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Moving the dial on prenatal stress mechanisms of neurodevelopmental vulnerability to mental health problems: A personalized prevention proof of concept

Lauren S. Wakschlag[1,2] | Darius Tandon[1,2,3] | Sheila Krogh-Jespersen[1,2] | Amelie Petitclerc[1,2] | Ashley Nielsen[1,2] | Roozbeh Ghaffari[2,4] | Leena Mithal[4,5] | Michael Bass[1,2] | Erin Ward[1,2,3] | Jonathan Berken[2,6,7] | Elveena Fareedi[1,2] | Peter Cummings[1,2] | Karen Mestan[2,6,8] | Elizabeth S. Norton[2,9] | William Grobman[2,10] | John Rogers[2,4] | Judith Moskowitz[1,2] | Nabil Alshurafa[2,11,12]

[1]Department of Medical Social Sciences, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[2]Institute for Innovations in Developmental Sciences, Northwestern University, Chicago, IL, USA

[3]Institute for Public Health & Medicine Center for Community Health, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[4]Department of Materials Science & Engineering, McCormick School of Engineering, Northwestern University, Chicago, IL, USA

[5]Department of Pediatrics (Infectious Diseases), Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[6]Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL, USA

[7]Department of Pediatrics, Feinberg School of Medicine, Chicago, IL, USA

[8]Department of Pediatrics (Neonatology), Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[9]Department of Communication Sciences & Disorders, School of Communication, Northwestern University, Chicago, IL, USA

[10]Department of Obstetrics & Gynecology (Maternal-Fetal Medicine), Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[11]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

[12]Department of Computer Science, McCormick School of Engineering, Northwestern University, Chicago, IL, USA

Correspondence
Lauren Wakschlag, Department of Medical Social Sciences, Feinberg School of Medicine, Northwestern University, 625 N Michigan Avenue, Suite 2100, Chicago, IL 60611, USA.
Email: lauriew@northwestern.edu

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Abstract

Prenatal stress exposure increases vulnerability to virtually all forms of psychopathology. Based on this robust evidence base, we propose a "Mental Health, Earlier" paradigm shift for prenatal stress research, which moves from the documentation of stress-related outcomes to their prevention, with a focus on infant neurodevelopmental indicators of vulnerability to subsequent mental health problems. Achieving this requires an expansive team science approach. As an exemplar, we introduce the Promoting Healthy Brain Project (PHBP), a randomized trial testing the impact of the Wellness-4-2 personalized prenatal stress-reduction intervention on stress-related alterations in infant neurodevelopmental trajectories in the first year of life. Wellness-4-2 utilizes bio-integrated stress monitoring for just-in-time adaptive intervention. We highlight unique challenges and opportunities this novel team science approach presents in synergizing expertise across predictive analytics, bioengineering, health information technology, prevention science, maternal–fetal medicine, neonatology, pediatrics, and neurodevelopmental science. We discuss how innovations

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across many areas of study facilitate this personalized preventive approach, using developmentally sensitive brain and behavioral methods to investigate whether altering children's adverse gestational exposures, i.e., maternal stress in the womb, can improve their mental health outlooks. In so doing, we seek to propel developmental SEED research towards preventive applications with the potential to reduce the pernicious effect of prenatal stress on neurodevelopment, mental health, and wellbeing.

KEYWORDS
developmental origins of health and disease, maternal stress, neurodevelopmental risk, prenatal prevention, wearable devices

1 | INTRODUCTION

Prenatal stress exposure has been linked to virtually all forms of psychopathology including the most common and preventable pediatric onset syndromes and their neural substrates (Betts et al., 2014; Buss et al., 2012; Demir et al., 2016; O'Connor et al., 2014). At the same time, advances in developmentally based methods (e.g., infant imaging, dimensional phenotypes), as well as emphasis on transdiagnostic common pathways (e.g., emotion dysregulation as infant risk phenotype) now enable detection of neurodevelopmental vulnerability to subsequent mental health problems beginning at birth. Capturing this vulnerability in proximity to exposure is critical when testing plasticity of causal pathways (Beauchaine & Cicchetti, 2019; Finlay-Jones et al., 2019; Graham, Pfeifer, Fisher, Carpenter, & Fair, 2015; Graham, Pfeifer, Fisher, Lin, et al., 2015; Hartman et al., 2019; Wakschlag, et al., 2019). Joining a burgeoning call for action (Davis et al., 2018; Doyle & Cicchetti, 2018; Gelaye & Koenen, 2018; Glover, 2014; Goodman et al., 2018; Heim et al., 2018; Shonkoff, 2016), we aim to move the translational dial on prenatal stress research from robust observational evidence to a preventive approach, with promise for improving lifecourse health.

2 | MENTAL HEALTH, EARLIER FRAMEWORK

Our conceptual framework draws from our Mental Health, Earlier roadmap (Wakschlag, et al., 2019) with two key pillars: *Pillar I: Earlier* calls for identification of mental health risk as early as possible in the clinical sequence, aligned with the Research Domain Criteria (RDoc; Casey et al., 2014; Mittal & Wakschlag, 2017). One crucial component is targeting neurodevelopmental vulnerability to mental health problems based on probabilistic risk rather than full-blown clinical disease. This requires developmentally specified dimensional tools, joint consideration of brain-behavior patterns, and a transdiagnostic approach (Finlay-Jones et al., 2019; McGorry & Nelson, 2016; Wakschlag, et al., 2019). Another vital element is extending this emphasis even *earlier* in development to the prenatal environment that shapes fetal neurodevelopment (Buss et al., 2012; Davis et al., 2018; Spann et al., 2018). Preventing stress exposure during pregnancy may have outsized impact on neurodevelopment because this is a sensitive period for development of neural structure, connectivity, and function with implications for postnatal neural integrity (Buss et al., 2017). *Pillar 2: Healthier* shifts away from traditional reactive and treatment-focused approaches towards a preemptive, population-based translational approach by changing the risk set-point. A key element is the acceleration of the translational pipeline to *prenatal* prevention, as earlier intervention has greater impact and lower costs (Bullock, 2015; Heckman, 2007).

2.1 | Why target prenatal psychosocial stress?

Prenatal psychosocial stress connotes maternal response to exposure to a stressful situation (including acute stressors and normative life transitions), which causes psychological and physiologic stress responses. Psychological or "perceived stress" reflects appraisal that this stressful exposure exceeds coping ability (Huizink & de Rooij, 2018; Lazarus & Folkman, 1984). A host of co-occurring adverse prenatal exposures have been linked to early emotion dysregulation and later psychopathology, and their prevention shares common elements (Clark et al., 2016; Dimidjian et al., 2016; Goodman et al., 2018; Lester et al., 2009; Urizar & Muñoz, 2011). Prospective studies demonstrate impact on both brain structure and function in offspring of mothers who experienced stress during pregnancy. This suggests that prenatal stress-reduction interventions have the potential to reduce the incidence of later psychopathology in children (Buss et al., 2012; Niehaus et al., 2019; Sandman et al., 2012).

2.2 | Personalized prevention as engine: a one-size fits all prenatal stress-reduction intervention may fall short for altering neurodevelopmental outcomes

Behavioral and physiologic responses to stress vary extensively by individual with concomitant variation in gestational environment. Thus, tailoring a stress-reduction intervention to maternal individual stress appraisal is more likely to significantly improve neurodevelopmental outcomes (Doyle & Cicchetti, 2018; Graignic-Phillippe et al., 2014). Personalizing delivery of content via a just-in-time

adaptive intervention (JITAI) may also boost outcomes as it is designed to address the "dynamically changing needs of individuals via provision of type and amount of support needed, at the right time, and only when needed" (Nahum-Shani et al., 2014). The proliferation of mobile and sensing technologies in health behavior intervention enables individualized action based on real-time information (Nahum-Shani et al., 2014; Spruijt-Metz, 2014). A personalized preventive approach requires stress monitoring that capitalizes on technological innovation, such as wearable sensors that measure objective stress experience using electrocardiograph (ECG) signals to capture heart rate-related predictors (Peake et al., 2018). We know of no personalized prenatal JITAI studies designed to impact neurodevelopment that leverage these emergent passive sensing technologies.

2.3 | Moving the dial: It takes a transdisciplinary scientific village

This shift to *Mental Healthier, Earlier* personalized prenatal prevention is designed to accelerate the transition from observational to experimental stress research towards alteration of neurodevelopmental outcomes. Engineering a scientific paradigm shift requires transdisciplinary integration enabling synthesis of highly disparate perspectives to unify around a common objective and drive innovation (Adler & Stewart, 2010; Mâsse et al., 2008; Rosenfield, 1992) (Figure 1).

To advance the study of stress, early experiences and developmental (SEED) science, we introduce the *Promoting Healthy Brain Project (PHBP)* Study as an exemplar of this approach. PHBP is a randomized trial testing our novel *Wellness-4-2* personalized prenatal intervention. In the sections that follow, we provide an overview of the Wellness-4-2 intervention and subsequent observation of offspring, followed by discussion of research opportunities and challenges regarding key components of the study: bio-integrated stress monitoring, tailored intervention, and neurodevelopmental assessment of mental health risk. Challenges are drawn from the extant science base, our prior experience on related studies, and where noted, lessons learned from our pilot study. Our work to this point also reveals exciting opportunities and directions for future research.

2.4 | Wellness-4-2: A personalized prenatal stress prevention approach

2.4.1 | Personalized prevention

The central tenet of Wellness-4-2 is that tailoring intervention delivery to maternal subjective experience of feeling stressed ('perceived stress") is most likely to improve fetal neurodevelopment. We are conducting a randomized controlled trial with 100 racially and ethnically diverse pregnant women, with 50% receiving the Wellness-4-2 personalized prenatal stress intervention and 50% in a stress monitoring comparison group. An overview of the PHBP study design is provided

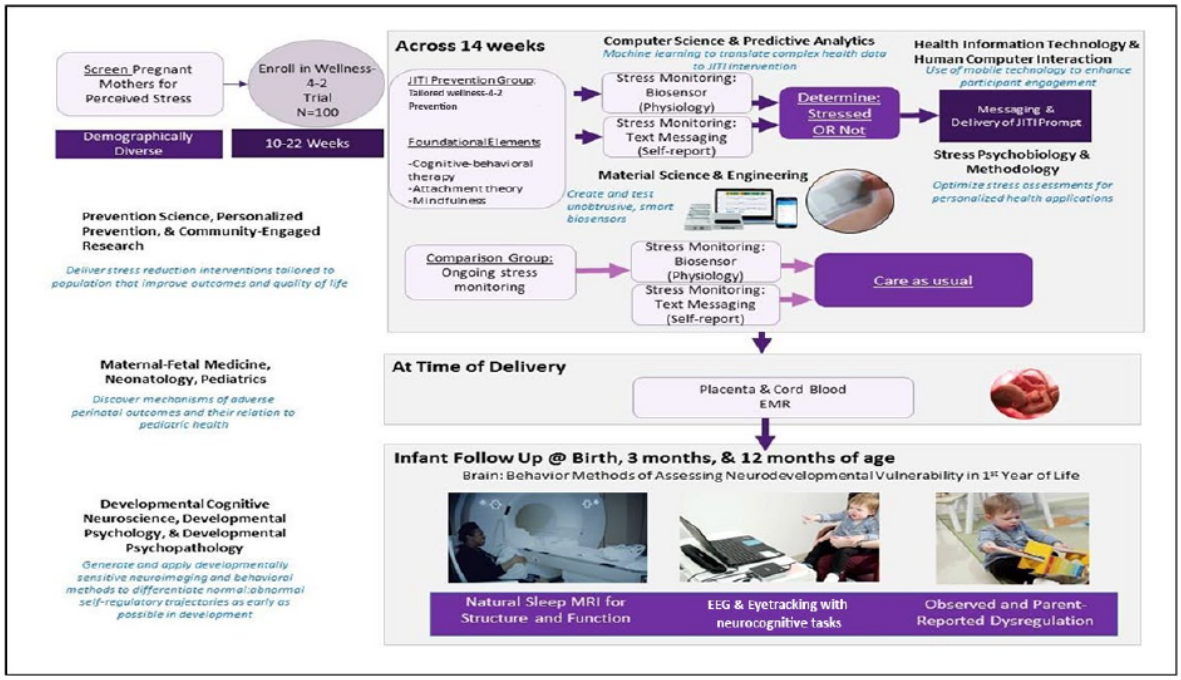

FIGURE 1 Overview of Promoting Healthy Brain Project (PHBP) Study Design. Participants' stress was monitored across a set 14-week period; Wellness-4-2 Prenatal Stress intervention sessions were flexibly scheduled to accommodate participants. Note. JITAI, just -in-time adaptive intervention; MRI, magnetic resonance imaging; EMR, electronic medical records

in Figure 1. Women are recruited at 10–22 weeks gestation and followed through their infant's 1st birthday. Real-time stress monitoring is conducted over a 14-week period and combines biologic and self-reported data. Wellness-4-2 is a JITAI adaptation of the well-validated *Mothers and Babies (MB)* prenatal distress reduction course (Muñoz et al., 2007). In addition to the 12 MB sessions, participants receive additional intervention via text messages (JITAI) when they reach a certain threshold of stress based on biologic or self-reported data. The threshold for biologic indication of stress was developed via machine learning. The JITAI are intended to reinforce key intervention content by promoting maternal practice of intervention skills learned in intervention sessions aimed at reducing stress. By providing mothers prompts to implement skills learned in relation to real-time experience of stress, these JITAI heighten maternal awareness of state in a manner tied to specific coping strategies learned in the intervention. The MB sessions are delivered within the 14-week stress monitoring period, with timing of MB completion individualized according to the participants' availability. Wellness-4-2's key neurodevelopmental outcome is infant trajectories of dysregulation assessed via brain and behavioral markers across the first year of life. Maternal–fetal specimens, including cord blood and placenta, are collected at birth as a potential mediating mechanism.

2.4.2 | Overview of intervention structure (prenatal)

The participants randomized into the Intervention group receive the 12-session Wellness-4-2 intervention starting in the second trimester of pregnancy and extending for as long as 14 weeks. The Wellness-4-2 intervention incorporates the MB intervention and JITAI delivered based on real-time bio-integrated stress monitoring. Stress monitoring is conducted over a set 14-week period that occurs after randomization and applies to both the intervention and control groups. Both ecological momentary assessments (EMA) of subjective stress collected via text message and heart rate data measured via unobtrusive wireless electrocardiogram (ECG) biosensor are used to indicate when a woman meets the "stressed" threshold as a prompt to receive a JITAI. The JITAI is delivered automatically via text message. JITAI content emanates from the most recent one-on-one MB intervention session and may consist of skills reinforcement, self-monitoring, and homework reminders. The Stress Monitoring (comparison) group does not receive the MB intervention or JITAI. However, all participants received ACOG (American College of Obstetrics and Gynecology) recommended standard of care. This includes perinatal depression screening at designated timepoints and referral to behavioral health resources, as well as a list of resources for perinatal wellbeing and mental health support. All study participants also receive a list of phone, text, web-based/remote, and in-person perinatal mental health services at the time of randomization that includes information from Postpartum Support International, National Suicide Prevention Hotline, NorthShore Perinatal Support, and Northwestern Memorial Women's Behavioral Health Clinic. Finally, comparison group participants also receive a seasonal newsletter via email that includes recommendations for stress-reducing activities (e.g., device-free walks).

Wellness-4-2's 12 MB sessions are delivered one-on-one by a trained interventionist through a flexible delivery schedule and modalities to accommodate individual participant needs, including delivery by phone, Skype, or in person. The original MB is a manualized intervention for maternal distress (i.e., mood and stress) tailored to needs/issues women experience during the perinatal period (Muñoz et al., 2007), based on both Cognitive Behavioral Therapy and attachment theory (Ainsworth et al., 1978; Lewinsohn et al., 1986), and provides a toolkit of behavioral, cognitive, and social support skills. We enhanced the MB intervention with mindfulness content for this study. The Wellness-4-2 MB intervention is divided into three sections: (1) Pleasant Activities; (2) Thoughts; and (3) Contact with Others. Participants receive skills training in each of the three sections, intended as a "toolkit" of approaches to improve/ manage stress and mood. The MB curriculum also emphasizes developing the parental bond with the baby. All sessions follow the same structure: (1) session topics with key points and a communication guide; (2) interactive learning activities; and (3) a personal project assignment.

2.4.3 | Post-Trial stress monitoring assessments

All participants complete assessments at set timepoints during the 14-week period and afterwards. Every month after the main 14-week stress monitoring period and before the child's birth, participants in both groups receive a week-long run of four daily EMA prompts to provide ongoing information about prenatal stress patterns. Upon completion of the MB sessions, participants are administered surveys/exit interviews about utility and feasibility of the intervention and/or stress monitoring protocol, including acceptability of the sensor and EMA.

2.4.4 | Maternal–fetal specimens (birth)

Placental tissue and cord blood plasma are collected immediately post-delivery using published biospecimen collection protocols: Placental tissues are sent for standardized gross and histopathology review (Mestan et al., 2009, 2017). These are conducted routinely by a perinatal pathologist masked to outcomes using established protocols based upon Amsterdam workshop criteria (Khong et al., 2016) and include assessment of presence and severity of placental lesions among four domains: acute and chronic inflammation, maternal vascular/villus pathology, and fetal vascular pathology.

2.4.5 | Assessment of infant dysregulation (0–1, 7–9, and 12 months)

We use well-validated performance-based assessments of regulation, surveys assessing affective and other regulatory functions and

developmental functioning, and assessments of nascent executive function and emotion processing via eye tracking. Direct observations of parent–infant interactions provide an indicator of the impact of the intervention on maternal parenting behavior. (Note: Our original design included neonatal, 3 and 12 month time points. However, COVID-19-related disruptions necessitated a shift from a 3 month to a 7–9 month timepoint.) At 12 months, developmentally sensitive clinically informative interviews (adapted for administration at age 1 year) are administered to assess dysregulatory symptoms and interference with developmental functioning (Egger & Angold, 2004; Wakschlag, et al., 2019). MRI and EEG are used to assess brain structure and function linked with infant dysregulation (see Table S1). We have also obtained funding to conduct a 24 month follow-up to obtain clinical outcomes via the PAPA gold standard interview, which has established the validity of internalizing and externalizing syndromes at toddler age (Egger & Angold, 2004) along with the Early Childhood Irritability Related Impairment Interview (E-CRI; Wakschlag, et al., 2019).

2.4.6 | Pilot study

We conducted a pilot study to guide the JITAI for Wellness-4-2 personalization of the validated Mothers and Babies (MB) prenatal intervention and to provide preliminary data on acceptability and feasibility of Wellness-4-2. Seventeen women were recruited from prenatal clinics affiliated with a large urban university-based hospital in the U.S. Midwest. They were racially and ethnically diverse (41% White, 24% Asian, 18% non-Hispanic Black, 12% Hispanic, and 6% other), mostly married (94%), working full-time (82%) and educated (all had at least a college degree). Their household income ranged from $45,000/year to $350,000/year with 65% reporting income >$100,000/year. We used pilot data to inform: (1) development of algorithms for real-time stress monitoring based on biosensing and EMA data to determine timing and frequency of JITAI in the main trial; (2) refining the inter-session JITAI prompting skills reinforcement, self-monitoring, and homework reminders; and (3) integrating standardized mindfulness content into MB to enhance its stress-reduction qualities. The participants received five EMAs per day for 12 weeks to assess subjective stress using twelve questions commonly used to assess perceived stress, including the Perceived Stress Scale (PSS-4; Cohen et al., 1983). Participants were trained in the use of the BioStamp sensor (https://www.nature.com/articles/s41746-018-0023-7), which they were asked to wear during waking hours for the duration of the pilot study (12 weeks). Based on additional in-lab studies, participant preference for the Biostamp flexible sensor to wrist- and chest-based equivalents was established (King et al., 2019). During the pilot, all participants were offered the 12 MB sessions. Of the 17 participants, 13 (76%) completed all intervention sessions, three withdrew from the study (2 before starting the intervention and one before the completion of the intervention sessions) citing study burden as the reason for withdrawal. A fourth woman became lost to follow up after completing 2 MB intervention sessions. Participants across the pilot study received an average of 4.5 MB sessions in person and 7.5 sessions over the phone. Participants were asked to provide online feedback about the intervention at the end of each session. Because the stress detection algorithm was being developed as part of the pilot study, participants received the text-based interventions on a fixed interval, every other day, rather than just-in-time (JITAI) based on their individual stress level. Survey assessments occurred at baseline, immediately post-intervention, 1 month before due date, and 1 month after birth. An exit interview was also conducted to assess pilot participants' experiences with the BioStamp, the EMAs, and the adaptive intervention. We will integrate results from the pilot study that relate to the challenges and opportunities presented below to provide an enhanced perspective on the rationale for the PHBP Study.

3 | RESEARCH CHALLENGES/ OPPORTUNITIES FOR PERSONALIZED PRENATAL INTERVENTION TO ALTER NEURODEVELOPMENTAL RISK

3.1 | Bio-integrated approach to stress monitoring: Foundation for Personalized prevention

The Promoting Healthy Brains Project (PHBP) Study capitalizes on technological innovation by incorporating flexible wearable sensors to establish objective measures of stress. These sensors require advanced signal processing and machine learning methods to mitigate noise from the signals generated in the real-world and to infer moments of stress in a personalized way.

3.1.1 | Overview: Biosensing and health monitoring

Classes of health monitoring systems consist of biosensors that measure one or at most a few digital biomarkers. These wearable systems primarily include non-invasive monitoring devices (e.g., ECG monitors) or wrist-worn accelerometers, (e.g., activity trackers), which offer key insights about biophysical activity. However, the wired connections, straps, and bulky electronic modules represent significant limitations that prevent broad-scale deployment on different body locations. This limitation is even more salient to special populations since conventional monitoring devices are largely incompatible with the more sensitive skin of pregnant women and infants. Advances in flexible biosensor designs, mechanics, and manufacturing processes have helped lay the foundations for novel classes of skin-interfaced wearable systems that enable multimodal sensing at nearly any body location in real-world settings. Intimate coupling with the skin across different body positions (including the abdomen and limbs), are possible with minimal discomfort to the wearer. This contributes to improved compliance over the course of long duration wear cycles compared to conventional health monitoring systems.

3.1.2 | Need for sensor analytics

Specifying when and how often pregnant women feel stressed will ultimately improve ability to design effective personalized interventions that potentially mitigate and ultimately reverse the effects of stress on neurodevelopment. Machine learning is showing promise for building a data-driven approach to detecting stress from wearable sensors. Because there currently exists no ground truth for the measurement of physiologic stress, models must be built from stress induction in-lab. Further complicating this process, is that little is understood about the intersection of self-reported- and physiologic stress and how this relationship may differ in the context of the altered metabolism of pregnancy. Here we identify challenges and opportunities associated with advancing the ability to accurately detect bio-integrated stress signals in a real-world intervention. Below we discuss sensor and data analytic challenges and opportunities to advance our ability to detect and intervene upon stress in real time as a key building block of the Wellness-4-2 approach, building on our pilot study (Table 1).

3.1.3 | Sensor analytics challenge 1

Ensuring wearable sensor and user compliance

Since wearable biosensors are relatively new, it is challenging to achieve reasonable adherence to sensor wear over an extended period within research protocols. Watches and bandages are the most natural forms of wear but are still challenging for sustained use. Validation of participant compliance is also needed to determine study fidelity.

In the pilot study, we assessed burden related to wearing the biosensor using the User Burden Scale (Suh et al., 2016). Higher scores on this scale indicate higher burden on five subscales (difficulty of use, physical burden, time and social burden, mental and emotional burden, and privacy concerns). Within the pilot sample, average scores showed indicated that participants generally experienced low burden and high levels of comfort with the Biostamp: (1) Difficulty of Use ($M = 0.63$, $SD = 0.66$); (2) Physical Burden ($M = 1.4$, $SD = 1.31$); (3) Time & Social Burden ($M = 0.40$, $SD = 0.93$); (4) Mental & Emotional Burden ($M = 0.23$, $SD = 0.36$); (5) Privacy concerns ($M = 0.17$, $SD = 0.32$).

TABLE 1 Challenges and opportunities in developing sensor analytics for just-in-time adaptive interventions (JITAIs)

Challenge	Opportunity
1. Ensuring wearable sensor compliance and ability to validate participant compliance with intervention	1. Design unobtrusive and privacy-preserving sensors and test methods to improve and validate adherence
2. Lack of wearable sensor-based models that automatically predict perceived stress in real-world settings	2. Develop cold-hot models (generalized models that become personalized) that map physiology to perceived stress response and can adapt to changes in pregnant women's perceived stress response
3. Limited understanding of predictors (objective and subjective) physiologic manifestations of stress in different populations and how to establish ground truth of physiologic stress in real-world settings	3. Determine relationship between physiological manifestation of stress and perceived levels of stress and health outcomes in prenatal population and identify clusters/groups of pregnant women that manifest stress in a detectable manner (e.g., facial expressions, changes in skin conductivity across the body, heart-rate, analytes); understand how physiology agrees with self-reported stress, and design sensors that can estimate blood pressure when people are moving in the real-world
4. Limited understanding of best modes (including EMA compliance) and times of day of remote delivery of mindfulness-based interventions after a stressful episode	4. Identifying novel and personalized methods of remote intervention delivery (e.g., using environment, wearable sensor, and methods with fewer questions and quick glance/tap method) and develop/text micro-randomized trials to determine the ideal intervention time post occurrence of stress (i.e., taking into account duration of stressful episode, surrounding context, participant lifestyle)

Abbreviations: JITAI, just -in-time adaptive intervention.

During an exit interview, we queried pilot participants about wearability and usability of the sensors ($n = 10$ respondents). When asked to rate how likely they would be to wear the Biostamp during daily activities (on a 5-point scale from extremely unlikely to extremely likely), six of the 10 participants said they would be likely or extremely likely to do so, one was neutral, one said unlikely, and two said extremely unlikely. Participants reported very little impact of wearing the biosensor on their daily life. The responses suggest significant variability in participants' experience of discomfort with the sensor, however, particularly during specific activities (e.g., exercise). Data from the pilot study indicated that multiple participants exhibited skin irritation after prolonged use. As a result, we adapted our protocol for the RCT to reduce sensor wear to the minimum needed to determine physiologic stress (i.e., 2 weeks on/1 week off). Participants in the RCT are also instructed to take a break from sensor wear if they experience physical discomfort. To determine adherence, ECG and accelerometry signals determine signal quality and wear time (Zhang et al., 2018).

3.1.4 | Sensor analytics opportunity 1

Design unobtrusive sensors and test methods to improve and validate adherence

Wearable biosensing systems that interface with the human skin have fundamentally changed the way devices are deployed in remote ambulatory settings. However, the design and validation of these novel skin-interfaced devices requires significant electromechanical and on-body testing. Clinical field tests provide crucial feedback loops for engineers to iterate on designs that are not only comfortable, but also address significant human factor challenges in terms of usability, application/removal instructions, and compliance (Heikenfeld et al., 2018). Moreover, it is critical to study participant irritation with devices, and to take precautions to ensure participants have a positive experience (Alshurafa et al., 2018). In order to build models that detect physiologic stress, studies like PHBP allow us to test acceptability and adherence of an unobtrusive wireless ECG sensor (Biostamp) that is soft, flexible, and worn on the chest using a medical-grade adhesive for continuous monitoring of raw ECG data and accelerometry (i.e., 24+ hr of continuous wear). It can be worn under typical conditions with minimal intrusion (e.g., replacing adhesive, charging). The Biostamp family of devices, including the BiostampRC (used in the pilot study) and nPoint (next generation used in the Wellness-4-2 trial) have been used in several clinical studies. The Biostamp nPoint is FDA-approved for use in clinical trials.

3.1.5 | Sensor analytics challenge 2

Lack of wearable sensor-based models that automatically predict perceived stress in real-world settings

Extant stress models using wearable sensors to capture respiratory inductive plethysmography and ECG signals have been built from artificial in-lab stressors, such as socio-evaluative challenges (preparing and delivering a speech), cognitive (performance on mental arithmetic tests), and physical (cold pressor test) stressors. However, these predict in-lab induced stress, and then link these stressors to perceived stress. This does not capture the variability of the physiologic response that occurs in response to real-life stressors that are multifaceted and induce stress in varying doses across people (Hovsepian et al., 2015; Plarre et al., 2011).

3.1.6 | Sensor analytics opportunity 2

Develop generalized models (stress algorithms) that map physiology to perceived stress response and can adapt to changes in pregnant women's perceived stress response

Very limited research exists that tests the ability to detect perceived stress in pregnant women using physiological responses. We performed lab-based stress induction (e.g., Trier Social Stress Test; Kirschbaum et al., 1993), using novel approaches to stress assessment that have been shown to be efficacious in pregnant and maternal populations (e.g., parenting stress related to infant crying; Out et al., 2010). To further understand the relationship between physiological and perceived stress, we built two separate stress detection models. The first was based on physiology (Physiologic Stress algorithm) and the second was based on self-reported responses from daily EMA self-reports (EMA Stress algorithm using Cohen's Perceived Stress Scale; PSS-Q4; Cohen et al., 1983, see Figure 2). We then integrated the two algorithms to build an Integrated Stress model that serves as a bio-integrated indicator of maternal stress.

To determine physiologic stress, we applied a machine learning algorithm called the Support Vector Machine (SVM; Cortes & Vapnik, 1995) using pre-pilot data collected from an in-lab stress induction protocol to build a minute-level stress detection model. To build the model, stressful activities were separated by non-stressful activities of rest, conversation, and eating (King et al., 2019). In preparation for JITAI interventions in Wellness-4-2, a physiologic stress algorithm was designed using the machine-learned model to calculate the total minutes of stress throughout the day. For the EMA-based perceived stress algorithm, participants who scored above the population average of 4.7 (Cohen et al., 1983) were perceived to be stressed for that day and to warrant an intervention (stress-reduction) prompt. For bio-integration, we then combined the two predictors in an "OR" model, where an intervention prompt was deployed to the participant if the pregnant women were physiologically stressed or reported high stress perceptions. This ensured that the model would work if one of the data sources was missing. Since it is unknown whether to intervene based on physiologic or perceived stress, we modified our algorithm to be able to intervene on both physiologic and/or self-reported stress. Current models used in Wellness-4-2 are generalized. However, data collected over the course of the Wellness-4-2 trial will allow us to see whether cold-hot models (generalized models that become personalized over time as data are collected), will improve the stress detection

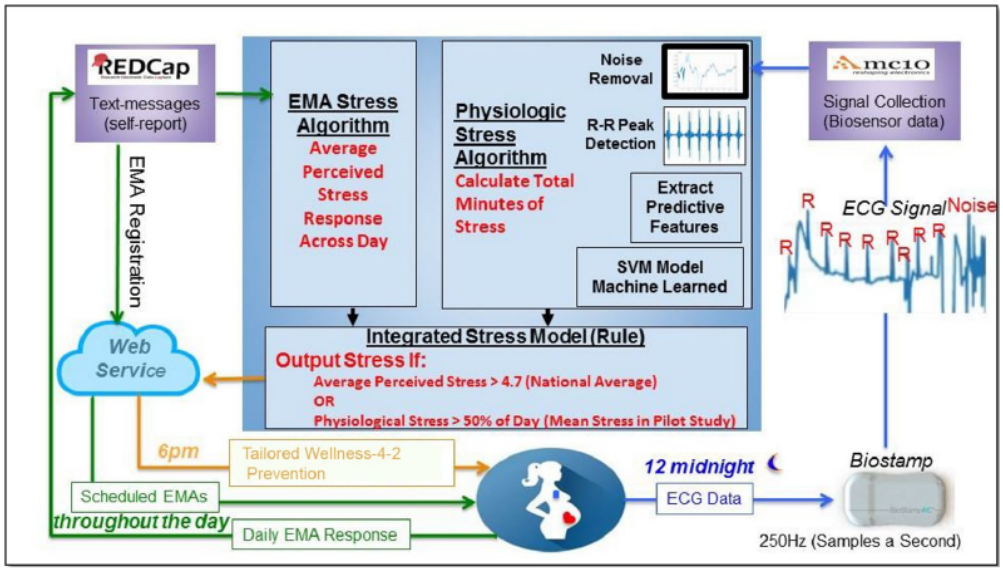

FIGURE 2 Overview of Promoting Healthy Brain Project (PHBP) Stress Detection Model. Note. EMA, Ecological Momentary Assessment; SVM, Support Vector machine; ECG, Electrocardiogram; R-R-Peak, Inter-beat interval between PQRST waves

algorithm and mapping between physiological and perceived stress data. During the pilot study, we found an average value of 4.68 for daily perceived stress (close to the national cut-off for high stress). An average of 49.9% of total minutes of activity logged throughout the day were estimated as physiologic stress from our algorithm (see also Figure S1a,b). Thus, as implementation for the Wellness-4-2 trial, we set 4.7 as the daily average cut-off for determining EMA-based perceived stress (in agreement with the national average), and 50% (greater than or equal to) of the minutes during the day as a cut-off for determining a physiologically stressful day. We analyzed the slopes across time during the intervention, comparing the percentage of physiological stress and perceived stress from participants in the pilot study. This shows that *over time* there is agreement in trends across days between physiologic and perceived stress. For example, of the 11 women that provided sufficient data between sensor and self-report to be analyzed, eight showed agreement in slope between physiological and perceived stress, nine showed a decrease in physiological stress over time, and seven showed decreases in self-reported stress over time. Thus, at a macro-level the two metrics showed agreement. In contrast, on a micro- or *daily* level, the two methods did not correlate. This shows that further research is needed to investigate the relationship between physiologic and self-reported stress in real time.

3.1.7 | Sensor analytics challenge 3

Limited understanding of the population variability in predictors (objective and subjective) and establishment of ground truth of physiologic stress in real-world settings

One of the main challenges in characterizing physiologic stress for clinical application is high variability in its manifestation. Some people sweat when they are stressed, while others experience an increase in heart rate variability or respiration rates. Some people show signs of stress from their facial expressions, while others do not.

3.1.8 | Sensor analytics opportunity 3

Determine clusters of pregnant women that manifest stress in a detectable manner

Developing machine learning models that predict perceived stress based on real-world data is feasible, because people can self-report their feelings of stress using EMAs. However, physiologic stress is a challenge to validate in real-world settings, because there is currently no gold standard approach to measure stress in a population that is unobtrusive, wearable, and automated. Capturing how physiological measures manifest in pregnant women (e.g., facial expressions, changes in skin conductivity, heart rate) will enable reliable methods to detect stress in real-world settings. This will allow us to build more reliable machine learning models customized for prenatal stress prevention. Blood pressure is perceived to be a validator of physiologic stress in the real-world. However, a wearable that provides continuous reliable estimates of blood pressure in free-living populations is not currently available. There is also no robust evidence base on the concordance of physiological and reported stress. This gap constrains JITAI applications, which rely on a clear indicator of when adaptive intervention is needed. Based on heart rate and ECG data and in-lab stress induction, our physiologic stress model acts as our PHBP ground truth of physiologic stress in real-world settings. This lays the groundwork for future work to test other validators of physiologic stress (e.g., facial expressions, skin conductance,

and blood pressure), as reliable technology feasible for use in the real world becomes more available.

3.1.9 | Sensor analytics challenge 4

Limited understanding of best modes (including EMA compliance) and times of day of remote delivery of stress-reduction interventions after a stressful episode

It is unrealistic to assume that people will wear any sensor every day all-day and/or respond to EMA queries with high frequency. Problems due to sensor wear and response bias may also exacerbate measurement error. Thus, stress reduction algorithms are needed that mitigate error variance within and across stress monitoring modes.

3.2 | Sensor analytics opportunity 4

Identifying novel and personalized methods of remote intervention delivery

Due to the high error associated with single measures of stress, a daily measure of stress is needed to ensure reliable intervention delivery. Knowing when to intervene and whether participants are "available" to receive intervention is critical (Klasnja et al., 2015). Our PHBP study allows us to identify the times participants are most likely to respond to EMAs and JITAI interventions using our Configurable Assessment Messaging Platform for Interventions (CAMPI) system, CAMP1 relies on short message service (SMS) to deliver both assessments and interventions, so participants can use their own smartphone without the need to download applications. The CAMPI system is built to integrate with REDCap, a widely used data collection platform (see Figure S2) (Harris et al., 2009). The system also allows us to determine when participants engage with the text messages and EMAs sent to them, allowing us to estimate times of day when pregnant women are most likely to be available.

Data from our pilot study importantly informed our approach. For EMA responsiveness, we found a daily average response rate to the text messages of 2.35/5 (47%) with a standard deviation of 1.36 over 12 weeks (84 days). Importantly, response rates started lower (about 1.5/5 per day), quickly increased to 3.71/5 per day (74%) and then slowly tapered off toward the end of the pilot study. The minimum response needed for the algorithm to work properly is two responses per day. Based on this, we determined that we would be able to maintain ≥the 2 responses necessary by sending four text messages daily. Further, over the 12-week duration of the intervention, participants wore the BioStamp for an average of 5.1 hr/day (SD = 2.7 hr), which was sufficient for the algorithm to work. We also asked participants questions about usability of the smartphone surveys (n = 10 respondents). In terms of acceptability of the number of EMA surveys they received each day, seven found it slightly unacceptable, one was neutral and one found it acceptable. Based on exit interviews, participants were more accepting of four EMAs a day, and as a result we reduced the number of EMAs for the RCT to reduce burden (from five to four), which still would provide sufficient variability of stressors throughout the day. To further enhance engagement, we modified compensation based on adherence to EMA responses and provided weekly adherence messages (e.g., "Well done! You have reached your goal every day this week for responding to EMAs"). Data from the larger PHBP study will further optimize the number and times of day with which EMAs are delivered to participants by shedding light on times of day where participants are most available to respond to study material, as well as on changes in stress response across EMAs throughout the day. Based on our experience in the pilot study, the PHBP JITAI are delivered the day after (rather than same day) stress is detected by the bio-integrated algorithm at the end of each day. This was based on lessons learned from the pilot study that participants were less receptive to an intervention prompt at the end of the day. Based on feedback, we standardized receipt time for intervention prompt delivery as 6 p.m. the day after high stress was detected.

3.3 | Tailoring the MB Framework for just-in-time adaptive intervention (JITAI)

MB is a widely used prenatal preventive intervention. It has demonstrated efficacy in preventing pre-perinatal distress, and worsening of postpartum depression through a series of randomized controlled trials in prenatal and pediatric care and home visiting settings including group and individual formats (Le et al., 2011; Muñoz et al., 2007; Tandon et al., 2011, 2014, 2018; Urizar et al., 2019; Urizar & Muñoz, 2011). The Wellness-4-2 adaptation of MB provides an exciting opportunity to augment the core MB intervention with JITAI content that is personalized based on real-time stress response and enriched for mindfulness. There are several challenges and opportunities for innovations associated with this adaptation (Table 2).

3.3.1 | Tailoring MB intervention challenge #1

Appropriate identification of participants needing JITAI content in real time

Accurate detection of prenatal stress is essential for deploying just-in-time content. Relatively poor correspondence across measurement levels is a particular challenge for a bio-integrated stress detection approach. Indicators of physiologic stress are affected by other aspects of an individual's health status. Self-reports of perceived stress provide accurate representations of subjective experience but may be biased by maternal mental health (Najman et al., 2000). By integrating biologic and self-report indicators of

TABLE 2 Challenges and opportunities in mothers & babies (MB) tailoring for wellness-4-2 JITAI

Challenge	Opportunity
1. Appropriate identification of participants needing JIT content	1. Wellness-4-2 uses both self-reported perceived stress (via EMA responses) and physiologic stress (via biosensors)
2. Ensuring adequate delivery of core MB content to determine when additional JIT content is warranted	2. MB 1-on−1 allows for flexible delivery in terms of number of sessions delivered at a time and modality of delivery (e.g., in-person, phone). This flexibility is emphasized in Wellness-4-2 to ensure that core MB content is received by participants. By doing so, we will be able to determine whether MB content—augmented with JIT material—is associated with improvements in maternal self-report of distress
3. Prior research suggesting heterogeneity of participant response to MB intervention	3. Despite MB's efficacy overall, some participants do not respond as well to the MB intervention. By assessing stress and emotions multiple times per day, Wellness-4-2 will allow for precise identification of these "non-responders" which can help guide future MB (and other intervention) trials with perinatal populations
4. MB efficacy data have largely focused on maternal mental health outcomes	4. Wellness-4-2 will follow the mother-baby dyad until 2 years after birth, therefore allowing for examination of the impact of a prenatal preventive intervention on both maternal mental health and infant neurodevelopment outcomes

Abbreviations: JITAI, just -in-time adaptive intervention.

stress, stress algorithms can leverage unique information provided by each source and reduce error.

3.3.2 | Tailoring MB opportunity #1

Wellness-4-2 integrates self-reported perceived stress (via EMA responses) and physiologic stress (via biosensors) to tailor JITAI content

Wellness-4-2's bio-integrated robust approach to stress monitoring is an innovative effort to increase likelihood of improving the gestational environment and concomitant neurodevelopmental trajectories. However, it is not yet known what source and combination of personalized information is critical for this purpose. Importantly, while PHBP is complex and comprehensive, it is intended to determine feasibility and to establish whether employing a bio-integrated JITAI approach improves neurodevelopmental trajectories. It is not designed to test the incremental utility of this approach relative to traditional MB, a crucial next step for a multi-arm trial. Should Wellness-4-2 prove effective at altering neurodevelopmental outcomes, a critical next step towards scalability will be optimization trials. These are necessary to advance scalability, e.g., to determine the lowest burden approach to stress monitoring for personalization with adequate intensity for achieving desired outcomes (Glasgow, 2013). For example, should there be high concordance between stress detected by biosensor and self-report on average across the RCT, future trials would be able to confidently rely on self-report data for personalization.

3.3.3 | Tailoring MB challenge #2

Ensuring adequate delivery of core MB content to determine when additional JITAI content is warranted

Pregnant women in the Wellness-4-2 trial are receiving 12 brief MB intervention sessions focused on stress management techniques. Perinatal women with distress are less likely to engage in intervention than women in the general population and evidence of varied rates of intervention completion in prior trials (Dennis & Chung-Lee, 2006; O'Mahen & Flynn, 2008; Tandon et al., 2018). These are recognized barriers to adequate intervention delivery which create a conundrum. If study participants do not receive the full dose of the MB intervention, they may be *more* likely to experience elevated stress, but *less* likely to receive tools and JITAI content to help alleviate stress. Thus, flexible approaches are needed to increase the likelihood that study participants receive the full dosage of the MB intervention along with just-in-time content to bolster information uptake.

3.3.4 | Tailoring MB opportunity #2

MB 1-on-1 allows for flexible delivery in terms of number of sessions delivered in one session and modality of delivery

Although flexible delivery has been a hallmark of the MB intervention, we have more fully embraced the notion of flexible intervention delivery in Wellness-4-2. Specifically: (*1*) facilitators

are on-call at the time of randomization to deliver the first session while the participant is onsite or remotely within 24 hr; (2) MB sessions can be coordinated with prenatal visits; (3) sessions are offered by phone or video (e.g., Skype) to fit with participants' schedules and preferences; and (4) intervenors have flexibility to condense multiple sessions into a single delivery point.

3.3.5 | Tailoring MB challenge #3

Heterogeneity of response to MB intervention

Prior studies have shown reductions in maternal distress in MB intervention participants, but with differential responsiveness patterns. Recognition that a "one size fits all" approach may not meet the needs of an entire study population signals the need for an adaptive intervention design in which women not responding to core intervention content (expressed as elevated levels of stress) may benefit from additional just-in-time material.

3.3.6 | Tailoring MB opportunity #3

Wellness-4-2 will allow for precise identification of intervention "non-responders"

An important step in the JITAI approach is identifying women who do not appear to be responding to the intervention in real time. Non-response to the intervention may be due, in part, to participants' limited practice and use of MB skills between sessions. The use of biosensors and EMAs can assist in identifying women who have elevated stress despite receipt of MB content. In doing so, the present study lays the foundation for addressing non-response in real time with additional just-in-time content to "non-responders." In this scenario, just-in-time content can help to reinforce key MB content and/or encourage the practice of MB skills between intervention sessions. Enabling JITAI content to be delivered on a selected, rather than universal, basis has considerable resource implications for intervention studies. In Wellness-4-2, we are employing the bio-integrated stress algorithm described above to identify participants with increased need for intervention and/or specific MB intervention content areas needing reinforcement. Following elevated stress detection, participants receive a text message related to the most recent MB session, focused on content reinforcement and encouragement to practice new skills and mindfulness. This approach allows for adaptive intervention delivery tailored to individual needs of pregnant women whose stress levels require additional management. These dose-response data, combined with an extensive baseline assessment battery and a comparison stress monitoring condition, will inform understanding of participant factors related to intervention responsiveness.

3.3.7 | Tailoring MB challenge #4

MB efficacy data have largely focused on maternal outcomes

Previous MB RCTs have focused primarily on short-term effects on maternal distress although there is preliminary evidence of longer-term impact on parenting and child outcomes (McFarlane et al., 2017; Urizar & Muñoz, 2011). The limited focus on parenting and child outcomes developing in previous trials is, in part, a function of funding mechanisms with timeframes that constrain longitudinal follow-up and disciplinary divides placing varied emphasis on maternal versus child outcomes.

3.3.8 | Tailoring MB opportunity #4

Wellness-4-2 allows for examination of the impact of a prenatal preventive intervention on both maternal distress and infant neurodevelopmental outcomes

In recognition of the powerful impact of the gestational milieu on infant neurodevelopment outcomes (Brown et al., 2020), this multifaceted project explicitly focuses on examining the impact of a preventive stress-reduction mental health intervention delivered during pregnancy on postnatal outcomes for both mother and child, with state-of-the-art neurodevelopmental outcomes. We also assess the broader, multifaceted construct of "prenatal maternal distress," reflecting a broader range of maternal emotional states and experiences that impact wellbeing negatively. Distress encompasses a range of psychological stressors (pregnancy-specific and general), and exposure to stressors (e.g., acute and historical life events), emotional distress (e.g., depression and anxiety), and stressors prevalent in minority populations (e.g., discrimination stress) (Emanuel & St. John, 2010; Huizink & de Rooij, 2018; Turner, 2013) (see Table S2). This will be important for shedding light on the impact of Wellness-4-2 within the context of mothers' broader stress profiles.

3.4 | Targeting infant neurodevelopmental vulnerability to mental health problems

The central objective of the PHBP Study is reduction of infant neurodevelopmental vulnerability to subsequent mental health problems, as measured by alteration of stress-related dysregulation trajectories. The current state of the science offers a tremendous window of opportunity along with challenges in advancing a translational Developmental Origins of Health & Disease (DOHAD) agenda in the mental health arena (Table 3).

TABLE 3 Challenges and opportunities in detecting impact of Wellness-4-2 on reduction of neurodevelopmental vulnerability to mental health problems during infancy

Challenge	Opportunity
1. Mental health frameworks have traditionally not been applied to babies	1. Accelerate capacity to detect prenatal intervention effects on mental health risk in close proximity to intervention delivery and identify malleable targets at the very early phase of the clinical sequence
2. Mechanisms at the maternal-fetal interface in stress-related neurodevelopmental research are poorly understood	2. Elucidating mechanisms by which maternal prenatal stress affects fetal and neonatal health will serve as a mechanistic bridge between exposure and neurodevelopment
3. Few neuroimaging studies have emphasized engagement of culturally diverse populations, especially in longitudinal studies	3. Melding neuroscientific and community-engaged approaches can generate culturally sensitive protocols to enhance representativeness of neurodevelopmental research
4. Knowledge to Action (KTA) Gap: Robust evidence links' adverse exposure and mental health risk but unknown whether improving the fetal environment will reduce risk	4. Closing the KTA gap: Demonstrate causal relation via experimentally altering gestational environment and specify those features of dysregulation that are malleable to prenatal intervention

3.4.1 | Neurodevelopment challenge #1

3.3.1.1. Mental health frameworks have not traditionally been applied to the first year of life

Historically, a major impediment to altering the developmental origins of mental health problems has been a reliance on DSM frameworks that (1) are categorical and relatively uninformative mechanistically; and (2) preclude or discourage identification of common exposure-related syndromes in children <age 6 (Wiggins et al., 2020). This clinical:developmental divide presents major translational challenges (Calkins et al., 2019; Morris et al., 2020; Wakschlag et al., 2010).

3.4.2 | Neurodevelopmental opportunity #1

Accelerate capacity to detect prenatal intervention effects on mental health risk in close proximity to intervention delivery

Our approach conceptualizes clinical phenomenology as a developmentally unfolding transdiagnostic risk spectra within a developmental origins perspective in early life, emphasizing nascent self-regulatory structures and processes that have been robustly linked to adverse prenatal exposure (Casey et al., 2014; Graham, Pfeifer, Fisher, Carpenter, et al., 2015; Graham, Pfeifer, Fisher, Lin, et al., 2015; Wakschlag et al., 2018). This is conceptualized as *probabilistic* risk of subsequent mental health problems (Beauchaine & Cicchetti, 2019; Doyle & Cicchetti, 2018; Finlay-Jones et al., 2019; Luby et al., 2019; Wakschlag, et al., 2019). Precisely assessing neurodevelopmental vulnerability to mental health problems requires a transdiagnostic approach, potentially allowing for earlier and more effective preventive intervention with population health impact (McGorry & Nelson, 2016; Smith et al., 2019; Walkup et al., 2017). Its characterization rests on a neurodevelopmental phenotype that is dimensional, developmentally meaningful, and measurable in very young children and has coherence with clinical phenotypes at older ages.

In PHBP, we focus on emotion dysregulation as the optimal neurodevelopmental phenotype for assessing vulnerability to mental health problems as it is (a) measurable beginning at birth; (b) ubiquitous across most internalizing and externalizing disorders; (c) associated with corollary prefrontal disruptions; and (d) strongly linked to prenatal stress exposure from early in life (Beauchaine & Cicchetti, 2019; Davis et al., 2018; Finlay-Jones et al., 2019; Hartman et al., 2019; Wakschlag, et al., 2019) (see Table S1 for multi-level

measurement specifics). In particular, we have emphasized atypical expressions of irritability as our central behavioral phenotype because it is a highly salient pattern identifiable in very young infants that is a transdiagnostic risk marker (Toohey & DiGiuseppe, 2017; Wakschlag, et al., 2019). We draw on a suite of tools we have developed to assess the normal:abnormal spectrum of irritability within developmental context including the Multidimensional Assessment Profile of Disruptive Behavior (MAP-DB) survey, the Disruptive Behavior Diagnostic Observation (Schedule) DB-DOS standardized observation, and the Early Childhood Irritability-Related Impairment Interview (E-CRI) (Wakschlag et al., 2008, 2012; Wakschlag, et al., 2019). We have coupled this behavioral phenotype with measures of the structure, function, and connectivity of the neural circuitry linked to prenatal stress exposure and emotion dysregulation. This neural circuitry, including the amygdala and prefrontal cortex, exhibits reduced grey matter volume (Buss et al., 2012), elevated responses to emotional stimuli (Niehaus et al., 2019), and augmented functional coupling (Graham, Pfeifer, Fisher, Carpenter, et al., 2015) in children that experienced prenatal stress. Since these neural markers may also indicate transdiagnostic risk for later psychopathology (Buss et al., 2010; Snyder et al., 2017), determining the impact of prenatal intervention on this neural circuitry and its development over the first year of life has broader implications for neurodevelopmental vulnerability to mental health problems. Lastly, nascent executive function, which plays a key role in modulation of emotion (Nigg, 2017), will be assessed using eye-tracking methods especially suited for infants because they obviate the need for behavioral response (Krogh-Jespersen & Woodward, 2018).

3.4.3 | Neurodevelopmental challenge #2

3.3.3.1. Lack of integration between maternal–fetal mechanisms of stress exposure and neurodevelopmental vulnerability impedes translation (DiPietro et al., 2015; O'Connor et al., 2019)

Assessment of maternal and fetal measures, and important intermediates, such as placental regulation and cord blood sampling, can elucidate mechanisms by which prenatal stress reduction may improve the fetal environment and subsequent neurodevelopmental health of the offspring. To date, maternal–fetal mechanistic studies have largely been conducted in animal models, are observational, not linked to mental health, and suffer from disciplinary divides (DiPietro et al., 2015; O'Connor et al., 2019). Maternal and fetal heart rate and motor parameters are linked, suggesting that experimental reduction of stress-related arousal would positively impact gestational health (DiPietro et al., 2015). The fetal programming model holds that the fetus adapts to in utero exposures, impacting the development of later health and disease (Glover et al., 2018). The impact of maternal stress on fetal pathophysiology may include: stress physiology, alterations of placental biology and function, inflammation, and changes in microbiota (Hartman et al., 2019; O'Connor et al., 2019).

Practical challenges of research at the maternal–fetal interface include the time-sensitive nature of collecting and processing samples for current and future assays. Collection of cord blood and placental tissues, in particular, requires effective integration of outpatient prenatal tracking with inpatient labor and delivery teams, requiring close collaboration with investigators in obstetrics, maternal–fetal medicine, and pediatrics. With the vast expansion of big data technology and next gen sequencing approaches, the opportunities for biomarker discovery in placental tissues, maternal and fetal blood have grown. Therefore, strategic planning is critical for targeting the most relevant biomarkers and optimal strategies for archiving samples for future study (Baqui et al., 2017). Thus, a continuous cycle of basic science coupled with translational research, leveraging interventional trials, is key to advancing clinical applications of DOHAD.

3.4.4 | Neurodevelopmental opportunity #2

Perhaps the timeliest opportunities for biomarker and pathway discoveries at the maternal–fetal interface are through recent developments in metabolomics (Fanos et al., 2013; Papadopoulou et al., 2019), proteomics (Tarca et al., 2019; Vora et al., 2019), RNAseq and transcriptomics (Jóźwik & Lipka, 2019). These platforms are promising for identifying novel biochemical, genetic, and epigenetic targets that may play a role in causal pathways between maternal perceived stress, fetal brain development, and neurodevelopment. Outcomes encompassing neuroendocrine physiology, immune state, and microbiome are proximal to the gestational environment and can potentially provide mechanistic information on maternal–fetal interactions. The placenta plays a critical role in regulating the fetal environment and may reflect dynamic interchanges between maternal and fetal physiology throughout gestation (O'Connor et al., 2019). Histology coupled with gene expression and other assessments may provide a unique record of fetal exposures (Janssen et al., 2016; Kratimenos & Penn, 2019; O'Connor et al., 2019). Inflammatory/immune mechanisms are another route by which placental function may modulate prenatal exposure and influence fetal health. Imbalances in inflammatory cytokines can alter fetal neurogenesis at critical gestational timepoints and affect neurodevelopmental trajectory, though there is need for further study, including in humans, of the pathways that mediate these changes (Buss et al., 2017). Thus, interventions like Wellness-4-2 that use personalized methods to reduce maternal stress in real time should be transduced via the placenta. Incorporation of placental structure and function into pathways from prenatal stress reduction to neurodevelopmental outcomes is critical to model specification (Janssen et al., 2016; O'Connor et al., 2019).

In the PHBP Study, clinical collaborations with obstetrics and neonatology enable us to align specimen collection with routine prenatal and perinatal care. Cumulative biomarker data will be acquired

over time to build an expansive multiplex database of longitudinal biomarker levels linked to each mother-infant dyad. These data will be linked to the data being acquired through collaborating neurodevelopmental researchers and experts in gestational biology from maternal–fetal medicine, placental and cord blood analysis from neonatology, and biomarkers of neuroimmune response from pediatric infectious diseases (with most immediate focus on inflammatory and microbiotic markers). Our goal is to uncover bridges from the gestational immune environment to proximal maternal–fetal mechanisms to neurodevelopmental outcomes. For example, we have used Luminex multiplex immunoassay technology to measure over 25 immune biomarkers in cord blood plasma, using less than 1ml of sample per patient (Matoba et al., 2009). These data can be linked to placental histology to study interactions between placental immune response and cytokine levels (IL6, IL-8, TNF-alpha), growth factors (VEGF, fibroblast growth factors), and neurotrophic (NT) factors (e.g., brain-derived neurotrophic factor, NT-3, NT-4) at birth (Mestan et al., 2009, 2017). As the placenta crucially modulates the impact of maternal exposure on the developing fetus, advanced technologies with even greater biomarker output can be used in the future on archived samples. Promising areas for future investigation include fetal brain biomarkers and imaging, stress-induced microbiota changes with associated gut–brain axis neuroendocrine and immunologic mediators, and epigenetic mechanisms (Frasch et al., 2018; Janssen et al., 2016; Thomason et al., 2018).

The PHBP's central focus at the maternal–fetal interface is constrained to established mechanisms that can be captured as part of routine clinical and/or standard clinical research practice and are "lowest hanging fruit": (1) *Maternal heart rate variability via biosensor*. Our key maternal biologic indicator of stress, i.e., maternal heart rate variability assessed via biosensor, is the maternal parameter most closely linked to fetal indicators (DiPietro et al., 2015); and (2) *Inflammatory/neuro-immune biomarkers* obtainable from placental tissues and cord blood.

3.4.5 | Neurodevelopmental challenge #3

Few developmental neuroimaging studies have emphasized engagement of culturally diverse populations

Cognitive neuroscience studies have largely focused on non-representative populations, which introduces bias and reduces generalizability (LeWinn et al., 2017). This is of particular importance in stress-related research where elucidating mechanisms of disparities is especially imperative (Turner, 2013). Although the advent of national infant imaging studies with representative populations and examinations of poverty-related neural alterations is encouraging (Howell et al., 2019; Lawson et al., 2013; Luby et al., 2013), representation by families with racial, ethnic, and socio-economic diversity is still relatively low in many studies. This challenge is amplified in studies such as PHBP where recruitment occurs during the prenatal period.

3.4.6 | Neurodevelopmental opportunity #3

Melding neuroscientific and community-engaged approaches in stress-related neurodevelopmental research enhances engagement of diverse populations

Community-engaged research ensures that scientific approaches are sensitive to the needs, values, and concerns of diverse populations (Pacquette & Ross, 2017). Since mothers being recruited into the Wellness-4-2 trial will be diverse, we believed it was especially important that our recruitment materials and procedures be informed by input from these stakeholders. We drew on information from focus groups with 14 diverse pregnant women. In general, women expressed a desire to participate in stress-related research of importance to infants' wellbeing. However, concerns about participation in the MRI neuroimaging protocol were prominent. Focus group participants made helpful suggestions to ensure women's comfort with all aspects of the study, including provision of more detailed information about rationale and potential benefits to infants (Table S3). We note that the use of a smartphone as an eligibility criterion may impede participation of some low-income women, which may impact scalability in the long term. However, the recent Pew survey indicates that > 96% of individuals in the US have smartphones (>70% across demographic strata), with rates higher in young adults (Pew Research Center, 2019).

The PHBP Study incorporated information from the focus groups into the development of recruitment materials and study procedures for the neuroimaging portion of the study. This included creating materials that were in accessible language, were engaging and informative, and framing the procedure as *Lullaby MRI*. Our recruitment scripts and consent forms were reviewed by multiple diverse staff with varied levels of training to ensure language was clear and informative, and a set of tailored FAQs was then derived to provide additional information. We created an explanatory video about the MRI procedures viewed during the consenting process and families with concerns also have access to discuss questions or concerns with study neuroscientists.

3.4.7 | Neurodevelopmental challenge #4

Significant Knowledge to Action (KTA) gap

Improving the gestational environment via prenatal stress and distress reduction holds out tantalizing possibilities for improving young children's neurodevelopmental health (Doyle & Cicchetti, 2018). However, the lack of evidence that fetal neurodevelopment is malleable via improving the gestational environment large-scale constrains real-world application. This is a critical knowledge to action (KTA) gap (Graham & Tetroe, 2009). Recent systematic reviews show small but significant effects of improving the gestational environment by reducing maternal depression on infant outcomes ($g = 0.15$), with strongest effects on our central neurodevelopmental phenotype, dysregulation (Goodman et al., 2018). Interventions included were very diverse and

none used a personalized JITAI approach. Further, many of these interventions were not a priori designed to alter neurodevelopment (Brown et al., in press). Finally, studies have not typically tied alterations in neurodevelopmental constructs (e.g., dysregulation) to actual risk of developing mental health problems. As mental health disorders are multi-determined, the challenge is (1) identifying brain: behavioral targets that are malleable and then (2) demonstrating that such changes reduce probabilistic risk of mental health problems.

3.4.8 | Neurodevelopmental opportunity #4

We posit that the use of a personalized approach is most promising for improving the gestational environment with promotive impact on neurodevelopment because it is tied directly to real-time maternal psychobiologic state. The use of state-of-the-art neuroimaging and neurobehavioral methods tracing brain-behavior trajectories of dysregulation from birth-age 1 has high potential for specifying those processes impacted by improved gestational environment, which has greatest impact on risk of psychopathology.

We take a multi-level, developmentally sensitive approach to measuring dysregulation in the first year of life, with assessment at birth and two additional timepoints to generate dysregulation trajectories (supplemental online Table S1). Key aspects of this protocol are indicators of brain functional and structural connectivity, observed dysregulation across varied demand contexts, and nascent executive function. At 12 and 24 months, these trajectories will be linked to symptoms of dysregulation and impairment in functioning.

4 | CONCLUSIONS AND FUTURE DIRECTIONS

Drawing on a burgeoning body of work, we have proposed that the time has come to accelerate SEED science via translation to prevention applications. The cornerstone of this is a personalized JITAI approach, which holds most promise for improving the gestational environment by accounting for individual differences in stress experience. This combined with advances in neurodevelopmental understandings of emergent psychopathology sets the stage for altering the stress-mental health pathway even before birth. Doing so requires a highly synergistic translational team science approach. We have illustrated this by drawing on the development of our feasibility study of the Wellness-4-2 intervention to underscore the opportunities and challenges inherent in the process of operationalizing a translational scientific vision in the real-world, complexities which often get short shrift. We are keenly aware of the trade-offs we have made in so doing. For example, the burden and intensity of the Wellness-4-2 bio-integrated stress measurement limits widespread dissemination. Similarly, our neurodevelopmental outcomes are multi-level and intensive, again limiting generalizability to community settings. Here too, we have used all the tools at our disposal as a means of increasing the likelihood of nuanced detection of intervention impact. For this first stage attempt to move the dial, we have chosen an approach that we theorize will have the highest likelihood of impact, via harnessing both stress biology and subjective experience in our JITAI process and tracing outcomes from the maternal–fetal interface through the development of regulatory processes and brain structures across the first year of life. The integration of more pragmatic tools in these multi-level prenatal and neurodevelopmental assessments will lay the foundation for subsequent efforts to optimize this approach for scalability. Thus, the work laid out here is but a first step in harnessing the power of personalized prevention to reduce stress-related population attributable risk of mental health problems. It targets a developmental period recognized as one of heightened parental motivation for behavior change to promote infants' healthy outcomes and optimal neuroplasticity.

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CONFLICT OF INTEREST

John Rogers and Roozbeh Ghaffari hold equity in the company MC10 that makes Biostamp devices for other applications.

AUTHOR CONTRIBUTIONS

All authors contributed to the paper in drafting and reviewing drafts. Lauren Wakschlag, Darius Tandon, Nabil Alshurafa, Leena Mitthal, Sheila Krogh-Jespersen, Amelie Petitclerc, and Karen Mestan did first drafts of various sections. Nabil Alshurafa John Rogers, Darius Tandon, Judy Moskowitz, Sheila Krogh-Jespersen, Mike Bass, Laurie Wakschlag, Roozbeh Ghaffari, William Grobman, Elizabeth Norton, and Amelie Petitclerc contributed to the design of the study.

ORCID

Lauren Wakschlag https://orcid.org/0000-0001-9511-2299
Michael Bass https://orcid.org/0000-0002-7732-6557

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