidence for intergenerational transmission of stress effects extends to outcomes across development, suggesting persistence of effects into early childhood and adolescence in the form of socioemotional and behavioral problems as well as a full range of more specific indicators of neuro-development, cognitive development, negative affectivity, difficult temperament and psychiatric disorders (Van den Bergh et al., 2020). Using externalizing problems as an example, a recent meta-analytic review of 55 studies (Tung et al., 2023) found that psychological distress during pregnancy was uniquely associated with increased risk for child externalizing problems (age 2–18 years), including aggressive, disinhibited, and impulsive behaviors. Notably, these effects were largely similar across the range of externalizing outcomes examined, although the size of effects was larger for aggressive behaviors than nonaggressive rule-breaking behaviors. In addition, Tung et al. found evidence for persistent small effects from early childhood through adolescence, suggesting they occur across developmental periods. Although such overviews of findings are suggestive, limitations in study designs across all types of psychopathology outcomes make it difficult to discern whether effects arise early in life and are maintained, may reveal themselves for some subsets of children only at later period of development, or occur with some combination of timing effects

Notably, very few studies have examined prenatal stress effects into adulthood. In one exception, a very small sample using the naturalistic experiment of a severe ice storm found associations between maternal pregnancy exposure and broad autism pheno-type in offspring during young adulthood (Li et al., 2023). In a larger sample, extensions of the Dutch Famine Study into late adulthood (mean age 73 years) continue to find effects of adversity in pregnancy and psychological health at these older ages (Hilberdink et al., 2023). Although multidecade follow-up is still rare, the findings published to date suggest persistence of risk for many individuals. Collectively, the data spanning small studies with deep phenotyping, larger epidemiological studies with more limited measurement quality but greater power to examine small and across-cohorts consistency of effects, and quasi-experimental designs, point to the same conclusions that prenatal stress associates with offspring outcomes.

Origins of intergenerational stress-transmission work

It is important to note that the majority of empirical work within the field of study of intergenerational transmission of stress effects on child health (regrettably, my own team's included) typically fails to acknowledge the breadth of theories and thought leaders that have informed the field, particularly in the context of considering the impact of historical traumas such as the Holocaust, slavery, and colonization. This is, in part, likely due to the disparate areas of study, professional societies, and journals the experts have published in, or because graduate training and mentorship has not highlighted these cross-over works. However, in the current era of comprehensive internet search capacity and rightfully increased demand for inclusive scholarship, it is imperative that we better consider and acknowledge key figures whose work contributes to understanding the intergenerational impacts of stress in these historical contexts. It is worth noting that many of the strongest voices in this space are women with lived experience as mothers and birthing supporters and their wisdom may not be accepted or amplified as robustly as that of the father of "the Barker Hypothesis" (Barker, 1990) due to the marginalization of women and their voices in academia and centers of power and knowledge, more broadly. These thought leaders have played significant roles in shaping our understanding of intergenerational transmission of stress effects on child health, particularly in the context of historical structural harm inflicted upon marginalized groups, e.g., slavery, colonization. For example, focusing on the historical trauma experienced by Indigenous populations, Dr Maria Yellow Horse Brave Heart developed the concept of "historical unresolved grief" to explain the intergenerational impact of settler colonialism and forced assimilation on the mental health of Native American communities (Heart, 1999), which scholars continue to advance within multilevel frameworks to address individual, family, and community impacts (see for review Evans-Campbell, 2008). Dr Rachel Yehuda and colleagues, who appear to have brought the concept of intergenerational trauma to the psychiatric literature (see Yehuda et al., 2008), have extensively studied the effects of trauma on Holocaust survivors and their descendants, exploring the transmission of trauma-related stress and its impact on mental health across generations (Dashorst et al., 2019). Dr Joy DeGruy, in her book "Post Traumatic Slave Syndrome," (Degruy-Leary, 2017) describes the intergenerational effects of centuries of slavery on African American communities, discussing how historical trauma continues to shape the psychological and physical health of descendants. Dr Arline Geronimus, who developed the "weathering hypothesis" to describe the process by which repeated stress activation in response to socially-structured stressors can contribute to risk of disease in marginalized groups, has highlighted the value of considering these processes across the life course, using a DOHaD framework (Geronimus, 2013) and recently reminded us of the importance of "centering on the margins" to prioritize the perspectives about stress during pregnancy provided by the populations at highest risk of concerning outcomes, and considering maternal-specific weathering (Geronimus et al., 2023). These examples provide just a small set of examples of an important body of work that contributes to ongoing discussions on resilience, healing, and the development of effective interventions, and we should endeavor to integrate it more fully within our work.

Evidence for maternal preconception stress/childhood adversity

Although the bulk of DOHaD science has focused on pregnancy exposures, and society is increasingly aware of those potential effects on offspring, the concept of preconception adversity effects crossing generations is rarely considered and remains poorly understood. From a life course development framework, however, childhood and pregnancy are each sensitive periods for women during which exposure to stressors may affect women's bodies and behavior in a manner that can impact offspring development and health. Indeed, an emerging line of investigation, leveraging insights from experimental animal research, has found that exposure to traumatic events during one's own childhood predicts one's health and well-being but also that of the offspring, with greater adversity associated with increased risk for early birth (Smith et al., 2016) and psychopathology (Schickedanz et al., 2018). Systematic review of this newer literature found, across 12 studies, consistent positive associations between maternal childhood adversity and their child's internalizing problems (Rowell & Neal-Barnett, 2022), although the authors highlighted limitations of that work, including underrepresentation of low-income families and families of color, and that internalizing was assessed entirely via parent report. Meta-analysis of 12 studies (Su et al., 2022) has also shown that maternal childhood maltreatment has small effect on offspring depression and internalizing, with stronger effects for children of color.

Multiple periods of maternal adversity

A few teams have considered preconception and pregnancy distress simultaneously to discern independence. One study using a biomarker of HPA axis functioning during pregnancy (Thomas-Argyriou et al., 2021) and another that assessed maternal anxiety and depression during the perinatal period (Letourneau et al., 2019) found independent contributions of adversity at each period with parent-reported early childhood internalizing symptoms. Our work in the national ECHO PATHWAYS 3-cohort consortium confirmed that maternal exposure to childhood trauma and pregnancy adversities were independently associated with children's total behavioral and mental health problems beyond the preschool period both continuous dimensions of psychopathology symptoms as well as greater odds of having mental health problems at or above borderline or clinical thresholds (Bush et al., 2023). Findings suggest that maternal childhood exposure effects on offspring are not merely operating through greater risk for adverse exposures during pregnancy. Notably, our group found maternal childhood trauma did not predict children's self-report of anxiety and depression at age 8 (Noroña-Zhou et al., 2023), suggesting that maternal childhood trauma effects may not persist to that age, at least in terms of youth-report of internalizing, although we did continue to find prenatal stress effects on continuous and clinical threshold anxiety. That said, the sum of the limited evidence suggests that both periods of maternal trauma/adversity exposure can lead to distinct, clinically meaningful impacts on children.

Some literature related to potential mechanisms for these maternal childhood-specific effects has accumulated as well. For example, our findings from a rigorous study of a small sample of women with a history of considerable adversity exposure across their lifetimes revealed that adversity exposures during childhood and pregnancy uniquely predicted maternal immune responses in adulthood (Aschbacher et al., 2021), providing some evidence of sustained impact on immune functioning of relevance for fetal gestation. Evidence from our larger cohort study showed maternal history of childhood trauma exposure, but not stressful events during pregnancy, predicted variation in the pregnancy hormone pCRH (Steine et al., 2020), which has critical roles in fetal

development and birth timing and is related to both offspring neurodevelopmental outcomes and maternal psychopathology. Thinking developmentally, it is clear that experiences decades prior carry forward in bodies, and future research into the processes by which mothers' own childhood experiences affect their reproductive physiology will be important for rounding out understanding.

Broad adoption of these newer findings is delayed in our field though. For example, in what appears to be the first systematic review and meta-analysis of mediators of the link between maternal childhood adversity and children's socioemotional and behavioral development (Ma et al., 2022), there is discussion of some evidence for antenatal or lifetime maternal depression and maternal perinatal health (e.g., gestational diabetes, abortion history and smoking during pregnancy) as mediators, but most associations reviewed in that paper well null, and prenatal programing was not mentioned/considered as a mediating process by the authors. Beyond the focus on children's mental health outcomes, however, scholars are paying increasing attention. Our examination within the ECHO national consortium sample, drawn from 21 cohorts, found that children born to mothers with histories of maltreatment had greater risk for a range of negative child health outcomes, including clinical levels of internalizing problems, autism spectrum disorder, asthma, and obesity, as well as higher risk of multimorbidity, with patterns of associations suggesting a dose-response relationship as the count of types of maltreatment exposure increased (Moog et al., 2023). Further, a recent systematic review of 19 studies of parental ACEs and offspring health (N > 120,000; Arnold et al., 2023) found negative effects on prematurity and low birthweight risk, childhood obesity, infant bronchiolitis, child brain development, cognitive delay, and a range of developmental outcomes such as expressive language, and health risk behaviors, such as childhood smoking. Although the effect sizes for each predictor are typically small for exposures, when considering their transdiagnostic impact, and that their effects early in development affect subsequent trajectories across the life course, a thoughtful focus on maternal childhood trauma exposure in the intergenerational transmission of stress literature seems quite merited.

Variability in effects

As is common in developmental psychopathology, there is considerable variability, i.e., multifinality (Cicchetti & Rogosch, 1996), in the associations between prenatal stress and child developmental outcomes. For example, prenatal stress may only result in differences in offspring mental health when potentiated by other risk factors. A study of adolescents born to women exposed to the violence of South African Apartheid (Kim et al., 2023) found that prenatal stress appeared to sensitize youth to the risks associated with young motherhood and household adversity. Individual differences in reactivity and regulation can greatly affect people's susceptibility or sensitivity to context (Bush & Boyce, 2016; Ellis et al., 2011), and this sensitivity to the effects of environmental exposures may occur at the maternal or fetal level. Further, perception of stress in the face of adversity, and whether it activates biological stress responses or behavioral differences relevant for fetal development matters considerably. As an illustration of this, the effects of more objective counts of major stress exposures during pregnancy on infant stress physiology have been found to only be significant for dyads where mothers reported feeling moderate to high levels of stress during their pregnancy (Bush et al., 2017).

In addition, building upon considerations of historical trauma, other factors related to marginalized status may explain variability in intergenerational transmission of stress. For example, the insidious stressor of experiencing racism harms people across levels, from interpersonal interactions to institutional policies and cultural norms, and has been shown to be highly relevant to the quality of care pregnant women receive (McLemore et al., 2018; Nguyen et al., 2023) and their and their children's health outcomes within those systems of care. Clear evidence for this can be seen in health disparities for Black pregnant individuals, who are several times more likely to experience complications or death related to childbirth, and to lose their infants to death in the first year of life, compared to White individuals (Keating et al., 2020). Higher levels of race-based discrimination have also been repeatedly found to be associated with increased risk for low birth weight and short gestational length (see for a review Heard-Garris et al., 2018), key mediators of risk for developmental challenges later in life. Notably, however, prenatal programing constructs and biological processes are not often emphasized in work highlight intergenerational impacts of structural racism and trauma on mental health (e.g., Hankerson et al., 2022), suggesting opportunities to build bridges between realms of science.

Intersectionality, a concept initially introduced by Kimberlé Crenshaw (1991), emphasizes the interconnected nature of social categories such as race, gender, class, sexual orientation, disability, and other forms of identity. When applied to prenatal stress and child health, it highlights the unique and compounded challenges faced by pregnant individuals who navigate multiple intersecting identities simultaneously and may experience cumulative stressors related to multiple social categories. Prenatal stressors, such as discrimination or socioeconomic challenges, as well as access to resources, including healthcare, education, and social support, disproportionately affect certain groups and can contribute to heightened stress during pregnancy, leading to disparities in maternal health and well-being and child health outcomes. Given this, the effects of prenatal stress on child health cannot be understood in isolation but rather as part of a broader network of social structures, including systems of oppression and privilege, that influence health outcomes. The impact of intersectionality on prenatal stress effects on child health is a complex and multifaceted area ripe for study.

Although this is shifting, the majority of extant intergenerational stress-transmission work to date has focused primarily on risk factors for child psychopathology, with minimal empirical examination of factors that may buffer risk either at the level of maternal exposure or later in the environmental context of the child's ongoing development. Findings from my teams have shown, across two different cohorts and study designs, that responsive caregiving (using rigorous observational coding) can meaningfully offset the risk for greater infant physiological stress reactivity (Jones-Mason et al., 2023) and child behavioral-emotional problems (Ahmad et al., 2022) associated with prenatal stressor exposure. We've also found that greater levels of caregiver knowledge of infant development can buffer offspring from those risks (Ahmad et al., 2022). Understanding the resilience and coping strategies developed within communities facing intersecting challenges, and recognizing these strengths, is essential for developing effective interventions to mitigate the impact of prenatal stress on child health. Intersectionality recognizes the importance of cultural nuances in shaping experiences and outcomes within specific communities. For example, Brave Heart et al. (2011) highlight how tribal cultural and regional

differences may impact how the wounding across generations are experienced and addressed (2011). Although examination of potential buffers is increasing, the work in this space is relatively limited, despite its importance for identifying solutions.

Whether because of risk or protective factors, at the individual, family, or societal level, exposure to adversity is clearly not deterministic, and there is incredible heterogeneity of effects across individual people. Drawing upon insights related to ACEs screening not predicting disorder well at the level of the individual (Baldwin et al., 2021), one must be careful to ensure work is written and interpreted to communicate group- or population-level risk, rather than individual determinism. Just as is true for postnatal stress effects on psychopathology (Masten & Cicchetti, 2016), prenatal stress effects also are dependent on contextual factors, outcome, timing of exposure, and outcome being considered (Van den Bergh et al., 2020).

Generalizability of findings across populations

Although there are important exceptions, the bulk of early empirical evidence for associations between prenatal stress and childhood mental health was developed from samples predominantly consisting of middle- to upper-income, White families drawn from countries with enormously different healthcare and social/economic systems to support families, relative to the United States (e.g., Canada, Northern Europe). This work has been incredibly valuable, and the findings that stress crosses generations to impact health is important in any context. However, the differences in populations and social settings have called into question whether such findings were generalizable to the U.S. and across subpopulations with large disparities in environmental supports and stress exposures. Notably, the evidence from more socioeconomically, racially, ethnically, and regionally diverse samples appears to align with the patterns found in samples with lower risk. For example, across our 3-cohort U.S.-based sample of sociodemographically diverse mother-child dyads from six distinct geographic regions, we found consistent patterns of findings for maternal childhood and pregnancy adversity on child mental health in early and middle childhood, in the full national sample and when the sample was restricted to various subsets of the seven data collection sites (Bush et al., 2023; Noroña-Zhou et al., 2022). Although there are certainly differences across countries in culture, policies, and perinatal care and within countries in terms of exposure to harms and access to resources, the relative consistency of associations found across the literature suggest associations can be expected in a range of populations and are important for all societies to address.

Can we leverage intervention to positively program offspring outcomes?

Very recently, experimental and quasi-experimental evidence in humans has provided exciting evidence that positive inputs, and resultant decreases in distress or poor health during pregnancy, can lead to improvements in child outcomes. For example, our team found that infants born to women who participated in an 8-week group-based wellness intervention that reduced stress and depression showed more optimal sympathetic nervous system and behavioral regulation stress responses to a laboratory stressor than infants in the treatment as usual group (Noroña-Zhou et al., 2022). A small randomized controlled trial of a nutrition+exercise intervention during pregnancy found that babies born to women in the intervention group demonstrated greater expressive language and general adaptive behavior on the Bayley at age 1, although no

differences were seen for cognitive, receptive language, motor, or socioemotional outcomes (Amani et al., 2023). In addition to providing encouraging evidence for solutions, the assignment to groups and resulting "control" over some social exposures during pregnancy has led to increased confidence in the causality of those exposures. Other groups also have ongoing studies of prenatal interventions with mothers to reduce stress and improve their mental health, in an effort to document the benefits for offspring brain development, behavior, and health (Davis et al., 2018; Lugo-Candelas et al., 2023). Related work targeting health system-level changes to provide trauma-informed obstetric care for adolescents showed that intervention eliminated racial disparities in preterm birth and low birth weight for young Black mothers (Noroña-Zhou et al., 2023), which will likely have beneficial impacts on developmental trajectories for those babies.

Some key questions remaining in prenatal stress-transmission work

Sensitive periods for exposure

One of the greatest challenges to this field is to discern potentially sensitive periods of exposure, both within the prenatal period as well as over the preconception lifetime of birthing people. One reason is because very few studies have simultaneously examined distinct effects of maternal stress exposures during *and* prior to pregnancy, and few have the data necessary to parse out the influence of potent stressors during a particular trimester. This is, in part, because many stress exposures are not acute nor neatly temporally delineated. For example, although divorce or separation from a coparent may occur on a given day, the conflict leading to the termination of the relationship occurred prior, and the effects post-divorce are typically pervasive and long-standing (with tremendous variability in experiences ranging from relief from interpersonal violence to distress due to loss of income and/or housing security). Even natural disasters, though their onset may be abrupt, allowing for clear determination of the initial timepoint of exposure, their maximal activation of stress levels may be somewhat acute (such as an earthquake or hurricane) but they can have consequences that can be comprehensive and long-standing (physical harm or death, loss of housing or childcare, etc.). For structural-level stressors, such as racism, which are typically pervasive and long-standing, it is nearly impossible to discern an onset of exposure to such stress in order to identify sensitive periods. That said, researchers do and should continue to attempt to untangle timing. Notably, the meta-analysis of studies predicting children's externalizing problems revealed that prenatal stress effects on child externalizing did not vary based on type and timing of psychological distress during pregnancy (Tung et al, 2023), although effects were larger for earlier outcome timepoints and greater instability of distress between the pre- and postnatal period was associated with larger effects on children's behavior.

Again, work reviewed above considering stressor exposures across maternal life course has shown independent effects of childhood and pregnancy adversity on child risk for psychopathology (and physical health problems); and maternal childhood trauma exposures have been associated with lasting effects on the functioning of women's reproductively-relevant biological systems during adulthood (Aschbacher et al., 2021) and pregnancy specifically (Steine et al., 2020), moreso than pregnancy stress exposures. Our group even found that maternal histories of childhood trauma amplified the harmful association between pregnancy stressors and children's mental health (Bush et al., 2023), demonstrating how exposure across

sensitive periods might interact, potentiating risk at later time points. As noted earlier, DOHaD science will benefit from more carefully considering exposures to life stressors prior to conception, as limiting study to prenatal exposures obscures etiologic understanding of the impact of risk exposures that occurred earlier in maternal lives. Pinpointing the most impactful windows of development for upstream trauma prevention will be time well spent.

Considering postnatal stress and depression

Related to sensitive periods challenges, it is often challenging to know how and when to adjust for postnatal maternal distress when attempting to untangle prenatal effects on offspring. It is likely that in most contexts, both prenatal programing of fetal development and postnatal difference in childrearing environments (such as through stress-related behavioral changes in parenting) account for associations found. While it is important to adjust for postnatal environment, we must consider that postnatal distress is often a mediator or a factor that lies "on the path" between prenatal stressors and child outcomes, thus default adjustment may eliminate variance of interest, depending upon your question. One way to unpack this involves modeling repeated measures of maternal distress during and after pregnancy and examining the transactional relations with child developmental outcomes. Strong examples include Browne et al. (2022) and Roubinov et al. (2022) cross-lagged models that showed pre- and postnatal direct and indirect effects of maternal histories of trauma on children's developmental and mental health outcomes. Other approaches examine, in sensitivity models, how inclusion of postnatal stress or depression affects the patterns of findings. For example, the effects for both maternal childhood and pregnancy stressors maintained significance, although effects on child mental health were attenuated, after adjustment for maternal postnatal depression (Bush et al., 2023; Noroña-Zhou et al., 2022), and adjusting for maternal depression reduced the effect size of maternal maltreatment on offspring's depression and internalizing disorders (Su et al., 2022). It is also important that models consider including adjustment for current maternal depression and other various maternal factors that may impact her report of child functioning, although this effect has been found to be negligible (Olino et al., 2021). Postnatal distress, including perceived stress, anxiety, and depression must be acknowledged and modeled as one likely mediator of intergenerational transmission of stress in addition to its potential role as a confounder.

A related major critique of much of the work in this domain is that maternal stress exposure during childhood and pregnancy are typically assessed retrospectively and may suffer from recall bias, particularly due to concern that histories of trauma will cloud perceptions of the past. Prospective collection of stress exposure is certainly ideal, however retrospective reports of the occurrence of major negative life events (such as divorce, death of a close relative, incarceration, homelessness, or severe illness) have been found to be valid and robust to recall bias over time (Krinsley et al., 2003; Ramos et al., 2020). It is also difficult to capture total pregnancy exposures without waiting until after the birth, given its unpredictable timing and the difficulty accessing birthing parents during the precious period surrounding birth.

Sex-specific effects?

The biological sex of the child in utero, and the associated sex-specific differences in intrauterine hormonal milieu, may play an important role in the impact of maternal stress exposures during pregnancy on child developmental outcomes (Bale & Epperson, 2015). Numerous theoretical papers and reviews articulate the rationale for sex differences in prenatal programing, and a considerable body of evidence from non-human animal experiments support it, however the broader literature in human studies remains inconclusive. For example, some prior work has found evidence for sex-specific effects of maternal pregnancy distress on young child internalizing (Davis & Pfaff, 2014; Letourneau et al., 2019). In contrast, studies in larger samples at older child ages have found no moderation by child sex in the prediction of maternal report of child internalizing at age 4 ($N = 1948$; Bush et al., 2023); or age 4–13 internalizing ($N = 7,944$; O'Donnell et al., 2014); or age 8 youth self-report of depression or anxiety ($N = 1,389$; Noroña-Zhou et al., 2022). The recent metanalysis of maternal distress effects on externalizing (Tung et al., 2023) also found no support for child-sex-specific associations. It is quite possible that biological sex differences may be more important for other child outcomes or for developmental periods, such as adolescence, where pubertal onset and associated hormonal shifts play in important role in the development of mental health (Gunnar et al., 2009). To truly understand, examinations across all developmental timepoints, across exposure and outcome types, will be important. It is intriguing to note that in one of the few prenatal programing studies of older adults (Hilberdink et al., 2023) the consequences of pregnancy adversity on psychological health persisted into late adulthood only for men. Certainly, more work in this space will be informative.

Confusion about when to include race/ethnicity in models

An important area for growth in this field, and psychology more broadly, is to evolve our conceptualizations, modeling, and interpretations around indicators of race and ethnicity. In addition to the aspects of this much-needed work described elsewhere in this article, the "simple" issue of considering covariation and confounding in our analytic models is important to untangle. Race is a sociopolitical construct, rather than a biological variable, and thus can serve as a proxy for the impact of racist practices and structural inequality (Bryant et al., 2022), although using it as a proxy for unmeasured variables requires considerable thought. We need to appreciate the clear guidance provided by experts, reminding the field to shift habits and rethink training when necessary to ensure we are not including race or ethnicity as a "covariate" to capture unmeasured biological differences, not interpreting covariates if they ARE included to address social confounding, and to be sure to not examine group differences by default, without a clear a priori rationale for why processes might differ between cultural groups and a robust modeling framework to specifically test that question (Cogua et al., 2019; Duncan & Montoya-Williams, 2024).

Examples from our work reveal how problematic default inclusion of race as a covariate can be. When examining geospatially derived neighborhood environmental quality in a region where race-based housing segregation has long-divided communities and racist policies have created heinous disparities in resources and opportunity, inclusion of a covariate for race eliminated the predictive value of objectively assessed neighborhood quality (Noroña-Zhou et al., 2022) and violent crime (Ahmad et al., 2022) on early and middle childhood mental health outcomes, potentially misleading researchers to believe neighborhood does not matter for child mental health. Neighborhood resources and burdens are not distributed equally and result from

de facto residential racial segregation via redlining (Heard-Garris et al., 2021), and the potential for community social capital to support mental health has been found to differ based on children's interpersonal experiences of racial/ethnic discrimination (Okuzono et al., 2023), thus, future work to untangle intersections between racism and neighborhood quality are important for improving understanding of neighborhood effects and their relationship to maternal stress exposure effects on children's mental health.

Reflections on lessons learned

Words matter

Over the years of presenting this work, I've been struck by a few encounters that highlighted for me how important it is to put oneself in the audiences' shoes while designing your studies and presenting your findings on this topic. Earlier in my career, I often was so focused on demonstrating the harmful effects of stress during pregnancy in a world not yet aware/convinced that I sometimes failed to consider what it felt like to hear these hypotheses and findings, particularly if listeners were currently pregnant or already had children and struggled with high levels of stress during pregnancy. Such a concern is not specific to pregnancy effects, but can be particularly pronounced for pregnant persons given the dominant culture of blaming mothers for child outcomes (both within and outside of scientific contexts), the relatively little control pregnant people have over most stressors (particularly macro-level factors, such as racism, disparities in pay by gender, and neighborhood violence), the increased risk due to employment stigma/discrimination, and lack of social policies in the U.S. to protect pregnant people. Winett et al. (2016) wrote an excellent piece regarding considerations in this space, emphasizing strategies we should all take to avoid "mother-blame" in communication about intergenerational health impacts. Further, ask yourself whether your interpretation of the impact of prenatal stress presents what may be appropriate fetal adaptations as "disordered" or "dysregulated"? This is important, both in terms of avoiding pathologizing adaptive coping strategies but also in terms of potential for stigmatizing children who have the misfortune of being reared in contexts of harm. When engaging in this work, take time to ensure that your work and communication about it does not promote stigma, individual blame for societal shortcomings, or a sense of guilt or doom.

A related caution involves use of the word or theories of "resilience". Focusing on factors that promote resilience has long been considered critical for the study of developmental psychopathology and for identifying buffers to amplify in order to prevent or intervene to support child development (Luthar & Cicchetti, 2000; Masten et al., 1990). The body of work in this domain has exploded the past decade, influenced by developmental systems theory and considerations of cultural processes, and it has evolved considerably (Masten & Cicchetti, 2016; Masten et al., 2021; Ungar, 2021), although conceptualizations within psychology have often failed to focus on or acknowledge the societal systems and structures of power and privilege (e.g, racism, colonialism, patriarchy, and capitalism) that greatly affect individual experiences and capacity to adapt or cope with adversities. Some have also shown that expectations of resilience are typically disproportionately placed upon excluded and oppressed individuals and communities and that indicators of "resilience" are, at times, akin to scar tissue or evidence of an adverse event (Suslovic & Lett, 2024). Moreover, although many individuals provide high-quality

rearing environments despite prior exposure to adversity, we cannot rely on individuals to offset the risk presented by social adversity. To truly understand the phenomenon of intergenerational transmission, the future of this work must consider the long histories of people, the communities they come from, and work from models that center those marginalized by mainstream society as well as the societal systems of harm (Anderson et al., 2023; McLean et al., in press).

Development and mental health are health

Psychology-focused scientists are often siloed, and our work is often considered outside of the context of "health". Yet, mental health IS health. Development IS health. Also, understanding the etiology of healthy and atypical brain and behavior development is foundational to other fields, such as pediatrics, and to promoting population health more broadly. We must play an active part in bridging fields and ensuring that our developmental and behavioral outcomes research is prominent within the broader health landscape. This means that you should work to publish your findings in journals within and outside of psychology. Medical and public health journals are often less interested in behavioral/mental relative to medical health outcomes, but this appears to be shifting, particularly in the context of U.S. Surgeon General Murthy's emphasis on post-pandemic child mental health as a public health crisis that requires prioritization (General, 2021).

In a related vein, although there is huge value to deeply focusing on studying a particular child outcome, I have found that my career (and personal interest in my program of research) has benefitted from evaluating the *transdiagnostic* impact of stress exposures. While one might study a range of diagnostic outcomes within psychology, broadening your study of outcomes to include physical illnesses as well allows you to expand the impact and potential uptake of your work, because it amplifies the range of stakeholders and advocates interested in your findings. For example, if you have deep expertise in children's stress biology as it relates to depression, you may find it feasible to also evaluate effects on asthma, which is also linked to stress levels. As noted earlier, our team has found that the same maternal prenatal stress exposure indicator stressful life events during the year prior to birth predicts offspring autonomic nervous system reactivity, obesity risk, and child psychopathology (Bush et al., 2017, 2023; Felder et al., 2020). This transdiagnostic approach is most sensical if you can study outcomes with shared underlying stress-transmission mechanisms and sufficient incidence (health outcomes are often measured categorically) to be studied within your sample's size (and budget). It also requires careful partnerships with others who can bring the needed relevant expertise outside of your field.

A primary factor in my success in this transdiagnostic space has been multidisciplinary, team science. Multidisciplinary science has a tremendous capacity to advance health sciences. I had the opportunity to pursue my interest in the study of intergenerational transmission while a Robert Wood Johnson Health and Society Scholar at the UCSF-UC Berkeley joint program, where leaders supported me in journeying through literature from a range disciplines. I learned about European epidemiologic famine studies, tightly-controlled experimental cross-fostering animal placental transmission science, and cardiometabolic disease transmission, and I cobbled all of those literatures together with my child clinical intervention science training to support my first NIH-funding application, which leveraged the experimental design of an existing pregnancy wellness-promotion intervention

to answer some key questions in prenatal programing. It is important to note that, although I did achieve the aims of that R01, I struggled a lot initially as I attempted to integrate a lot of literatures, and my multidisciplinary study rarely met the ideal standards of each field. For example, to collect behavioral coding and biological data, I needed a smaller, more intensive visit, necessitating a more limited sample size, which prohibits me from publishing those findings in many of the epidemiological and public health journals my work had been inspired by. Through subsequent projects, I've partnered with extensive teams representing pediatrics, epidemiology, obstetrics, biological sciences, social work, public health, and beyond, to conduct and publish large-scale etiologic studies, which have found their homes in journals from a broad range of fields. Lately, I oscillate between those worlds, attempting to fill in gaps from multiple directions, striving to leverage learnings from each context to inform the studies I run in the others. Although such complex career interfacings are not for everyone (and wise mentors will tell you to stay focused initially in your career to ensure you achieve the milestones needed to advance), researchers should look across fields for evidence and inspiration, to best advance the science.

Inclusive, reality-focused science

As is true of most fields of science, including clinical psychology (Roberts et al., 2020; Rodriguez-Seijas et al., 2023), the field of prenatal programing research is embedded in the context of oppressive systems and has largely failed to contend with systemic racism, sexism, and classism in our work. As my study of this field has expanded, I have been struck by how rarely I was exposed to writings from scholars of color or disciplines that explicitly address structural factors that serve as a fundamental source of many human stressors. Inspired by others endeavoring to acknowledge and self-reflect upon their own contributions to this problem, I have been working to revise my approaches to the scientific and theoretical scholarship in this space, and the work will be ongoing. Future scholars are encouraged to think more critically about how they might address these challenges pervading our academic and clinical institutions to move the field forward in actively anti-racist, anti-sexist, decolonized, and anti-classist manner (Lett et al., 2022; Rodriguez-Seijas et al., 2023). Particularly when discussing solutions, we need to take care not to offer individual-level interventions as the solution to structural toxins (Suslovic & Lett, 2024). Moreover, when you build your team, remember to seek partnership from scholars from marginalized backgrounds (and do the necessary personal work beforehand and ongoing to ensure your collaboration with them does not perpetuate historic harms [Lett et al., 2022]), as they have often been excluded or sidelined despite the excellence and advancements that diverse perspectives bring to teams. In particular, our work needs to better center women of color not only to rectify epistemic injustice and ensure lived experience informs the work, but also because the support advances their success in academia, which is critical (Mangurian et al., 2024). Involving nonprofessional "citizen scientists" from the community you are studying also has the capacity to enhance the value of the work, through engaging the expertise of those with positionality, community knowledge and insights, and lived experience (Lett et al., 2022). To develop those partnerships, we must spend time with community advisory boards, volunteer in the spaces we hope to learn from, and form genuine connections that we lift up to guide the work.

Publish and emphasize null findings

As is true in other fields, our results aren't always in support of our hypotheses or in line with the prior findings of influential others, and to optimize our knowledge, others need to know. Don't neglect publishing sufficiently-powered non-significant results, or you risk contributing to the replication crisis and biasing effects size estimates in meta-analyses. Although reviewers and editors sometimes find the lack of significant associations to be uninteresting, or they demand a greater burden of evidence for null than significant findings (Franco et al., 2014), certain strategies can enhance success (Schuengel, 2022). Although this article has emphasized cases in which stress was significantly associated with child outcomes, the circumstances in which effects were not found (e.g. no total lifetime or pregnancy stress effects on pCRH; the attenuation of maternal ACEs associations with child mental health between ages 4 to 8 years; the lack of moderation by child sex in many studies) are among the most informative.

Use your voice, advance the science

One of the most important lessons I've learned is that few people will care about your questions and ideas more than you do, and I was going to need to advocate and initiate to get the data I needed to test my questions. More often than you may realize, you have the capacity to advocate to get your topics measured within studies, and it often will not happen without your exceptional effort. I've found this to be the case in both small and large study contexts. For example, my first prenatal programing R01 study was the result of my idea to add a child follow-up component to a pregnancy intervention not designed to consider 2nd generation impacts. As another example, it may not be too late to add pregnancy stress to a study of children. My colleague, Dr Melanie Thomas, wisely added the Pregnancy Stressful Life Events retrospective recall of events scale (Centers for Disease Control and Prevention, D. o. R. H., 2005) to our study 6 months after babies were born, and it has been one of the most important, highly predictive measures I've ever used. I subsequently advocated to add it, retrospectively 4-8 years after birth, in 3 other extant child cohorts and have found it to be a powerful predictor of a range of physical and mental health outcomes in those contexts, too, resulting in attention from policy-making leaders. This measure is now being added (albeit later than would have been ideal) to the ECHO consortium, where I hope it contributes to years of discovery related to prenatal exposure to maternal stressors. It's also critical that scholars with positionality that enables power use their voices to advocate for more inclusive science, for richer study of factors like racism, so the burden for this advocacy does not fall upon those that have been and continue to be marginalized and harmed by the structures we need to study.

Policy implications and future directions

Collectively, this research suggests that the causes of psychopathology and other health and disease outcomes take root much earlier than previously understood or currently communicated. The potential impact of this research on population health and policies that support public well-being is substantial. Given this, I would argue that the most important future direction is building partnerships with policy makers and power-brokers to change the landscape in which exposures to adversity are prevalent to identify and prioritize prevention efforts informed by this research!

Our public health priorities must include the elimination or reduction of exposure to severe stressors, and the provision of stress buffers, to break cycles of adversity, improve women's health across the lifecourse, and bestow greater health onto future generations. National policies that increase resources for pregnant people and other caregivers that have evidence of benefits to expectant and new families include increases in parental leave supports, enhanced insurance coverage, and perinatal cash transfer programs (Roman et al., 2014; Troller-Renfree et al., 2022; Van Niel et al., 2020). Providing universal access to populations destigmatizes those services, providing further potential benefits in term of stress reduction. Importantly, policies addressing prenatal stress and child health need to consider the diverse needs of individuals with intersecting social identities to reduce disparities and promote equitable health outcomes. As such, the field requires deeper inquiry into modifiable, structural-level health-promoting factors that influence intergenerational pathways underlying health to inform the development of specific policies.

Engaging with policy stakeholders and makers is certainly more challenging to do at early career stages, but research that is designed with these partnerships in mind, informed by input from stakeholders, is much more likely to result in impact. Sometimes it starts small, such as sharing the evidence to empower local community programs that support pregnant people, so they know their work matters for multiple generations and they are encouraged to continue or have helpful empirical information to help with fundraising for their programs. At times, bigger opportunities for impact might materialize, such as the emerging conversations with health care systems to develop partnerships to test health care reimbursement structures that will support pregnant people experiencing high levels of adversity, stress, or mental health challenges as a means of reducing health impairment across two generations. Broad, public health initiatives to promote maternal and child well-being have even greater potential, thus we need to partner evaluate the effectiveness of public health programs aimed at improving maternal nutrition, mental health, and overall well-being – beginning when they are young, well before conceiving.

Prevention of exposure to adversity is ideal, but as noted earlier, some of the most exciting work is that which demonstrates, using quasi or experimental designs, that investments to reduce stress exposure and/or provide supportive buffers to stress can have beneficial effects on offspring development. In addition to the studies with two-generation benefits noted earlier (Noroña-Zhou et al., 2022), other studies are underway also investigating the potential for psychosocial interventions during pregnancy to promote health and well-being in children (e.g., Davis et al., 2018). Researchers might consider a range of interventions that are aimed at improving prenatal conditions, including but not limited to mitigating maternal distress during pregnancy, and evaluating their effects on offspring risk for psychopathology. There is also value to identifying optimal timing and refinements via cultural adaptations to approaches for interventions that show positive influences child health outcomes. To develop impactful programs and policies that will positively benefit children and their families, more sophisticated examinations of modifiable sources of potential resilience and protection, particularly those at the level of systems, are needed. As many risk-focused studies fail to assess such indicators, researchers need to endeavor to include more of these measures in their studies, using target-community input to ensure designs are culturally-informed and tailored for sharing back useful findings to support the communities. Intervention

development should occur in partnership with community stakeholders, centering those most affected, to mitigate the negative effects of adversity across generations. That said, although interventions are promising, it is important to recognize that, despite the increasing efforts to screen individuals for histories of adversity or active distress, the shortage of available effective resources to address harms makes prevention the more sound target.

Beyond those imperatives, some other promising avenues for future investigation include more explicit examination of the impact of social determinants of health (e.g., socioeconomic factors, access to healthcare, neighborhood environmental conditions) during pregnancy on prenatal programing of offspring health disparities. To untangle these structural factors, large datasets are required. Readers should be aware of the publicly available Environmental Child Health Outcomes (ECHO) program database, which offers multidisciplinary opportunities to study infant and child neurodevelopment and health outcomes using de-identified longitudinal data from more than 63,000 participants across the U.S. (Bush et al., 2020; LeWinn et al., 2022). Researchers can submit a request to the NICHD DASH Data Access Committee to access and use these data (See https://echochildren.org/dash/).

As discussed above, future research should include long-term follow-up studies on cohorts with known prenatal stress exposures to prospectively track the health outcomes of individuals into adolescence and adulthood to identify patterns, associations, and potential late-onset consequences of prenatal programing. In addition, studies need to more deeply consider multisystem adversity and resilience-promoting factors that interact to effect outcomes (Ungar, 2021). The study of fathers is notably absent in this field, despite the clear role of coparents in both the biological transmission and their role in buffering stress pre- or postnatally (Cardenas et al., 2022). The role of other close kin or primary care providers in exacerbating or buffering prenatal programing effects is also of interest, although, as noted earlier, focusing on more structural, rather than individual, problems should be the priority (Suslovic & Lett, 2024).

Advances in a range of technologies (biologic, informatic, etc.) are enabling a range of exciting new areas of study. For example, the increased ease of collecting and processing biomarkers is allowing for a deeper understanding of processes by which stress transmission can occur and unveils potential targets for interventions (Shonkoff et al., 2022; Sullivan et al., 2024). Research into epigenetic mechanisms for the impacts of stress on fetal development is burgeoning (Van den Bergh et al., 2020; Yehuda & Lehrner, 2018), and further exploration of epigenetic modifications, how the epigenetic landscape influences gene expression and phenotype, and the association between epigenetic marks and susceptibility to diseases is likely to be fruitful. Our team recently demonstrated linkages between maternal childhood and pregnancy psychosocial adversity exposures and placental transcriptomic signatures derived from RNA sequencing that have been implicated in adverse pregnancy, birth, and child health outcomes (Baker et al., 2024), highlighting additional biological pathways of importance. Several research teams are currently investigating the role of maternal pregnancy health conditions, including gestational diabetes, hypertension, and immune activation, as well as the maternal and fetal microbiome (Monk et al., 2019; Van den Bergh et al., 2020) in prenatal programing. Placental CRH is often noted a key maternal-fetal stress-transmission factor in reviews (Entringer et al., 2015; Monk et al., 2019), although we

were surprised to note it was predicted by maternal childhood trauma, but not total lifetime or pregnancy stressors in our large, southern sample (Steine et al., 2020). Greater understanding of the influence of a vast array of factors outside of social stress on pCRH levels and rise, as well as more accessible rigorous assays of this complex hormone, is likely necessary before the role of this biomarker in stress transmission is clarified. Wearables, particularly those that provide repeated reliable measurements of pregnant people's arousal and recovery from remote locations while they go about their daily lives, are another avenue that will enhance our ability to monitor and understand the dynamic processes occurring during prenatal development. Delving into these exciting areas in future research may help to unravel the complexities of prenatal programing and pave the way for innovative, holistic prevention programs and interventions that positively influence health across multiple generations.

Conclusion

Mental health is a foundational component of the health of our population. Identifying risk and protective factors for developmental psychopathology, including factors preceding birth, is critical for *preventing* long-standing impairment to individuals, as well as social and economic costs to society. Collectively, evidence to date points to the need to simultaneously consider stressors experienced across multiple key developmental periods in the mother's lifespan, and their potential interaction, to capture the intergenerational impact of maternal stressors on her child's developmental and psychological outcomes. The historical and cultural contexts of these stressors is also critical to consider, as intergenerational transmission isn't limited to two generations. The prevalence of adversity nationally and globally compels us to consider major stressors during childhood and pregnancy need to be important targets for prevention efforts, with potential benefits across generations. That said, many individuals live with histories of harm, and effective interventions during pregnancy to improve outcomes for caregivers and their children are being identified. As scholars, our work advancing this science must ensure that we do not solely frame our questions or solutions at the level of the individual, and instead work to understand the influences of larger context of social and structural determinants in which individuals develop. Moreover, we have the opportunity to bring rigorous methods from the field of developmental psychopathology to partner with other fields, build multidisciplinary teams, and address intersectional challenges to developing optimal health.

Prenatal stress science findings from our field have the capacity to influence policies at the local, state, and national level, as well as within institutions (health care, education, insurance companies, employers). The next generation of research should be designed, in partnership with those in the communities of interest and other key stakeholders, with those targets in mind. The next generation of researchers in this space have an opportunity to use our science in the pursuit of social justice and the potential to play a powerful role combating the current mental health pandemic.

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