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What's next for the field of multigenerational mental health? The need for deep behavioral phenotyping via a prenatal mental health registry

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Abstract

From its inception, development and psychopathology theorists have sought to uncover the earliest forms of risk for mental health challenges in children, to prevent the development of more severe, intractable manifestations of psychopathology. Large familial risk registries have advanced our understanding of early, potentially modifiable factors that could prevent or mitigate the expression of challenging symptoms of neurodevelopmental conditions, and similar registries have been proposed to advance understanding of ADHD and related phenotypes. Data from single-site studies, largely focused on perinatal exposure to maternal mood disorders, reveal that a robust predictor of child psychopathology is parental psychopathology. However, early developmental trajectories of psychopathology risk may be better captured using transdiagnostic approaches in pregnancy, capturing the full range of mental health symptoms. We describe here the need for a parental mental health registry that begins prenatally that includes deep behavioral phenotyping across a range of transdiagnostic indicators of mental health risk to prevent psychopathology in children. This registry has the potential to uncover pathways to psychopathology risk in childhood and support the discovery of novel mechanisms to be targeted for prevention and intervention.

Keywords: development and psychopathology; prenatal mental health registry; research domain criteria

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Prenatal exposure to parental psychopathology is common, costly, and compromises the health and well-being of two generations: parent and child. As many as 1 in 5 mothers experience mental health challenges during pregnancy in the United States, making them the most common complication of the perinatal period (Fawcett et al., 2019; Gavin et al., 2005). Untreated mood and anxiety disorders experienced during pregnancy costs society $14.2 billion in the United States alone (Luca et al., 2020). Of course this financial toll does not begin to capture the emotional impacts of untreated mental illness for the family. Prenatal exposure to parental psychopathology is a significant and well-known risk factor for mental health risk in children. For example, children whose parents have a mental illness have a 50% chance of developing a mental illness themselves (Leijdesdorff et al., 2017). We have made significant strides in our ability to document risk and protective factors for child mental health, largely using single-site studies that document outcomes following prenatal exposure to a specific diagnosis, such as maternal depression or anxiety. Few studies measure parental mental health prenatally using a transdiagnostic perspective, and those that do are also typically limited to a single site. Larger registries are becoming more common, but phenotypic markers of mental health are limited and are not assessed transdiagnostically. We articulate here for the need for a national prenatal mental health registry, one that includes deep behavioral phenotyping of mental health challenges from a transdiagnostic perspective and is informed by development and psychopathology theory.

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National registries: what has been done so far?

National registries are large databases that store enormous amounts of information relevant to constructs of interest with the idea that the whole is greater than the sum of its parts: that we can advance the pace of scientific discovery through combining data relevant to particular exposures and outcomes of interest with the ultimate goal of advancing public health. There are three types of registries that address at least some aspect of science relevant for developmental psychopathologists: population-wide, familial risk, and hybrid approaches.

Population-wide, national registries attempt to represent of the larger population of families from a particular country and typically include a wide range of exposures and outcomes of interest. Examples in the United States include the Environmental influences on Child Health Outcomes (ECHO; Blaisdell et al., 2022), Adolescent Brain Cognitive Development (ABCD; Casey et al., 2018) study, and Healthy Brain and Child Development (HBCD; Price et al., 2023) NIH initiatives. These national registries have led to tremendous scientific advances for the prenatal programing field. For example, findings from ECHO revealed that

prenatal substance exposure and maternal psychosocial and economic challenges during pregnancy predicted more behavior dysregulation across early childhood, from 18 months to 6 years (Hofheimer et al., 2023). In a sample of 10,414 adolescents from ABCD, prenatal cannabis exposure revealed stronger outcomes on cognitive abilities and brain volumes in 11 year-olds compared to 9 year-olds, suggesting latent effects of prenatal cannabis exposure on neurodevelopment (Hiraoka et al., 2023). Given the breadth of exposures measured in these important population-wide registries, concerns raised by ECHO include the large protocol, and implementation of data collection for all cohorts. Given the ambitious ECHO goals, the program is also expensive. It may also be challenging to measure a particular exposure or outcome in depth. For instance, measures of depression might be limited to a single, short-form version of a questionnaire, and there is not an explicit focus on including transdiagnostic measures. Nevertheless, the large sample sizes and breadth of exposures available for study are impressive and have the potential to significantly improve the health and well-being of children.

Familial risk registries tend to focus on risk for a specific neurodevelopmental outcome of interest that expresses itself in an older sibling. For example, researchers using data from the Baby Siblings Research Consortium have made tremendous scientific progress uncovering the etiology, clinical course, early intervention, and best treatment approaches for autism spectrum disorder (McDonald et al., 2020). Findings from this consortium have pinpointed when symptoms of autism spectrum disorder emerge, that social communication challenges may indicate early risk for autism spectrum disorder, information about recurrence rates of autism spectrum disorder in families, and the likelihood of symptom improvement with early intervention (Szatmari et al., 2016). Similar familial risk designs have been proposed for other neurodevelopmental conditions, such as ADHD (Miller et al., 2023). These registries will likely yield the kinds of data needed to identify early, modifiable risk factors for the development of ADHD and related phenotypes. Importantly, they also allow for deep phenotyping of exposures and outcomes of interest given the specific families they are targeting for research. As noted by registry researchers, these registries are limited in that they only include the siblings of an affected child, which limits understanding of how a particular neurodevelopmental condition may develop in families without known risk factors.

We propose here the need for a hybrid registry that incorporates the primary advantages of both kinds of registries: representativeness of the population but including the deep phenotyping characteristic of the familial risk designs. A prenatal mental health registry is more targeted than a population-wide approach but captures a broader range of families than familial risk registries. We believe this approach will allow for the measurement of the full range of transdiagnostic constructs of interest that could emerge early in life, including irritability, behavioral inhibition, emotion dysregulation, and frustration tolerance. An example of this hybrid approach comes from the AURORA national registry that recruits women from emergency rooms who have recently experienced sexual trauma to better understand who is at risk for post-traumatic stress syndromes, the clinical course of trauma, and how best to intervene to prevent mental health suffering following a traumatic event (McLean et al., 2020). A similar approach to targeting a group at high risk for mental health challenges in children is needed.

We propose the creation of a national prenatal mental health registry, beginning in pregnancy, enriched for: (1) a wide range of parental prenatal mental health symptoms measured via traditional and transdiagnostic approaches (e.g., dimensionally rather than categorically); (2) racial, ethnic, sexual minority, and socioeconomic diversity, which as we describe below is missing in many other larger registries. Given the significant advances these registries have made toward etiology, prevention and treatment for autism spectrum disorder (Szatmari et al., 2016) and traumatic stress (McLean et al., 2020), we expect that a prenatal mental health registry would advance our ability to identify a wide array of early-life mechanisms to be targeted for treatment to reduce the burden of mental illness in children as early in life as possible.

Why do we need a national perinatal mental health registry?

Our vision of a national registry would allow researchers to combine and store data relevant to our exposure of interest – prenatal mental health from both the birthing parent and the baby's father. The overarching goal is to support the creation of knowledge to address the significant burden of mental illness in children. However, as a scientific discipline, psychologists and psychiatrists neglect studies of child psychopathology. As described in this landmark paper on the importance of studying and treating youth mental health challenges, approximately 75% of mental health disorders begin before age 25 (Solmi et al., 2022; Uhlhaas et al., 2023). Furthermore, rates of youth psychopathology are increasing and first episodes of mental illness are occurring at younger ages (Lebrun-Harris et al., 2022). These trends are particularly concerning given that early-onset of many forms of psychopathology predicts a more severe clinical course (Zisook et al., 2007).

One of the strongest predictors of child psychopathology is parental psychopathology. Children of parents with depression are 2-4 times more likely to develop depression than their peers with no family history of depression (Apter-Levy et al., 2013; Goodman & Garber, 2017). Children exposed prenatally to maternal anxiety are twice as likely to show mental health challenges compared to their unexposed counterparts (Monk et al., 2019). Furthermore, mental health challenges are highly heritable (e.g., 0.7–0.8 for ADHD; Faraone & Larsson, 2019; .69 for depression; .37–.67 for anxiety McGue & Christensen, 2003). Importantly, these heritability estimates also suggests a significant environmental contribution to mental illness that could be measured and might yield potential targets for intervention. These findings suggest that targeting parental psychopathology in pregnancy could yield an enriched sample of children at risk for mental health challenges themselves.

A national prenatal mental health registry provides an opportunity to evaluate mental health risk in children from a transdiagnostic, RDoC-informed lens. The RDoC approach provides a framework for studying the pathophysiology of mental health challenges, studied dimensionally as opposed to categorically (Cuthbert, 2014). The goal is to develop neurobiologically and behaviorally informed psychiatric nosologies rooted in rigorous science, as opposed to disorder descriptions (Cuthbert, 2014). As we described in an earlier publication, because young children are rarely given formal, DSM diagnoses, mental health risk could be evaluated transdiagnostically, and indeed this is the approach of developmental and psychopathology-informed scholars beginning in the 1960s (Conradt et al., 2021). Therefore, including transdiagnostic measures of risk for mental health problems, beginning

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in pregnancy, will likely reveal important modifiable mechanisms to target for later intervention.

Targeting pregnant people with a current diagnosis could save costs and more efficiently support early identification of children at risk for mental health challenges. Cost savings of a targeted approach to recruitment into the registry could allow for more funds to be spent on deep behavioral phenotyping: biomarkers and biological mechanisms. Very little is known about multilevel (e.g., genetic, epigenetic, hormonal, physiological, neurobiological) risk for child mental health problems. Many physiological biomarkers and potential mechanisms of mental health risk can be measured noninvasively and are affordable. For example, in our work we study respiratory sinus arrhythmia as a biomarker of emotion dysregulation in pregnant people (Lin et al., 2019) and their infants (Gao et al., 2022). Systems for measuring heart rate and heart rate variability are now integrated into wearable technology that, if validated, could improve early risk prediction of mental health challenges (Perochon et al., 2023). Consistent with the RDoC framework transdiagnostic processes could be measured at multiple levels of analysis in a prenatal mental health registry, yielding even greater knowledge base of biological predictors, mediators, and moderators, pointing to specific target mechanisms for child mental health treatment.

Data from a national prenatal mental health registry could also be used to develop risk prediction models for specific disorders to inform later clinical decision-making. For example, Wakschlag et al. (2023) used harmonized data across two longitudinal early childhood samples to develop an algorithm for early prediction of risk for internalizing and externalizing behavior, based on early indices of irritability in early childhood and adverse childhood experiences (Wakschlag et al., 2023). Expanding on this approach at the national level, with the addition of important prenatal parental indicators of mental health risk could improve early prediction and expand our ability to model early risk for psychopathology using other transdiagnostic indicators. Leveraging prospective data, beginning in pregnancy, phenotypic risk scores can be developed for improved prediction of childhood mental health outcomes (Miller et al., 2023).

A prenatal mental health registry could remain agnostic towards mental health outcomes of interest, allowing researchers to model pathways to a wide range of mental health outcomes in childhood. This approach is consistent with the principle of multifinality, which suggests that early-life risk factors such as exposure to parental mental health challenges could lead to a wide range of mental health outcomes in children. For example, an infant that has difficulty soothing, is highly reactive, and has elevated activity level could, through later interactions with caregivers and environmental exposures over time, could be at elevated risk for a wide range of mental health outcomes from ADHD to ODD to anxiety (Luby et al., 2019; Wakschlag et al., 2018, 2023). We therefore expect based on developmental and psychopathology principles and empirical evidence to-date, that a prenatal mental health registry would reveal pathways of risk for a wide range of mental health challenges in children. This heterogeneity in early symptom presentation and environmental exposures is a significant advantage for a prenatal mental health registry and may be more cost-effective by allowing for the modeling of a wide range of mental health risk pathways in a single registry.

The majority of studies on parenting effects and child mental health risk comes from studying the mother-child dyad despite knowledge that child mental health risk emerges via dynamic interactions within the family system. However, few researchers integrate parenting data from both parents, and any other relevant caregivers such as aunts, uncles, and grandparents. Our statistical approaches and tools are finally catching up to our theories about the dynamic ways in which behavioral patterns develop within the family system. For example, in a group of Chilean families, greater maternal and paternal sensitivity during a triadic interaction with toddlers who were experiencing social and emotional challenges predicted positive family regulation during triadic play tasks (Olhaberry et al., 2022). A national parent mental health registry has the potential to illuminate bi- and tridirectional pathways from parenting to child psychopathology. A national parent mental health registry could therefore yield important insights into the dynamic moving target of child mental health risk.

In addition to these statistical advances, there have been rapid innovations in virtual data collection protocols and wearable technologies that are increasingly being used in studies since the COVID-19 pandemic. For example, early detection of autism risk is enhanced by digital behavioral phenotyping (Perochon et al., 2023). Dawson and colleagues found that an app designed to elicit behavioral symptoms of autism could be used to develop an algorithm to predict autism with high diagnostic accuracy (Perochon et al., 2023). This app was used in the context of busy pediatric clinics, further supporting the potential for apps to collect rich digital behavioral phenotypes in a scalable, cost-effective manner, enhancing the potential for use in the context of a larger prenatal mental health registry. In addition to behavioral measures, physiological measures are increasingly being used to collect data in participant homes. For example in our own work we describe how participants could be coached to collect their own and their toddler's physiology at home using videoconferencing (Gao et al., 2021). These approaches could be integrated into a parent mental health registry given technological advances in behavioral and digital phenotyping that are simpler and more cost-effective to implement.

When parents are asked why they participate in developmental studies they report wanting to advance child health outcomes (Fisher et al., 2011). This may be a particularly strong motivating factor for parents who experience mental health struggles, who may want to find ways to reduce the likelihood that their children develop psychopathology. Observational findings from a parent mental health registry could be used to identify malleable mechanisms to inform intervention, or ancillary pilot studies that directly target a mechanism of interest for intervention. For instance ECHO was designed to generate observational findings that could be used for intervention via their clinical trials network (Blaisdell et al., 2022). In addition, mental health researchers and clinicians have recently advocated for an experimental therapeutics approach to improving mental health by targeting specific risk mechanisms experimentally or via intervention that lead to specific mental health challenges (Zucker et al., 2023). The registry could therefore be used to advance basic science about child mental health risk as well as to develop cutting-edge preventive interventions that target mechanism(s) that may have been discovered through the observational research.

A prenatal mental health registry could also serve as the research home for a prenatal mental health research network, similar to the NICHD neonatal research network (NRN), or maternal-fetal medicine units (MFMU) networks. The MFMU and NRN were originally developed for observational studies and to test the efficacy of interventions for pregnant people and preterm infants across MFMU and NRN sites, with the idea that

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generalizability and evidence for efficacy will be stronger when tested across multiple sites rather than in one center alone. These research networks track cohorts of mothers and infants known to be at developmental risk, for example due to very preterm birth status, and provide researchers with the infrastructure to conduct multisite randomized clinical trials. Data obtained from sites collecting prenatal mental health data could be organized as part of the registry, to be used to develop observational studies and develop and improve perinatal mental health treatments for greater impact and generalizability.

Importance of enhancing diverse perspectives and experiences

Of utmost importance is that this registry represent, value, and uplift the experiences of children underrepresented and ignored in developmental science. Marginalized families have been excluded from all phases of the child mental health research process, from early discovery of risk mechanisms to clinical trials (Bibbins-Domingo et al., 2022). Inclusion of racial and ethnic diversity into national registries should be of utmost priority and considered at every stage of the process: from scientific leadership, to study design, recruitment, retention, and dissemination of knowledge. Leaders who have deep knowledge of the history and background of oppressive practices in each community and across states is critical for building trust and ensuring that barriers to research participation are minimized so that the voices and perspectives of historically excluded families can be included in research.

A deep characterization of how racism in all its forms is related to child mental health risk is paramount. Multidimensional measurement of this construct – from interviews to questionnaires to daily diaries should be an essential component of this registry given the wealth of evidence documenting how racism causes and exacerbates mental health challenges in children. Systems of oppression also increase risk for psychopathology. For example, Black postpartum women are at greater risk of perinatal PTSD and have the highest avoidance symptoms of any other racial or ethnic group (Thomas et al., 2021). Deep behavioral phenotyping of mental health challenges has the potential to uncover how experiences of racism could be transmitted across generations, potentially via prenatal parental mental health challenges. However, great care should be made to not over-pathologize minoritized children and their families due to stereotypes and bias rooted in longstanding historical and societal oppressive practices. In addition to documenting that these effects exist, sorely needed treatments could be developed to mitigate mental health risk transmission for marginalized postpartum people. In addition, culturally-relevant buffering factors and measurement of the ways in which children of color have adapted and thrived despite living in a society that systematically excludes and harms them will need to be incorporated into the larger study design. To hold scientists accountable a well-compensated advisory board of racially and ethnically diverse parents should be part of the registry's organizing framework.

It is critical that diverse families in all forms are included in this registry. Eliminating barriers to participation should be prioritized for racially and ethnically diverse families as well as parents across the gender spectrum, LGBTQIA + families, and economically disadvantaged families. For example, pregnant people who identify as American Indian and Alaskan Native are included in only .2% of research from the Maternal-Fetal Medicine Units Network, despite comprising 1.1% of all births (Yamasato et al., 2021). Furthermore, few pregnancy studies include data on sexual orientation; in many countries including those data could compromise the safety of participants (Darwin & Greenfield, 2019). The number of lesbian couples having children is increasing, approximately 15%–20% per year according to some estimates, but studies with these groups are typically limited to a focus on assisted and donor conception (Darwin & Greenfield, 2019). A prenatal mental health registry inclusive of racial, ethnic, family, and socioeconomic diversity will ensure that research findings are used to benefit and support all families, and that the support needed for particular groups are recognized and addressed.

To ensure that research findings benefit the marginalized communities, and consistent with community-based participatory research principles, a prenatal mental health registry should include processes by which findings are rapidly disseminated back into the communities contributing to this research. For example, the RAPID-EC is a national survey on household functioning, well-being, and stress, developed during the COVID-19 pandemic, to efficiently obtain data on the needs of underrepresented groups and amplify the needs of parents to inform policy (Ibekwe-Okafor et al., 2023). Accessible fact sheets and brief videos could be developed so that individual research teams can easily disseminate findings to their communities. A paid community advisory board developed for the needs of the local community where data collection occurs, can then use this knowledge to inform local policy or practice changes.

An inherent risk of these large registries is the misuse and misinterpretation of data on race, ethnicity, racism and discrimination in all its forms. Lett and colleagues have coined the term "health equity tourism" to refer to individuals who assume they can conduct research and publish in health equity spaces without engaging in the necessary training to do so in a way that doesn't harm marginalized communities (Lett et al., 2022). Often times groups may generate racist conclusions or study design – for example an inclusion of a white "control group" when examining the consequences of racism – when the appropriate scientific expertise is not included in the writing team. Some registries have somewhat mitigated this risk via Diversity, Equity, and Inclusion committees that review manuscript proposals, drafts, and submissions, but there continues to be a need for holistic examination of practices that can promote the benefits of large registries while offsetting the potential cost to disenfranchised groups.

How can development and psychopathology theory be used to guide a national prenatal mental health registry?

"There is now . . . an increasing acknowledgement of the need to do collaborative, multidomain, longitudinal studies of the varies psychopathologies . . . research into pathological conditions must go hand-in-hand with so-called basic research into human functioning (Cicchetti, 1984)."

From its inception, development and psychopathology theorists have articulated a need to chart mental health risk as early in life as possible using large, longitudinal studies. For example, the Minnesota Longitudinal Study was used to test core assumptions of development and psychopathology theory about the enduring effects of early-life experiences, multi-and equi-finality, and risk and adaptation. The Minnesota Longitudinal Study began with 267 first-time pregnant women in their 3rd trimester and now includes three generations: parents, offspring, and grandchildren (42 months old in 2023; Sroufe et al., 2009). These studies were ahead of their time given that decades later agencies across Europe

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and now the United States recognized the need for similar approaches to chart the early-life origins of a variety of disease outcomes.

A core central tenet of development and psychopathology theory includes processes of equi and multifinality (Cicchetti & Rogosch, 1996). Equifinal processes occur when diverse early-life pathways lead to the same outcome (Cicchetti & Rogosch, 1996). For example, in the transdiagnostic literature in early childhood, early emotion dysregulation, behavioral inhibition, and irritability could all lead to a diagnosis of disruptive mood disorder. With multifinal processes, a variety of different disorders may emerge as a result of similar early-life histories (Cicchetti & Rogosch, 1996). For example, young children with more emotion dysregulation may be at risk for disruptive mood disorder, attention deficit hyperactivity disorder, anxiety, and/or depression (Conradt et al., 2021). To date researchers interested in studying how this transdiagnostic risk unfolds have limited tools: they may not have the resources to study development across the lifespan, sample sizes tend to be quite small, and there are few replication studies, particularly in racially and ethnically diverse samples. Large, diverse, prospective longitudinal studies are needed to address strategic mental health priorities articulated by funding agencies to uncover robust processes of mental health risk across sensitive developmental periods.

Another core tenet of development and psychopathology theory is that there is a tremendous amount of heterogeneity across development that should be measured across levels of analysis to fully appreciate the processes that lead to mental health challenges in children(Cicchetti & Dawson, 2002). A disproportionate focus on one level of analysis – such as self-report or medical record review – prevents us from identifying the pathophysiology of childhood psychopathology, and likewise treatments that target particular mechanisms that give risk to mental illness in children (Pacheco et al., 2022). It has long been appreciated that single risk processes rarely have the power to lead to mental illness, particularly given the dynamic nature of childhood development (Cicchetti & Dawson, 2002). Instead, modeling of risk additively, as correlated risk processes, exponentially over time, and/or via risk profiles may be more fruitful in predicting child mental health risk (Walsh et al., 2019). Deep phenotyping approaches studied in the context of interdisciplinary teams that include observations of children, parent-child interactions, psychophysiology, neurobiology, genetics, and epigenetics, consistent with a multiple levels of analysis perspective could support our understanding of early etiology, disease processes, and could even help to identify personalized mental health risk trajectories (Conradt et al., 2021; Doyle & Cicchetti, 2018; Luby et al., 2019).

Of course development and psychopathology theory suggests that in order to develop the knowledge base for these mental health risk trajectories we need to better understand normative developmental trajectories. For example, approximately 50% of infants and toddlers who exhibit high levels of behavioral inhibition are diagnosed with social phobia in childhood, suggesting that behavioral inhibition may not be concerning for some infants and toddlers (Clauss & Blackford, 2012). A national registry could help us also understand typical development to help inform pediatricians and parents about when they should and should not be concerned about their child's behavior. Importantly, as we have articulated in a prior Special Issue, the integration of a transdiagnostic perspective that is informed by development and psychopathology theory will likely yield a more precise understanding of the complex multifinal outcomes that emerge for vulnerable infants (Conradt et al., 2021).

Why should a transdiagnostic perspective be included in a national prenatal mental health registry?

A national prenatal mental health registry represents a substantial shift over dominant research design methods that tend to focus on the effects of exposure to a single parental mental health diagnosis. Existing, largely single-site studies have typically focused on developmental consequences of prenatal exposure to a single disorder, such as depression or anxiety. These studies have yielded tremendous insights into the etiology, clinical course, and pathways to psychopathology risk for children exposed prenatally to these conditions. However, operationalizing psychopathology as single, discrete diagnosis neglects a large literature, deeply rooted in development and psychopathology theory, that mental health challenges later in life likely arise from complex equi and multifinal outcomes (Cicchetti & Rogosch, 1996). As we articulated in an earlier special issue in this journal (Conradt et al., 2021), a transdiagnostic perspective challenges this view and advances understanding of the processes and mechanisms by which earlier mental health challenges can give rise to more intractable forms of psychopathology. The knowledge gained from these studies are used to justify the necessity of a prenatal mental health registry that addresses many of the limitations of the single diagnosis research design.

In 2015, Crowell and colleagues highlighted how transdiagnostic perspectives can advance the development and psychopathology field by identifying early-emerging trait vulnerabilities for more entrenched forms of psychopathology (Crowell et al., 2015). They articulated that a variety of mental and physical disorders in adults have common, early origins in how individuals manage and express emotions in childhood and showed how emotion dysregulation is a model by which individual differences in early emotional expression can develop, through complex biological and environmental interactions, into emotion dysregulation in adulthood (Crowell et al., 2015). Our empirical and conceptual work has expanded on this model by uncovering how prenatal programing processes, in addition to early-life temperament, psychophysiology, and parenting practices could place young children at risk for emotion dysregulation.

Risk for emotion dysregulation in childhood likely has prenatal origins (Lin et al., 2019; Ostlund et al., 2019). Emotion dysregulation underlies almost all forms of psychopathology yet little is known about how it emerges very early in development. Our goal was to better understand how emotion dysregulation may manifest during pregnancy, and to obtain valuable clinical information to be used in subsequent treatment trials to prevent intergenerational transmission of emotion dysregulation. We used a novel design strategy to recruit women with a range of emotion dysregulation on the Difficulties in Emotion Regulation Scale (Gratz & Roemer, 2004) so that we achieved a uniform distribution: over-sampling women at the low and high ends of emotion dysregulation. Consistent with development and psychopathology principles, we measure emotion dysregulation at multiple levels of analysis: behavioral (self-report), observation of parenting behaviors, and biological processes (e.g., cortisol, epigenetics, respiratory sinus arrhythmia; RSA). Our initial work largely focused on RSA as a biological mechanism by which exposure to emotion dysregulation could affect fetal central nervous system development.

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RSA is a peripheral marker of parasympathetic nervous system functioning and measures beat-to-beat variability in heart rate that coincides with breathing (Beauchaine, 2015; Berntson et al., 1993). It is controlled by the vagus nerve that originates in the brainstem. Important for our work, the vagus nerve innervates the uterus, thereby providing a possible mechanism where by prenatal exposure to emotion dysregulation could impact infant outcomes. In non-pregnant adults, low baseline (resting) RSA and sharp decreases in RSA in response to emotional stress are associated with higher emotion dysregulation (Beauchaine, 2015). In our first series of studies, we found support for the premise that emotion dysregulation can be measured using multiple levels of analysis in pregnancy in a reliable and valid manner.

Pregnant women with high emotion dysregulation had more self-injurious thoughts and behaviors, even during pregnancy, as well as high rates of depression and anxiety (Lin et al., 2019). Pregnant women with high emotion dysregulation also had blunted, flatter levels of RSA in response to hearing an infant cry (Lin et al., 2019). Infants of mothers with high RSA also showed a blunted neurobehavioral profile characterized by low arousal and low attention (Ostlund et al., 2019), which may make it challenging for parents to engage in social interaction, at least in the newborn period. Given that newborn neurobehavior is largely independent of the postnatal environment prenatal exposure to emotion dysregulation could be related to a neurobehavioral phenotype characterized by difficulties alerting, orienting, and responding to the caregiver and other aspects of the caregiving environment, possibly shaping neurodevelopmental risk for emotion dysregulation at birth.

By seven months, we observed continued risk for emotion dysregulation in how infants responded physiologically to an attachment stressor. We found that infants of mothers with high emotion dysregulation took longer to recover from the stress of the still face; these infants had parasympathetic nervous system responses that took longer to return to baseline after the still-face episode than infants whose mothers exhibited less emotion dysregulation (M. (Miranda) Gao et al., 2023). Gao and colleagues found that 7-month old infants of women with high emotion dysregulation exhibit the same blunted RSA profile their mothers showed prenatally to an infant cry. There are likely genetic contributions to this parasympathetic nervous system profile. However, RSA is about 50% heritable (Snieder et al., 2007), leaving 50% of the variance attributable to important, and undiscovered environmental contributions.

One of these environmental contributions may be due to early-life parenting practices. Our early work from a sample of women living in poverty showed that infants whose mothers were less sensitive had blunted RSA responses to the stress of the still face (Conradt & Ablow, 2010). Brown and colleagues extended these findings to document that toddlers at highest risk for emotion dysregulation had both blunted RSA responses to the stress of the still-face episode and parents who showed less sensitivity during the still-face paradigm (Brown et al., in press).

Published research from independent laboratories show similar associations between emotion dysregulation, parental sensitivity, and early self-regulation outcomes in infants and toddlers, and have extended these associations to predict risk for negative affect in infants of women with high emotion dysregulation. At 6 months, mothers with lower RSA withdrawal in response to distress-eliciting dyadic tasks, possibly indicative of a blunted RSA response to stress, had more emotion regulation difficulties (Leerkes et al., 2020). These mothers also showed lower levels of sensitivity at 6 months. Furthermore, infants of mothers with high emotion dysregulation who showed high negative affect at 6 months were less likely to receive sensitive care at 14 months, which predicted greater emotional distress at 26 months (Bailes & Leerkes, 2023). These findings suggest, in independent groups, that physiological indices of self-regulation are possibly impaired in mothers with behavioral emotion regulation difficulties, and that these women may also struggle to interact sensitively with their infants and may be particularly distressed when parenting an infant higher in negative affect.

There is thus a clear motivation from the field that studying intergenerational transmission of risk for emotion dysregulation from a transdiagnostic perspective could help advance the development and psychopathology and infant mental health fields. A number of independent laboratories are charting their own pathways from early-life transdiagnostic risk factors to later, more entrenched forms of psychopathology. For example, incredible progress has been made towards early identification of trait irritability (Wakschlag et al., 2018), behavioral inhibition (Pérez-Edgar & Guyer, 2014), and dysregulation of positive affect (Vogel et al., 2023). Importantly, our research team and others all point to similar, early-emerging, temperamentally-based vulnerabilities for psychopathology in the form of high negative affect (Wakschlag et al., 2018), poor attention (Miller et al., 2023), and in our case blunted neurobehavior (Ostlund et al., 2019). These common early-life risk factors speak to the importance of creating a national registry so that pathways from these early vulnerabilities to later psychopathology can be identified.

Potential disadvantages of a national prenatal mental health registry

There already exist a number of prospective longitudinal registries beginning in pregnancy. What is the value added of a prenatal parental mental health registry, informed by a transdiagnostic, RDoC perspective? As we articulated above, hybrid registries allow for deep phenotyping unlike any other existing registry based on a well-known, robust exposure, prenatal parental mental health, that can have life-long mental health consequences for some children. Nevertheless, we acknowledge that existing registries may also be able to address gaps in our understanding of multigenerational mental health trajectories. Whether those studies can adequately represent the diversity of families in the United States using measures beyond questionnaire data is unclear.

Recruiting families based on mental health symptoms has the potential to stigmatize an already marginalized group. Similarly there is risk of over-pathologizing minoritized families and an over-emphasis on risk pathways instead of strength-based pathways. A prenatal mental health registry could include all pregnant persons in order to represent the full spectrum of mental health risk, consistent with an RDoC, dimensional approach. Furthermore, strength-based pathways of resisting mental health challenges that could be different across cultural and racial contexts should be thoughtfully measured after consulting with experts in these research areas.

A national prenatal mental health registry is also costly and, depending on how the registry is advertised, could prevent participation due to stigma. Other registries addressing the needs of marginalized groups have been developed to ensure that stigma is not a barrier to creating knowledge that could benefit these families. For example, federal funding, in addition to philanthropic organizations, have been used to develop a national registry to

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recruit victims of sexual violence, with protections in place to ensure the confidentiality of participants. This support is likely driven by knowledge that such a registry will improve the lives of millions of victims of sexual trauma. Likewise, we believe the time is right to invest in the mental well-being of children through a prenatal mental health registry.

From a study design perspective, and similar to other familial risk design registries, children at risk for mental health problems because of a prenatal parental mental health diagnosis will be targeted for recruitment. Not represented in this registry will be children who develop mental health problems even if the absence of a prenatal parental mental health diagnosis. Findings from this mental health registry may not generalize to children whose parents did not receive a mental health diagnosis. However, approximately 1 in 5 children (15%–23%) is raised by a parent with a mental illness, and these children have a 50% chance of developing mental illness themselves (Leijdesdorff et al., 2017). Thus, findings from a prenatal mental health registry will be able to contribute to prevention efforts for a substantial group of children.

Conclusions

The rise in childhood mental health problems has reached epidemic proportions. US surgeon general etc. From 2012 to 2018 there was a 34.6% increase in the prevalence of mental illness, with rates continuing to rise during the COVID-19 pandemic (Rask et al., 2023; Tkacz & Brady, 2021). Despite these devastating increases, there is a disproportionate lack of attention and funding paid toward addressing child mental health, despite knowledge that childhood is a time of tremendous brain development and developmental plasticity, and that earlier intervention reduces the intensity and severity of psychopathology. The cost of not acting is substantial: the lifetime cost of a perinatal mood disorder for just one individual is estimated to be $32,000–$112,299, totaling $42 billion annually (Luca et al., 2020; McDaid et al., 2019). Not addressing the child mental health crisis will exert and enormous toll on society. A 2019 economic study concluded that there is a "strong evidence base for action" to prevent mental health problems in pregnancy (McDaid et al., 2019). There is thus an urgent need to address this challenge for all children using the valuable resources at our disposal: national wealth, ethical duty, and scientific expertise.

Insights yielded from existing registries shows that we can gain a better understanding of the etiology and pathophysiology of a wide range of mental health disorders, as well as factors that protect against the development of psychopathology. A national prenatal mental health registry will uncover pathways to psychopathology risk in childhood and support the discovery of novel mechanisms to be targeted for prevention and intervention. We have a scientific duty to apply the lessons learned from decades of development and psychopathology-informed research to prevent psychopathology when possible, and to improve the mental health and well-being of the next generation. Unfortunately this sentiment is not a new one. We end with a prescient warning, articulated in 2004 by Dante Cicchetti (Cicchetti, 2004), to whom we dedicate this manuscript:

"We are headed down a slippery slope wherein only children with significant emotional and behavioral problems are targeted for intervention. This approach is shortsighted and will ultimately prove to be much more costly with respect to the toll in human suffering, as well as with regard to actual dollars expended. Prevention must be a national priority."

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