Computational Approaches for Connecting Maternal Stress to Preterm Birth

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KEYWORDS

• Stress • Preterm birth • Machine learning • Artificial intelligence

KEY POINTS

- Multiple studies hint at a complex connection between maternal stress and preterm birth (PTB), with PTB being the predominant cause of neonatal deaths globally.
- Novel technologies allow the profiling of stress exposures and responses in unprecedented ways and open avenues like the integration of multiple aspects of stress, continuous monitoring, or biological multiomics profiling.
- Machine learning and artificial intelligence methods can help reveal the underlying processes of stress and PTB but are currently not used to their full potential.

INTRODUCTION

Preterm birth (PTB), that is, a delivery before the 37th week of gestation, is the predominant cause of neonatal deaths,[1] and it can lead to severe long-term complications for mother and child.[2,3] Approximately 1 in 10 babies is born prematurely in the United States, incurring societal costs estimated at US$25.2 billion in 2016.[4] While the mortality rate of children aged under 5 years has significantly declined since 1990, the worldwide rate of PTB has, however, only been reduced slightly over the last decade, 13.4 million estimated in 2020,[1] urging for the development of effective and accessible interventions.

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Various environmental, biological, and socioeconomic factors contribute to PTB, such as maternal health, genetics, lifestyle choices, socioeconomic conditions, environmental temperature, and, particularly, physiological and psychological stressors.[3] Although the association between prenatal stress and PTB has been examined in numerous studies,[5] the complexity and heterogeneity of stress perception and its consequences for maternal immune tolerance toward the fetus makes it difficult to gain a comprehensive understanding of functional links.[5] Therefore, to enable the process of introducing stress-lowering interventions into routine pregnancy care, an in-depth understanding of the connections between stress and PTB are urgently required.

The term "stress" lacks precision and a universal definition is difficult. Stress can be defined as an individual's perceived capacity to manage external demands,[6] which may lead to disturbances, irritations, and/or anxiety and contribute to impairments in mental and physical well-being. In this context, stress perception is personal and based on internal stressors related to a person's character and their own self-expectations, aspirations, and perfectionism as well as external stressors including various factors such as environmental noise or extreme temperatures, and personal financial problems or life-changing events.[7,8] Particularly, pregnant women face "pregnancy-specific stress" involving the health of their fetus and their own well-being, anxiety about labor, and concerns related to impending parenthood.[9] However, the impacts on mother and fetus strongly depend on the severity of the stressor, its duration, time point of exposure during gestation, a person's resilience, existing coping strategies,[10] and the availability of social support[11] demonstrating the high interindividual variabilities. Hence, a wide array of stress assessment tools is required to capture the multifaceted range of stress factors and susceptibility.[12,13]

The underlying processes of how stress affects biological systems in PTB are also complex. To ensure proper fetal growth and development, the maternal immune system actively adapts to the semiallogeneic fetus to establish and maintain immune tolerance.[14,15] This includes the adjustment of the immunologic processes,[16] which are highly vulnerable to disruption by environmental factors including prenatal stress. Stress responses are connected to the autonomic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, which can affect various biological pathways, including neuro-endocrine-immune balance. The associated increase in cortisol production due to prenatal stress can reduce progesterone (P4) production and consequently to the disruption of its immune suppressive capacity[17] leading to immune inflammation. In addition to this stress-induced neuro-endocrine-immune imbalance, the cardiovascular system (eg, changing the heart rate, blood pressure of mother and fetus), on the metabolic system (eg, release of glucose and fats to facilitate energy availability), as well as the behavioral patterns (eg, such as harmful behaviors like smoking) can also be impacted,[3,18] which all can further aggravate endocrine and immune system as well as other biological systems via indirect pathways.

The complex interaction between prenatal stress and PTB calls for a holistic approach incorporating a full characterization of physiological and psychological stressors and the study of underlying biological pathways. To this end, the use of validated questionnaires allows the evaluation of various factors across different psychometric domains, electronic health records (EHRs) store demographic information and patient history, and recent biotechnological advancements toward high-throughput, multiomics approaches enable the measurement of biological systems in a comprehensive, untargeted manner,[19] for example. Integrating these different modalities, advanced computational tools from the field of machine learning (ML) and artificial intelligence (AI) hold the potential to untangle and understand the underlying processes and risk factors for PTB. However, computational tools have only recently been employed to address PTB.[20–22] Here, we provide an overview of the current approaches that apply modern computational tools to study the association between stress and PTB. We also discuss how novel methods from the field of ML and AI can further enhance the study of stress and PTB. We believe that applying these methods can help shape the direction of future research in this domain. An overview of the content covered here is illustrated in **Fig. 1**.

METHODS AND MODALITIES FOR ASSESSING AND QUANTIFYING STRESS

Stress is typically assessed from 2 perspectives[23]: (1) *stressor exposures*, that is, discrete events with the potential to affect an individual's psychological or physiologic performance and (2) *stress responses*, which includes behavioral, cognitive, biological, and emotional reactions to stressors. The following sections cover common as well as ML-enabled methods for assessing stress.

Questionnaires for Measuring Stressor Exposures and Stress Responses

For the measurement of stressor exposures and stress responses, many different validated guidelines and tools exist, for example, as provided by the Stress Measurement Network.[12] This particularly includes questionnaires.

Negative life events, racism and discrimination,[24] lack of social support,[25] and domestic abuse[26] are examples of stressor exposures that are associated with PTB and measured using questionnaires. Questionnaires have also been utilized to collect surrogates for stressor exposures, such as sociodemographic data, social interaction, and lifestyle profiles. In the context of PTB, commonly studied sociodemographic factors include age, race, socioeconomic status, marital status, education, income, medical history, alcohol consumption, and smoking.[27]

In addition to measuring stressor exposures, questionnaires are also used to assess stressor responses of the mothers before, during, and after pregnancy. The Center for Epidemiological Studies Depression Scale, Prenatal Distress Questionnaire (PDQ), Pregnancy Specific Anxiety Measures, and the Perceived Stress Scale (PSS) are questionnaires used to measure stress responses, including depression, distress, anxiety, and perceived stress during pregnancy.[8]

Toward Objective Methods for Stress Response Measurements with Machine Learning

While using questionnaires to assess stress responses can be helpful to capture personalized and compound effects, their results can be highly subjective due to self-reporting of perceived stress and prone to questionnaire-specific limitations, such as method biases or variabilities between individuals.[23] Therefore, while potentially not covering the full spectrum of perceived stress,[28] the implementation of objective stress response measures, such as biological or physiological markers, may be useful.

For example, biomarkers can be employed to assess stress response on a systemic level. Cortisol in blood, salvia, and hair is a marker of short-term and long-term stresses and reflects prolonged HPA axis activity. Significantly different levels have been reported in mothers with term and PTBs in the third trimester.[29,30] Also, serum levels of various cytokines released from inflammatory pathways are indicative of stress responses, for example, interleukin-6.[31] At the same time, emerging high-throughput multiomics technologies enable unprecedented insights into stress responses and PTB by using ML methods,[32–34] demonstrating their potential to identify pathways connecting stress, biology, and PTB. However, measuring and evaluating

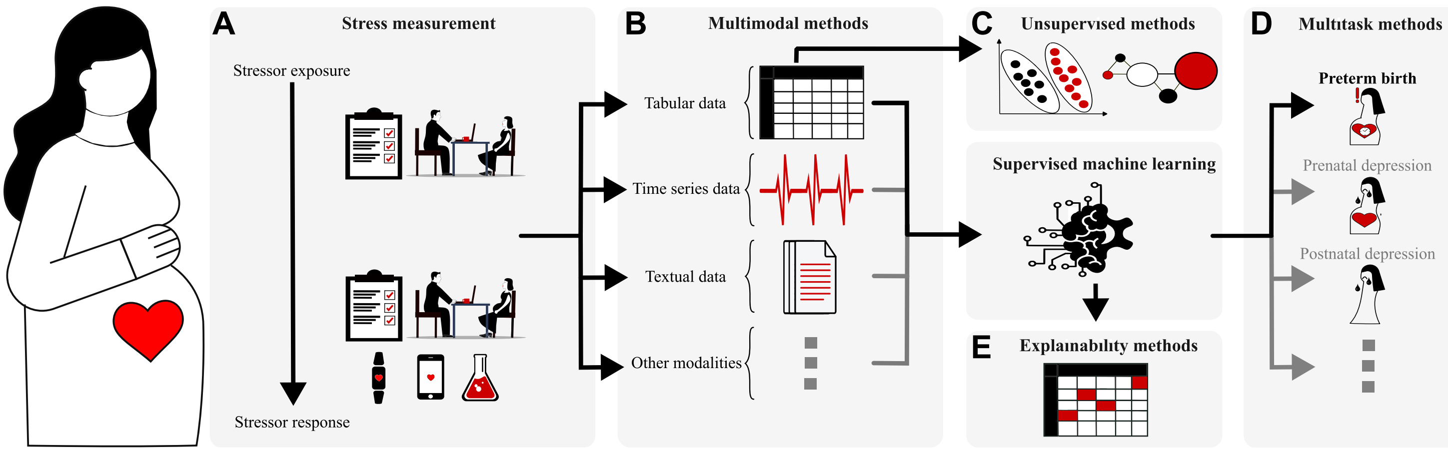

Fig. 1. Computational framework for analyzing the dynamic interplay between stress and PTB. (*A*) The image illustrates different assessment strategies to assess stress exposure and responses, yielding diverse modalities (*B*). These data types can be integrated by multimodal (*B*) multitask (*D*) ML models for a more holistic understanding of stress and PTB. (*C*) Similarly, unsupervised ML leverages identifies subgroups within across mothers and risk factors. (*E*) Explainability methods help understand complex ML methods.

biomarkers can be costly and time consuming and may be better suited for understanding underlying biological processes rather than for routine monitoring.

On the other hand, the Wearable Stress and Affect Detection dataset[35] illustrates more accessible and cost-effective tools that also enable long-term stress monitoring by ML. It incorporates a breadth of physiologic factors measured by wearable devices including blood volume, heart rate, electrical heart, skin, and muscle monitoring, respiration, body temperature, and physical activity, and uses ML methods to predict stress. Similarly, using ML, behavioral markers for stress can even be derived from social media comments, or even patterns from keyboard or mouse usage.[36,37] In the context of maternal stress, Bilal and colleagues,[38] collected a diverse dataset, incorporating questionnaire responses, mothers' voices, mobility metrics, smartphone usage patterns, data usage, and sleep patterns through a smartphone app designed to predict perinatal depression and PTB. Sarkar and colleagues[39] estimated cortisol levels, PSS, and PDQ stress scores of mothers from abdominal electrocardiograms (aECG), both using artificial neural networks. Finally, Ravindra and colleagues[40] employed a similar approach to predict gestational age at birth (GAB) from pregnant women's physical activity and sleep patterns, and indirectly established a connection between maternal stress and PTB.[41]

COMPUTATIONAL APPROACHES FOR UNDERSTANDING THE CONNECTION BETWEEN STRESS AND PRETERM BIRTH

The field of computational methods to study complex systems and their potential to be applied to stress and PTB is large. Here, we briefly review common univariable methods[42] (studying the connection between PTB and a single stress-related variable) as well as multivariable methods[43] (modeling the connection between PTB and multiple stress-related variables simultaneously). We then elaborate on ML methods that either have been applied in the context of stress and PTB or have the potential to significantly impact this domain. **Table 1** provides an overview of studies representative of applying the methods mentioned in this section.

Univariable and Multivariable Methods

Univariable analyses focus on the associations of each individual variable in a dataset (eg, anxiety level) to an outcome (eg, PTB). It can be used to study individual risk factors for PTB or to select variables for subsequent experiments or multivariable analyses.[44] Univariable associations measured by relative risks, odds ratios, or statistical tests have been used to identify potential stress-related risk factors related to PTB, including unintended pregnancy, lack of perceived social support, and pregnancy-related anxiety.[24,45]

In contrast to univariable methods, multivariable methods consider a combination of multiple explanatory variables simultaneously (eg, various stress and demographic factors) and assess their combined impact on the outcome—such as PTB or GAB.[46] While this collective approach may disregard individual effects of variables, the joint effects of factors such as stress-related variables, negative life events, racism and discrimination,[24] lack of social support,[25] and domestic abuse[26] have shown associations with PTB beyond univariable results. Common multivariable methods include linear regression, logistic regression, Poisson regression, and proportional hazard regression.[47] Note that such methods can be used to find multivariable relationships per se, or they can be used in predictive settings (eg, to estimate the risk of PTB in unseen patients).[47] However, particularly for predictive settings, ML methods can capture more complex relationships.[46]

Table 1
Overview of selected supervised and unsupervised computational methods utilized in analyzing stress and preterm birth. An "x" marks the covered aspects of the study.

Article, Year	Objective	Univariable	Multivariable	Supervised	Unsupervised	Multimodal	Multitask	Method	Data Description
Sarkar et al,[39] 2021	Classification: chronically stressed mothers vs controls Regression: PSS, PDQ values, and maternal hair cortisol level	—	x	x	—	—	—	Deep learning	aECG data
Ravindra et al,[40] 2023	Regression: Gestational age	—	x	x	—	—	—	Deep learning	Wearable sensor data
Huang et al,[22] 2021	Classification: PTB	x	x	x	—	x	—	Lasso logistic regression, SVM	Cortisol and metabolites along with psychological questionnaires
Waynforth et al,[52] 2022	Classification: PTB	—	x	x	—	—	—	Random forest	Questionnaire-based data
Becker et al,[20] 2022	Classification: Pregnancy complication	x	x	x	—	x	x	Deep learning	Stress questionnaires and single-cell immune system data
Lee et al,[51] 2021	Classification: PTB	—	x	x	—	x	—	Random forest	Demographic, socioeconomic, particulate matter in air

Becker et al,[21] 2023	Classification: PTB	x	x	x	—	—	—	SVM	Chronic stress and psychosocial factors
García-Blanco et al,[53] 2017	Regression: Gestational age	—	x	x	—	x	—	Parametric survival model	Cortisol, α-amylase, age, parity
Vovsha et al,[54] 2014	Classification: PTB	—	x	x	—	x	—	SVM and logistic regression	Demographic, vaginal microbiota, cervical examination, and cervical and vaginal fetal fibronectin, questionnaire-based data
Maxson et al,[60] 2016	Subgroup analysis	—	x	x	x	—	—	k-means clustering	Psychosocial health measures
Molenaar et al,[80] 2023	Subgroup analysis	x	x	x	x	—	—	Latent class analysis	Self-reported data

The breadth of applicable methods from ML and AI to understand the connection between stress and PTB is shown.

Supervised Machine Learning Methods for Preterm Birth Prediction Based on Stress-Related Variables

To fully capture the multilayered network of interactions between stress and PTB, recent work moves toward methods from ML and AI, following similar trends in the general study of adverse pregnancy outcomes[48,49] allowing for nonlinear relationships. Predominantly, the methods employed in this context are supervised (see **Table 1**), aiming to establish relationships between stress and PTB and a multitude of variables simultaneously by leveraging labeled data to predict outcomes like PTB for unseen patients.

Multivariable machine learning

Many ML algorithms exist to predict an outcome like PTB from multiple variables simultaneously in a nonlinear manner. This includes, for example, methods like support vector machines (SVMs) to predict PTB from stress-related variables.[21] Other applicable methods include random forests, XGBoost, or artificial neural networks.[46] However, these methods work on tabular data only with a fixed set of variables per patient and a single outcome limiting their capabilities to capture a holistic picture of stress and PTB.

Multimodal machine learning

Multimodal ML considers multiple sources of information to predict outcomes.[50] This can be particularly useful when not only stress-related variables are of interest but also information from other modalities such as multiomics data and biomarkers like cortisol, cervical length, or selected EHR variables. Modern deep-learning methods can even directly integrate imaging or time series data with limited manual preprocessing.[50] In the context of stress and PTB, a particular use case may be integrating stress-related variables with imaging modalities such as transvaginal ultrasound. Rudimentary versions of multimodal modeling have been applied in studies concerning stress and PTB. For example, some articles combine different questionnaires to assess the psychological, parental health, social, demographic, economic, and behavioral risk factors of mothers and used SVMs or random forests to predict PTB.[21,51,52] Others incorporated more diverse modalities of measures such as cortisol, α-amylase level, various metabolites, vaginal microbiota, cervical examination, and cervical and vaginal fetal fibronectin, alongside subjective measures.[22,53,54] While such studies already demonstrate the potential of multimodal ML to simultaneously consider different aspects of stress, they do not yet fully exploit the capabilities of directly integrating diverse modalities such as imaging, text, or time series data. However, such approaches may hold the potential to better model and understand the complex cross talk among stress, various biological systems, and PTB.

Multitask machine learning

Pregnancy complications are rightly interrelated.[20,55] Thus, modeling multiple pregnancy complications together PTB can greatly improve the understanding of their interrelations as well as increase the predictive power of the model.[20] In this context, multitask models are designed to predict multiple outcomes.[56] While multitask learning has been employed in different studies related to pregnancy and child health,[57,58] it is not employed frequently for studying the connection between stress and PTB. Becker and colleagues[20] first used multitask neural networks to predict multiple outcomes simultaneously including early gestational age (as a proxy for PTB) as well as pre-eclampsia, superimposed pre-eclampsia, gestational diabetes, body mass index, diabetes, and hypertension based on an extensive set of stress variables assessed by questionnaires. The authors demonstrated that predicting GAB using a multitask ML approach can increase prediction power and help understand the relationship between pregnancy complications, compared to a single-task setup. This points toward the potential of multitask approaches to capture more intricate relationships of the underlying processes of adverse pregnancy outcomes like PTB and motivates a more holistic approach of studying the connection of stress and adverse pregnancy outcomes rather than isolating PTB.

Unsupervised Machine Learning Methods

Unsupervised ML methods, in contrast to supervised ML methods, have no knowledge about the modeled outcome (eg, PTB) and try to find hidden patterns in the data.[59] They can play an important role in stress and PTB studies by enabling the exploration of patterns within complex datasets.[49] Clustering, a fundamental unsupervised technique can categorize pregnancies into groups based on similar stress profiles, aiding in the discovery of patterns associated with pregnancy outcomes such as PTB. For example, the k-means algorithm has been used to discover clusters of stress resiliency (defined based on measures of paternal support, perceived stress, social support, depression, and self-efficacy) that were associated with different pregnancy-related complications including PTB.[60] Similarly, latent class analysis was used in multiple studies to divide a population of pregnant women into several subpopulations and then compare the rate of PTB in each subpopulation.[61,62]

Similar methods can be used to cluster stress-related variables to gain deeper insights into the relationships between various stress factors and how groups of similar stress-related variables are associated with PTB. For example, Becker and colleagues[21] clustered stress-related variables according to their correlation profiles using k-means clustering. They found prominent clusters of similar variables, like perceived pregnancy risk, health concerns, and emotional state, which were highly associated with PTB.

Overall, unsupervised learning, especially cluster analysis, enables the discovery of multidimensional stress-related phenotypes for PTB, potentially enabling more precise profiling and more effective stress interventions.

CONFOUNDING FACTORS AND CAUSALITY IN COMPUTATIONAL METHODS

By integrating increasingly complex data using ML and AI methods, particularly in predictive, that is, supervised, settings, unexpected confounders can cause misleading interpretations.[63] Similarly, the common focus of ML methods on predictive settings[64] promotes associative analyses and neglects causal connections.

Confounders

Premature contractions, or previous premature delivery, can be considered to influence stress and PTB simultaneously.[65] However, even if such confounding variables are excluded from the data, ML methods may pick up related signatures from other variables, for example, a combination of lifestyle factors or biological profiles.[66] Thus, accounting for such factors is essential, for example, by comparing the final results (eg, trained model for PTB prediction) with models derived from distinct subgroups of potential confounding factors[67] (eg, groups with and without previous premature delivery). Alternatively, propensity score matching is used to define case and control groups where the influence of potential confounding factors is limited by creating groups that are balanced in terms of observed covariates.[68] Studies employing ML methods tend to recognize potential issues with explicit as well as hidden confounding factors and list them as limitation.[20] However, novel studies applying ML needs to carefully consider confounding factors and appropriate counter measures due to the capability of ML to uncover hidden and potentially unintended patterns.[69,70]

Causality

The sensitivity of ML methods to confounders is rooted in their focus on predictive settings,[64] thus finding associations but not causal pathways. However, computational tools exist that allow testing hypothesized (causal inference) and discovering novel causal relationships (causal discovery).[71] The field of causal inference is concerned with testing whether 2 variables are related and assessing the impact of one on the other. For example, Harris and colleagues[72] found a causal association between a preconception maternal stress and offspring birth. However, such approaches for learning causal effects require hypothesizing causal structures. To address this, the field of causal discovery aims to learn such relations directly from the data. A wide variety of algorithms can address this issue.[71] For example, Mesner and colleagues[27] use the Peter–Clark algorithm to derive a causal graph illustrating the interactions between various stressors, demographic factors, and biomarkers in relation to different pregnancy outcomes, including PTB. While this shows the potential of causal discovery to understand the relation between risk factors and PTB and potentially derive novel interventions, neither computational causal inference nor causal discovery methods are common tools in this field.

INTERPRETABILITY AND EXPLAINABILITY OF MACHINE LEARNING MODELS

ML and, particularly, deep learning approaches often produce black box models, that is, even if an ML model accurately predicts PTB risk from a set of stress-related factors, it may not be clear which factors it used and how they were used to derive the risk. This can be a major hindrance in understanding the underlying processes. Some studies use univariable analysis as a surrogate for identifying candidates for the most influential stress-related variables associated with the PTB,[21] others use models that are inherently interpretable such as linear regression.[45] However, most state-of-the-art ML models like SVMs, gradient boosting machines, for example, XGBoost, and particularly deep learning models[73] remain opaque even to domain experts due to their high number of parameters. Although explainable AI (XAI) and interpretable ML are still active fields of research, there is already a wide arsenal of post hoc explanation methods available for these approaches.[74] This includes Shapley values, which originated from cooperative game theory to compute the contribution of each player in a coalition game. In the context of predicting PTB from EHR data, Shapley Additive Explanations (SHAP)[75] have been used to determine the individual contributions of clinical input features to PTB risk predictions,[76] allowing to identify the factors most relevant for the model's decision. Similarly, Ada and colleagues[77] used SHAP values to conclude that the number of consecutive stress minutes is highly predictive for the physiologic stress of the next day, and PSS has the most effect on the next day's perceived stress. Thus, despite the limitations of state-of-the-art XAI methods (eg, no integrated causal or effect modification discovery[55,62]), it is already possible to overcome the black box nature of ML models[74] to some extent to gain deeper insights into the connection between stress and PTB, potentially leading to the discovery of novel intervention methods.

DISCUSSION

The different aspects of stress exposure and response are hard to capture and isolate. Thus, studying the underlying processes of the relationship between stress and adverse pregnancy outcomes like PTB is a challenging task. However, novel technologies, for example, wearable sensors,[35] novel biomedical assays (eg, single-cell analysis),[20] or social media monitoring,[36] can give deeper insights by connecting objective observations to the more common subjective information collected by questionnaires.[13] However, the increasing amount and variety of data pose challenges on how to integrate and analyze this data to connect the captured stress-related patterns to PTB and from there derive accessible interventions. We believe that the quickly progressing development in the field of ML and AI can provide the tools to accomplish this.

While we have seen that ML, in general, is already applied in a significant number of studies relating stress to PTB, these studies currently do not exploit the full potential of available ML and artificial ML methods. For example, while some studies combine multiple modalities (eg, questionnaires and biomarkers), they are often limited to features that are manually crafted from more complex modalities[53] and do not employ full-fledged multimodal models.[50] The handcrafting process can severely limit the amount of information extracted from modalities such as time series data (eg, accelerometer data, heart rate, ECG, or even continuous questionnaires collected via smartphones)[38] compared with allowing ML methods access to the complete time series. Similarly, multitask learning is an established field in the ML community and has only recently been applied to study the connection between stress and PTB in order to gain a more holistic picture by jointly modeling a variety of adverse pregnancy outcomes.[20] Beyond these relatively straightforward applications, the first articles already point toward explicitly modeling joint connection of the pathway from stress over biology to adverse pregnancy outcomes[20] and motivate combining multimodal and multitask methods as applied in other disciplines.[78] Finally, novel developments like large language models, for example, ChatGPT, may help to better understand the complex connections in unstructured or even multimodal data.[79]

We have also pointed out the limitations of current ML models including their black box and ultimately associative nature. Current research is actively developing methods to mitigate these limitations including explainability as well as causal inference and discovery methods.[27,72,77] Particularly, the latter may allow to go beyond predictive settings ultimately leading to the development of novel interventions.

SUMMARY

Stress and PTB are tightly interwoven. We advocate a more holistic approach of studying this connection enabled by computational methods: One the one hand, by integrating not only commonly used subjective measurements of stressor exposures and stress responses, but also objective measures, for example, physiological as well as biological modalities. And on the other hand, by integrating PTB into the more holistic context of other adverse pregnancy outcomes, we believe that ML and AI methods have the potential to open novel avenues for studying the complex relationship of stress and ultimately yield novel, easily accessible interventions.

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DISCLOSURE

The authors have nothing to disclose.

Best Practices

What is the current practice for employing computational methods to study the connection between stress and PTB?

- Many different measurement modalities are used to assess stressor exposures and stress responses and study its connection to PTB.
- Current methods are not exploiting the full potential of the quickly evolving fields of ML and AI.

What changes in current practice are likely to improve outcomes?

- ML and AI can unlock novel and more comprehensive profiling of stress responses, for example, through wearable devices or deep biological profiling.
- Multimodal and multitask ML may help to integrating multiple modalities for understanding the complex connections between stress and PTB as part of a more holistic view on adverse pregnancy outcomes.
- XAI methods can help to derive insights into otherwise black box ML methods to help identify novel stress-related interventions.

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