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Journal

Stress: The International Journal on the Biology of Stress, 27(1)

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Publication Date

2024

DOI

10.1080/10253890.2024.2321610

Peer reviewed

HHS Public Access

Author manuscript

Stress. Author manuscript; available in PMC 2024 July 01.

Published in final edited form as:

Stress. 2024 January ; 27(1): 2321610. doi:10.1080/10253890.2024.2321610.

Multi-omics in stress and health research: study designs that will drive the field forward

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Abstract

Despite decades of stress research, there still exist substantial gaps in our understanding of how social, environmental, and biological factors interact and combine with developmental stressor exposures, cognitive appraisals of stressors, and psychosocial coping processes to shape individuals' stress reactivity, health, and disease risk. Relatively new biological profiling approaches, called multi-omics, are helping address these issues by enabling researchers to quantify thousands of molecules from a single blood or tissue sample, thus providing a panoramic snapshot of the molecular processes occurring in an organism from a systems perspective. in this review, we summarize two types of research designs for which multi-omics approaches are best suited, and describe how these approaches can help advance our understanding of stress processes and the development, prevention, and treatment of stress-related pathologies. We first discuss incorporating multi-omics approaches into theory-rich, intensive longitudinal study designs to characterize, in high-resolution, the transition to stress-related multisystem dysfunction and disease throughout development. Next, we discuss how multi-omics approaches should be incorporated into intervention research to better understand the transition from stress-related dysfunction back to health, which can help inform novel precision medicine approaches to managing stress and fostering biopsychosocial resilience. Throughout, we provide concrete recommendations for types of studies that will help advance stress research, and translate multi-omics data into better health and health care.

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Disclosure statement

MPS is a cofounder and scientific advisor of Personalis, SensOmics, Qbio, January Ai, Fodsel, Filtricine, Protos, RTHM, Iollo, Marble Therapeutics, Crosshair Therapeutics, and Mirvie. He is a scientific advisor for Jupiter, Neuvivo, Swaza, and Mitrix. The other authors declare no conflicts of interest with respect to this work.

Keywords

Life stress; multi-omics; development; interventions; health; resilience

Despite breakthroughs in the scientific understanding of how stress affects psychological and biological systems in ways that, over time, lead to disease and disability, non-communicable disorders that are driven at least in part by stress are on the rise (Case & Deaton, 2017). In fact, nine of the top ten causes of death in the United States today are caused or exacerbated by stress (Bhushan et al., 2020). To address this sizeable public health problem, we need new scientific approaches that will enable researchers to elucidate the molecular mechanisms of stress-related processes, how stress response systems become dysregulated, and how the body returns from toxic stress physiology to a benign, or even healthy, state. New biological profiling technologies are emerging that will remove some of the barriers to accessing this knowledge, and we focus on one such promising approach here: multi-omics.

There are two key questions in stress research that can benefit greatly from using a multi-omics approach, leading not only to novel scientific advancements but potentially to new strategies for preventing and treating stress-related pathology. The first question is how, from a developmental perspective, do stress response systems become dysregulated in ways that lead to stress-related pathology? The second question is how, when, and in whom does stress-related pathology improve?

First, to understand how stress response systems develop, we need longitudinal studies that incorporate multi-omics, behavioral, psychological, and social-environmental assessments on diverse participants who are followed across the lifespan. These studies will be expensive, time consuming, and require multiple generations of scientists to conduct well, but they are vital. Luckily, some are already underway (e.g., Mariani et al., 2021). Second, to understand how we can prevent the development of stress-related pathology, or treat it once it develops, we need to deeply profile participants in intervention studies that are designed to reduce stress, and enhance health and well-being. in the context of multi-omics research approaches, immersive intervention studies (i.e., interventions which engage participants for many hours a day over a few days, as opposed to 1–2 hours a day/week over many weeks/months) are a promising study design that allows for intensive longitudinal sampling during a period when sizable psychological and biological changes are possible. Just as applying multi-omics approaches to developmental research designs can help us to better understand stress-related processes through examining the transition from health to stress-related dysregulation and disease, the application of multi-omics approaches to intervention studies will advance our understanding of stress-related processes through examining the transition from stress-related dysfunction back to health.

Multi-omics approaches are gaining popularity, although due to the technical and financial resources they require, they are not yet being widely used across research disciplines. To help advance understanding and appreciation of these approaches, we first provide a general introduction to multi-omics approaches. Second, we provide recommendations for types of developmental and intervention studies that are needed to move the field of stress

research forward using multi-omics approaches. Finally, we discuss several considerations, limitations, and future directions of multi-omics research approaches in stress research.

Multi-omics approaches

Multi-omics analyses enable researchers to quantify tens of thousands of molecules from a single blood or tissue sample. Multi-omics analysis is a scientific approach that uses multiple targeted and untargeted assays, along with multiplexed assays, to analyze biological samples. the term “omics” indicates a global or unbiased assessment of a set of molecules (Hasin et al., 2017). Each type of molecule within an organism can be classified within one, or sometimes multiple, different omics, depending on the levels of analysis considered. The different omics assessed in a multi-omics study typically include genomics, transcriptomics, proteomics, metabolomics, lipidomics, and metagenomics/microbiome (see Figure 1). Multi-omics approaches have the power to drive the field of stress research forward by giving researchers a comprehensive snapshot of the molecular processes occurring within an organism, from a systems perspective.

Systems-level information is exceptionally valuable when studying stress and the mechanisms through which stress-related pathologies develop. Stress responses are influenced by myriad biological and environmental factors, as well as developmental stressor exposures, cognitive appraisals of stressors, and psychosocial coping mechanisms. As such, research designs which isolate any one influence on stress responses or the development of stress-related pathologies are both challenging to design and are likely to produce results which are potentially meaningless outside of a broader context which considers all these factors at once.

Multi-omics approaches enable researchers to consider a far greater number of biological processes and how systems interact within the body to produce the limited analytes typically assessed in stress research. For example, exposure to social-environmental adversity is associated with elevated interuekin-6 (IL-6) levels (protein information; Olvera Alvarez et al., 2018). By assessing multiple systems, researchers have discovered that a single nucleotide polymorphism in the human *IL6* promoter (genomic information) alters the likelihood of threat-activated GATA1 transcription factors binding to DNA (transcriptomic information), and in turn, IL-6 levels and mortality risk. However, the impact of this genetic predisposition on mortality risk depends on one’s exposure to social-environmental adversity (i.e. environmental context; Cole et al., 2010; Slavich & Cole, 2013; Slavich et al., 2023), representing a conserved transcriptional response to adversity (CTRA). The multiple levels of data assessed enable researchers to characterize the mechanistic nuances of how, and in whom, social-environmental adversity predicts elevated mortality risk. The exploration of additional omics, such as the microbiome, metabolomics, lipidomics, and proteomics, could reveal even more.

Multi-omics approaches are already proving themselves invaluable in understanding many different types of disease states, such as type ii diabetes mellitus (Chen et al., 2012). For example, one multi-omics health study recently revealed more than 67 clinically actionable findings (Schüssler-Fiorenza Rose et al., 2019). Although most studies of disease states are

limited to correlational implications, the integration of omics data types can identify causal candidates in the progression of disease, which can then be tested in empirical studies (Hasin et al., 2017). Moreover, finding evidence of the same biological mechanism operating across omics layers increases confidence in biological results (Lancaster et al., 2022).

Despite the advances made in understanding of the etiology of many diseases using multi-omics approaches, a few issues make studying stress especially challenging. Beyond the complexities of the processes involved in the regulation of stress-related systems, the questions we need answered to move the field forward are difficult to study in a traditional laboratory-based research design. For instance, a person's stress response in a controlled laboratory environment may be very different from their stress response in daily life, making it difficult to generalize scientific findings to understand how stress-related processes impact health and disease in people's everyday lives. Moreover, although empirical models that experimentally assign organisms with different genetic predispositions to live in environments with differential stressor exposures and then track the development of stress response systems and stress-related pathologies throughout the organism' lifespans are feasible using animal models, this research is difficult to conduct ethically in humans.

Developmental designs: examining the transition to stress-related dysregulation

Early life stress has lasting effects

Although it is well understood that social-environmental experiences can have both an immediate and lasting influence on our health, there is also a large body of research describing how experiences in early life may be particularly impactful to development and adult health (Ellis & Del Giudice, 2019; Frankenhuis & Walasek, 2020; Gluckman et al., 2010). Specifically, research suggests that exposure to stressors during the perinatal period through adolescence can increase a person's risk for myriad physical and mental health problems later in life, even when their situation improves (Cohen et al., 2010; Hughes et al., 2017; Krushas & Schwartz, 2022). Although numerous scholars have identified associations between early life experiences—in particular stressful early life experiences, such as abuse and neglect—and negative health outcomes, less is known about the biological mechanisms underlying these processes. Moreover, even less is known about the biological underpinnings of susceptibility and resiliency factors—such as genetic predispositions and protective childhood experiences—that may moderate associations between early life stress and health.

Our ability to answer these questions has been hindered by domain-specificity of scholarly work. For instance, studying associations between childhood environments and health has typically occurred within the domain of developmental psychology. Although developmental theory and methods have provided many insights into *why* early life experiences are so impactful (e.g., developmental trajectories and sensitive periods), less attention has been paid to *how* these experiences get under the skin to impact health. An interdisciplinary approach that harnesses the strengths of developmental theory and methodology, coupled with systems-focused multi-omics techniques, would both redress gaps in our understanding

of how stress-related pathologies develop and inform interventions to ameliorate their harmful sequelae.

Recently, integrative frameworks grounded in both developmental psychology and stress biology have begun to address not only why but how early life stress impacts development. For example, Social Safety Theory posits that stress response systems—including the immune system—are attuned to social threats because throughout evolutionary history, these situations signaled elevated risk of injury and infection (see Slavich, 2020; Slavich, 2022; Slavich et al., 2023). There is also evidence that individual differences in the perception of, and response to, social threats are determined by aspects of the childhood environment (e.g., microbial exposure, social connection, culture) as well as their genetic vulnerability (see also two-hits hypothesis; Bilbo & Schwarz, 2009; Monroe & Simons, 1991). In addition, many have acknowledged the interplay of early and continued stress. For instance, the stress sensitization model states that early life adversity exposure increases a person's risk for pathology when faced again with stressors later in life (Hammen et al., 2000; Mclaughlin et al., 2010).

These frameworks have resulted in some of the first empirical findings using psychological, developmental, and biological methods to address questions about how early life stress influences health. For example, research has found that exposure to early life adversity (e.g. poverty, abuse) is associated with dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity (Heim et al., 2008; Kuhlman et al., 2017; Raymond et al., 2021) and elevated levels of peripheral inflammatory markers (Chiang et al., 2022; Milaniak & Jaffee, 2019), as well as greater release of proinflammatory cytokines in response to antigen stimulation *ex vivo* (de Koning et al., 2022; Ehrlich et al., 2016; Miller & Chen, 2010). Other researchers have found that lower childhood socioeconomic status (SES) is associated with poorer immune performance in functional immunoassays (Gassen et al., 2021) and an increased risk for viral infections (Cohen et al., 2010).

Empirical gaps

Despite these recent theoretical and empirical advances, limitations of this work have left much unknown about how stress-related pathology develops across the lifespan. First, most of the research examining associations between early life stress and health has explored the effects of broad or composite categories of adversity (e.g., socioeconomic status, sum of adversity categories) and a limited range of stress buffers (e.g., maternal warmth). in this way, it has overlooked substantial work in developmental psychology that describes the unique effects of specific stress dimensions, the importance of timing of stressor exposure, and individual differences in vulnerability and protective factors. For example, research conducted using broad, composite categories of early adversity overlook developmental frameworks that describe how different types of early life stressors differentially influence adult stress responsivity and health, such as the dimensions of threat, deprivation, and unpredictability (Ellis & Del Giudice, 2019; Sheridan & Mclaughlin, 2014; Simpson et al., 2012). However, few psychobiological studies have involved comprehensive surveys that measure each of these dimensions (Slavich, 2016; Slavich, 2019), which is necessary

to advance theory and inform precision interventions on the most influential sources of stress-related dysfunction.

Another limitation is that much of the current research on developmental stress physiology has been cross-sectional (Milaniak & Jaffee, 2019). This is a critical issue, as longitudinal studies are a cornerstone of developmental research insofar as they yield crucial information about trajectories of psychological and physical change that occurs across critical periods. Moreover, longitudinal designs can also provide opportunities for causal inference when experimental methods are unethical or not ecologically valid in humans (VanderWeele et al., 2016). Although numerous studies have retrospectively assessed whether early life adversity affects stress physiology and health in adulthood, there is a striking lack of well-powered panel data on trajectories of stress-related immune and endocrine markers across the lifespan.

Additionally, much of the existing research on this topic has focused exclusively on the impact of early life stress on health-related outcomes, without appreciating the unique experiences of marginalized groups. LGBTQ + communities (Diamond et al., 2021; Operario et al., 2015) and communities of color (Brondolo et al., 2011; Dolezsar et al., 2014; Gee & Ford, 2011; LaVeist, 2011) often have far worse health outcomes compared to heterosexual and white populations, and many suggest this is due to minority-specific stress faced via individual and structural experiences of discrimination and marginalization. These populations also face disproportionately high levels of childhood adversity such as abuse and neglect (Baams et al., 2018; Craig et al., 2020; Lanier et al., 2014; Shonkoff et al., 2021), which as articulated in developmental theory, could exacerbate the effects of more persistent stressors later in life (e.g., general stress, discrimination, stigmatization).

Another limitation of past stress-focused developmental research is a lack attention to how intersectionality impacts stress- and health-related processes (Cyrus, 2017). To date, multi-omics research examining intersectionality—or the impact of multiple intersecting marginalized identities such as race, gender, sexual orientation, and SES—is nonexistent, despite these studies being critically important to advancing a precision medicine approach to health. Every marginalized group experiences different forms of social threat and safety, and the interaction between two or more marginalized identities likely has a substantial impact on how one moves throughout their environment and the stressors they face. Related research investigating the impact of identity on life-long experiences with stress and, in turn, multi-omics, will not only advance basic knowledge on the stress biology of marginalized populations, but also increase representation and aid in the development of precision interventions that have the potential to reduce health disparities (Mengelkoch et al., 2023).

Finally, existing research on the impact of early life adversity on stress physiology has, for the most part, not used a systems approach that assesses multiple relevant biological systems in the same study, ideally concurrently, so that cross-system insights can be gleaned. instead, most studies have focused on a small number of analytes related to one or two systems in isolation (e.g., HPA axis and immunity), often due to knowledge or resource constraints. No bodily systems operate in a vacuum, and stress-related pathology often involves multisystem

dysregulation that cannot be fully understood by the sum of its parts. individual differences in stress susceptibility and resilience, too, involve a confluence of genetic and environmental factors whose interactions are just as important as their individual effects.

Incorporating multi-omics into developmental research designs

Building on current developmental theory and research, multi-omics studies are well-positioned to produce major breakthroughs in the understanding of the development of stress-related pathology. Proof-of-concept has already begun to emerge from cross-sectional studies integrating individual omics approaches to examine the impact of adversity on gene expression, metabolomics, and the microbiome. As described above, research in human social genomics has identified a CTRA (Cole, 2019; Slavich & Cole, 2013) that is characterized by increased expression of genes that promote the inflammatory response and decreased expression of genes that promote antiviral immunity and antibody production, leading to greater risk of both chronic inflammation-related and viral illnesses (Slavich & Irwin, 2014). Importantly, these findings are consistent with prior research showing that childhood stressors are associated with elevated levels of proinflammatory cytokines and increased risk of viral illnesses (Cohen et al., 2004; Milaniak & Jaffee, 2019; Miller & Chen, 2010). Adverse childhood experiences have also been related to altered microbiome and metabolomic signatures, which have downstream effects on peripheral stress and inflammatory biomarkers (Hantsoo et al., 2019; LaBarre et al., 2021; Michels et al., 2019).

Although powerful, high-throughput multi-omics approaches alone are just tools. When applied without careful forethought, these tools can generate results that, even if exciting, do not meaningfully move the field forward in understanding the development of—and recovery from—stress-related pathology across the lifespan. We propose that to fully realize the potential of multi-omics approaches in this context, future research should first consult the wealth of developmental theory and research before designing and implementing longitudinal studies focused on early life adversity and stress-related processes throughout development. Doing so offers countless advantages including, but not limited to, providing: (a) frameworks for developing testable predictions; (b) insights into the types of stressors or protective factors that may impact outcomes of interest, how and when they are best measured, and how they may interact; (c) information about how key variables are commonly distributed across a sample; (d) expected temporal associations between key factors; and (e) insights into the psychological constructs and behaviors that may covary with changes in stress-related physiology. in addition to these points, designing multi-omics research to specifically test tenets of developmental hypotheses will also promote the generation of novel, comprehensive theoretical frameworks that emphasize the role of stress physiology.

In addition to theory, methods from developmental psychology, and in particular longitudinal studies, provide a roadmap for multi-omics studies seeking to provide novel insights into how stress response systems develop, how that development is altered in the context of adversity, and what those alterations mean for health. Further, studies involving repeated sampling also enable both between- and within-person analyses, allowing researchers to explore the factors that influence individual differences in stress vulnerability,

as well as trajectories of pathology and recovery among those who are susceptible. Given the costs and potential burden on participants of comprehensive multi-omics approaches, it is important that researchers think carefully about the minimum sample sizes and observation frequencies required to answer their particular questions. These sample sizes will be unknown for many analytes of interest if data do not exist on their expected changes across development or in the context of early life adversity. Therefore, the field of developmental multi-omics is in dire need of researchers who are devoted to collecting longitudinal data, even if not perfectly at first, to lay the groundwork for future work. See Figure 2 for general recommendations and Box 1 for an example of a longitudinal study design that incorporates multi-omics approaches.

Integrating developmental methods with multi-omics approaches will require extensive interdisciplinary collaboration and will demand that interested researchers expand their understanding of human biology and systems modeling, longitudinal methods and statistics, and developmental theory, often outside the immediate domain of their expertise. Fortunately, there are countless workshops and comprehensive reviews of each of these topics available, as well as statistical tools for performing integrative multi-omics analyses (see Box 3 for resources). Quantitative developmental scientists will find that many of the statistical techniques common to psychology (e.g. mixed effects models) are also applicable to multi-omics research; efficiency in creating loops is often necessary to run models across thousands of analytes. Furthermore, although well-powered multi-omic studies can be cost-prohibitive, integrating multi-omics with developmental psychological theory to study stress and health, particularly when focused on mitigating health disparities, will likely be highly fundable for the foreseeable future. Moreover, some labs capable of performing multi-omics assays are willing to assist by providing methodology advice during grant preparation.

In summary, the marriage of developmental psychology and biological methods has already provided novel insights into mechanisms through which early life stress influences health (e.g., metabolic changes, inflammation). Further integration of multi-omics with developmental theory and methods holds promise to produce large gains in our understanding of how stress gets under the skin across the lifespan to impact health and well-being. Although financial, practical, and content knowledge barriers to entry in multi-omics research exist (see the “Considerations, limitations, and recommendations” section below), these barriers can be overcome through interdisciplinary collaboration, extramural funding, and access to existing academic resources (e.g., workshops, reviews) that introduce key concepts to interested researchers. Although it will be difficult, incorporating multi-omics into developmental research will help us understand how and why childhood environments affect multiple biological systems, develop new ways of conceptualizing toxic stress from a systems perspective, and determine how toxic stress contributes to disease risk.

Intervention designs: Examining the transition from stress-related dysregulation and disease to health

Just as research designs that closely monitor the transition to stress-related dysfunction or disease can inform prevention and treatment strategies, study designs that monitor the

transition from stress-related dysfunction or disease back to health are also extremely valuable. There are many types of interventions that have been found to reduce stress and enhance well-being and improve health (e.g., meditation: Black & Slavich, 2016; Goyal et al., 2014; residential retreats: Naidoo et al., 2018; cognitive behavior therapy: Shields et al., 2020). For example, Zadok-Gurman et al. (2021) investigated the impact of a blended inquiry-Based Stress Reduction (IBSR) intervention to improve the well-being of teachers during the COVID-19 pandemic. Conducted in Jerusalem, the researchers found that the IBSR program, which melds mindfulness and cognitive reframing, significantly bolstered resilience and well-being amidst the challenges of the pandemic and israel's lockdown in the intervention group. Conversely, the control group experienced increased burnout and diminished psychological well-being over the study period. These findings underscore the potential of IBSR to enhance teacher well-being during crises, and suggest that mind-body interventions may be helpful for reducing stress and enhancing well-being.

Although stress-reducing intervention studies have yet to fully incorporate multi-omics approaches, a few notable intervention studies have used biological data within one "ome" (e.g., genomics: Álvarez-López et al., 2022; transcripomics: Epel et al., 2016; lipidomics: Vishnubhotla et al., 2022) to discover molecular mechanisms of stress reduction attributable to the intervention. in one landmark study, Ornish et al. (2008) examined the impact of comprehensive lifestyle changes on telomerase enzymatic activity in 30 men diagnosed with low-risk prostate cancer. After a 3-month period of lifestyle changes, they observed significant increases in peripheral blood mononuclear cell (PBMC) telomerase activity, which correlated with decreased levels of low-density lipoprotein cholesterol and reduced psychological distress. This pilot study was groundbreaking as it was the first to suggest that comprehensive lifestyle interventions might lead to increased telomerase activity, implying a potential enhancement in telomere maintenance capacity in human immune-system cells.

In a follow-up study, Ornish et al. (2013) continued their exploration of the long-term effects of lifestyle modifications on telomere health. This research compared ten men undergoing comprehensive lifestyle changes (including dietary adjustments, increased activity, stress management, and enhanced social support) to 25 control participants who opted for active surveillance only. After five years, the intervention group exhibited increased relative telomere length when contrasted with the control group, indicating that the lifestyle modification group's comprehensive lifestyle changes positively impacted telomere health over the long-term. Using multi-omics approaches in such intervention designs would enable researchers to pinpoint which types of stress-reducing interventions and lifestyle modifications impact which biological processes, with higher precision than is gained by assessing only one or a few biomarkers associated with stress or immune function.

Immersive interventions and multi-omics approaches

Immersive interventions are growing in popularity in recent years and are exceptionally well-suited for multi-omics study designs (e.g., Ganz et al., 2022). These interventions typically last 2–7 days and engage participants around the clock, as opposed to only a few hours a day. Although most immersive interventions occur in-person, some have moved to virtual formats, enabling them to be attended by a relatively small or very large group of

participants. One feature that sets these interventions apart from traditional interventions is the sense of community that occurs while spending time with a group of people who are working toward similarly aligned self-improvement goals, which itself can be health-promoting insofar as it fosters a sense of social connection and belongingness that has been shown to improve well-being and resilience (Slavich et al., 2022).

However, what makes immersive interventions so well-suited to multi-omics research approaches is that they provide an ideal opportunity to conduct intensive sampling in a context where participants are in a controlled environment (for a discussion of the benefits of intensive longitudinal sampling in stress research, see Moriarity & Slavich, 2023). Namely, all participants attending the interventions are often eating the same diet, trying to sleep on the same schedule, and engaging in the same activities, thus providing researchers with a level of experimental control not often found in more traditional intervention studies. As discussed above, longitudinal designs that use repeated within-person measures are powerful in a multi-omics design as they enable the temporal order of biological mechanisms of change to be observed and control for between-person differences (Mengelkoch et al., 2023). in this context, researchers can collect many samples per participant and observe biological changes happening in nearly real time in response to the intervention. For example, during a 5-day intervention, a researcher might decide to sample participants twice a day and thus collect 10 samples per participant, which would enable the researcher to determine which day's activities were likely to have producedthe molecular changes observed and how these trajectories differed between participants. Temporal ordering that implies causal effects is often hypothesized in such studies but rarely investigated. immersive interventions help to strengthen the conclusions that can be drawn in this regard.

In general, the more biological samples a researcher collects during the intervention and follow-up period, the greater temporal resolution they have for elucidating molecular mechanisms of change. Additionally, as in developmental studies, it is recommended to collect as much biopsychosocial data as possible alongside the target biological samples (for detailed recommendations, see Mengelkoch et al., 2023). These data should include psychological survey data, health data, and demographic information. Having participants wear a smartwatch or other wearable device with sensing capabilities over the course of the study can also provide valuable information about a person's behavior and physiology (i.e., heart rate, blood pressure, physical activity, and sleep quality and duration). Finally, using ecological momentary assessment methods enables researchers to correlate biological changes with real-time changes in psychological states and health-relevant processes. in sum, collecting these rich, multi-faceted data provides a much clearer picture of what is changing—biologically, behaviorally, physiologically, and psychologically—when we intervene to reduce stress and enhance resilience in participants. See Box 2 for an example of an immersive intervention study design which incorporates multi-omics approaches.

Precision medicine approaches to stress and health

The use of multi-omics approaches in intervention studies also sets the stage for a personalized or precision medicine approach to stress-reducing interventions (Chen et al., 2012; Schüssler-Fiorenza Rose et al., 2019). By collecting rich data, researchers can

begin to piece together which between-person differences in life history or personality influence responses to different types of stress-reducing interventions, which within-person differences in biological responses to different types of stress-reducing interventions predict lasting stress reduction, and what other socio-environmental factors influence these associations. For example, perhaps people with certain genetic predispositions, microbiome compositions, or cognitive appraisal styles respond more favorably to interventions that incorporate diet and physical activity changes (through changes in their metabolic processes) whereas another subgroup responds more favorably to interventions that use socially supportive environments and community building (through changes in inflammatory-related gene expression). Both groups might also respond to interventions more favorably when living in environments that have less air pollution, income inequality, or discrimination, all of which can have negative interactive effects on health (Slavich et al., 2023). Using multi-omics approaches within intervention designs, stress researchers can begin to piece together what works best to reduce stress and stress-related pathology, and to enhance health and well-being in whom, under what conditions, and through which biological mechanisms, to better target effective intervention techniques and approaches to those who would benefit from them the most.

Considerations, limitations, and recommendations

Multi-omics studies are expensive and time-intensive, especially when collecting many samples per participant, and they also require advanced computational techniques and statistical approaches to interpret results. Moreover, as muti-omics technologies are still being developed and optimized, challenges associated with measurement reliability are ongoing. For example, different collection methods, assay approaches, and analytical techniques can yield drastically different results, creating inconsistencies and difficulty with replicability (Katz et al., 2022; Raffield et al., 2020).

While the approach of each researcher will depend upon their research question, resources, and experience, we have a few general recommendations to overcome barriers to conducting multi-omics research that can also increase replicability if widely accepted. Most omics can be assessed through collection of blood samples, and emerging micro-blood sampling devices (i.e., Mitra, TASSO, TAP II) allow for participant-administered collection of either whole blood or dried blood spot samples in the comfort of their home, which can then be shipped into research labs for storage and processing. Although whole blood or PBMCs are needed for some assays (e.g., single-cell transcriptomics), dried blood spot technologies are rapidly improving and are appealing as they require only a small amount of blood—reducing participant burden—and samples can be stored nearly indefinitely (Shen et al., 2023). Additionally, saliva is a minimally invasive collection option which can be assayed for genomics, transcriptomics, proteomics, metabolomics, and microbiome, and is often already collected in the context of stress research which assesses salivary cortisol (Pappa et al., 2019).

That said, not all sample types will produce the same results (Gautam et al., 2019). Although lacking access to key resources such as lab equipment, funding, or analytical expertise should not prevent the collection of these samples, given that many samples can

be banked for future analysis, we do advise including an experienced multi-omics researcher as a consultant when designing studies that might bank samples for future analyses. A multi-omics consultant can offer guidance on the collection and storage of biological samples specific to the research question at hand and assay types targeted. Moreover, many resources exist for inexperienced researchers to gain knowledge about multi-omics, including workshops and outstanding reviews (e.g., Athieniti & Spyrou, 2023; Mengelkoch et al., 2023; see Box 3 for more resources and recommendations). However, given the extensive conceptual, technical, statistical, and computational expertise needed to conduct meaningful multi-omics research, we recommend collaborating with researchers who have experience in these areas whenever possible.

Multi-omics studies with intensive sampling can also be burdensome to participants, and as such, auxiliary measures used to enhance multi-omics data should be selected carefully in the same respect. One way to collect additional data with minimal participant burden is to use wearables to collect passive physiological data, which is often correlated with biological processes of interest. For example, researchers using both multi-omics data collection and wearable data found heart rate data (e.g., heart rate variability, range, maximum heart rate) were associated with 447 molecules, most of which were lipids and cytokines (Shen et al., 2023). When designing multi-omics studies, it is also vital to consider participant diversity from the outset (Fatumo et al., 2022) and to design studies that are accessible to a wide range of demographic groups to avoid intensifying health disparities and limiting generalizability of findings (for an example and discussion, see Jatoi et al., 2022). For those interested in learning more about multi-omics approaches, including study design considerations and analytical approaches and tools, see Box 3 for additional resources.

Multi-omics approaches are beginning to reveal the complex biological processes through which stress and adversity lead to disparate health outcomes. They are also helping elucidate the pathways through which common stress-reducing interventions improve health outcomes. Although many scholars focus their work around specific disease outcomes—and have had substantial success in reducing the negative impact of such disease—the domain-general role that stress plays in the etiology of many diseases demands unifying frameworks to understand negative stress-related health outcomes. Specifically, multi-omics approaches within frameworks that acknowledge the general toxicity of stress would enable scholars to identify not just one pathway through which a given disease develops but to compare and contrast multiple overlapping and interacting processes through which stress promotes chronic diseases of aging, some of the primary causes for morbidity and mortality in western cultures. In addition to combatting biological reductionism, an adequately-powered multi-omics approach can also be used to explore if and how preexisting individual differences in stress-affected biological pathways (e.g., due to age, genetics) interact with stressful experiences to influence disease risk. Such an approach could, in turn, inform the development of precision interventions that may reduce the risk of a host of disease outcomes before they develop.

Conclusion

In conclusion, the health sciences in general, and stress researchers in particular, stand to benefit greatly from the adoption of multi-omics approaches. The past few decades have provided a very limited glimpse into which biological systems are affected by stress and can be normalized with effective interventions. Multi-omics approaches will bring this work into an entirely new frontier, providing a much higher-resolution picture of biological systems that link stress with human health and well-being. However, multi-omics approaches are just a set of tools, and even the best tools, when used ineffectively, will not advance the field in a meaningful way.

As we have described here, multi-omics research examining stress and health will be most effective if it incorporates a developmental perspective and is conducted using study designs that provide high temporal resolution during periods of change, minimizing unmeasured differences between participants when feasible. Whereas the former study design feature will afford researchers with a better understanding of how biological systems become dysregulated and then normalize across time, the latter will yield data that enables stronger causal inference and more effective and personalized intervention targets. Together, this work has the potential to greatly reduce suffering attributable to stress and adversity. To realize this potential, however, we will need high-quality, longitudinal and intensive study designs that use multi-omics approaches to assess the activity of multiple biological systems together with psychological, behavioral, and clinical data. Ultimately, these designs have the power to yield translational results that could, in turn, greatly transform human health and health care.

Funding

Preparation of this article was supported by grant #OPR21101 from the California Governor's Office of Planning and Research/California Initiative to Advance Precision Medicine. These organizations had no role in planning, writing, editing, or reviewing this article, or in deciding to submit this article for publication.

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Box 1.

Study design example: What can we learn about the onset of stress-related dysfunction from integrating multi-omics approaches into developmental designs?

Research Question	What is the biology underlying the development of mental health problems during stressful life transitions, and can insights into this biology inform predictive models that forecast risk of developing mental health problems?
Participants	Young adults transitioning into their first year of college (N = 300+)
Study Design	Longitudinal: baseline assessment prior to beginning of first semester, then monthly assessments during first semester (approximately 5 measurements); an assessment after school break, but prior to the beginning of the second semester, then monthly assessments during second semester (approximately 5 measurements). Collect demographic measures, mental and physical health history, and lifetime stressor exposure and perceived stress surveys (i.e., Stress and Adversity Inventory [STRAIN; Slavich & Shields, 2018], Perceived Stress Scale [PSS; Cohen et al., 1994]) at baseline sessions. Follow-up sessions will assess whether students have received a diagnosis for a mental health problem since their last session (and if they are taking medication for that condition), and will also involve completion of perceived stress, depressive symptomology (e.g., Beck's Depression Inventory; Beck et al., 1987), and anxiety scales (e.g., Generalized Anxiety Disorder-7 scale; Spitzer et al., 2006). TASSO devices or venipuncture for blood collection will be completed at each occasion for multi-omics analysis. Students will also wear Fitbits or other wearable devices to track activity and sleep during each semester.
Analytic Approach	First, generalized linear mixed effects models or joint longitudinal survival models will be used to identify which multi-omic analytes change alongside mental health disorder diagnoses over time. Next, mixed effect models will be used to identify which analytes covary with responses to stress, depression, and anxiety scales. Models that disaggregate within- and between-individual effects can help parse stable (i.e., trait) and time-dependent (i.e., state) relationships between analytes and risk for mental health problems (e.g., Curran & Bauer, 2011). Further, introducing time lags or using cross-lagged models (e.g., latent change score model) may lend insights into the temporal order of changes in symptoms and analyte levels (although these models should be interpreted with caution when using observational data). Downstream integrative multi-omics analyses will be used to identify focal biological pathways and disease processes. Machine learning approaches and development of prediction models (e.g., fused Lasso regression, elastic net, Bayesian network algorithms) will be developed to identify features that forecast the onset of mental health problems (e.g., using baseline measures).
Possible Outcomes	Identify multi-omic analytes associated with onset of mental health problems, stress, and both overall and specific depression/anxiety symptoms. Determine if correlates of diagnosis events (e.g., inflammation) are also associated with continuous ratings of symptomology. The analytes and biological pathways identified can be compared and contrasted with those found for stress levels. Exploratory analyses may examine whether multi-omic signatures predict both likelihood and type of mental health problem (e.g., anxiety vs. depression). The identified genes and pathways can be augmented with regulatory genomics data from the PsycheNCODe Consortium (Akbarian et al., 2015) to further the understanding of the biological mechanisms underlying the development of psychiatric disorders. Ancillary data (e.g., wearable) might provide insights into moderators and mediators (e.g., sleep quality) of the impact that stressful life transitions have on key biological pathways, and the effects that changes to these pathways have on mental health. Such information could also be used to strengthen risk prediction algorithms and lay the groundwork for developing just-in-time interventions to mitigate this risk.
Limitations / Considerations	Developing a standard workflow for multi-omic data reduction, regularization, and quality control is critical to minimize risk of bias or error introduced by sample assaying and data processing. More complex longitudinal models may be unfeasible due to computational burden, limited sample size, or aspects of data distributions (e.g., negative binomial distribution of RNAseq data; BinTayyash et al., 2021). Analytes might differ greatly in their autocorrelation or variance, which could require custom model fitting. Given that the study is observational, a strong adherence to best practices is necessary for reliable insights into mechanistic pathways. Domain knowledge is also important for interpreting results and assessing biological plausibility/relevance.
Implications	Results will elucidate the biological changes underlying the development of mental health problems during stressful life transitions in young adults.

Costs/Benefits of Multi-omics (What did multi-omics buy us here?)	Multi-omics analysis provides an opportunity to comprehensively assess contributions of diverse biological pathways, rather than inferring relevance of a pathway from only a few biomarkers. In addition to improving chances of discovery, this approach also takes a more systems-focused perspective that reflects the realities of how biology works. Using multi-omics in prediction models as opposed to single omes (Ghaemi et al., 2019) or clinical data alone (Schüssler-Fiorenza Rose et al., 2019) has been shown in other studies to improve predictive power of the models, potentially identifying biomarkers that predict poor mental health trajectories. Alternatively, it is possible that different people have different molecular entry points to poor mental health (e.g., depression) as has been shown in type II diabetes (Schüssler-Fiorenza Rose et al., 2019) and aging (Ahadi et al., 2020) and multi-omics can help identify different subtypes. Longitudinal multi-omics profiling can also identify shifts in biology that occur with different clinical states (Stelzer et al., 2021) and potentially provide biological markers of poor mental health onset which, with further validation, could eventually be used for diagnostics.

Box 2.

Study design example: What can we learn about recovery from stress-related dysfunction by integrating multi-omics approaches into immersive intervention designs?

Research Question	How does a three-day multicomponent immersive intervention designed to reduce stress and enhance well-being impact perceived stress?
Participants	Adults with elevated perceived stress levels (PSS-10 > 14); $N = 100+$
Study Design	Baseline day (7–10 days pre-intervention): Participants will be shipped a study package with a TASSO device, a smartwatch (measuring changes in activity, sleep, heart rate, heart rate variability, electrodermal activity, and caloric intake), and a QR code to access surveys. They will collect blood microsamples in the morning, mid-day, and evening using TASSO devices. Participants will be asked to wear a smartwatch for the full study period. Participant will complete a baseline questionnaire, which contains demographic questions; the STRAIN; trait measures of stress-related processes, mental health, physical health; and other key outcomes of interest to researchers. Participants will complete state survey measures using a smartphone at the same time as the midday blood sample. All samples will be stored in the participant's freezer, then shipped to study team the next day. Intervention period: Participants will take 3 blood microsamples per day during the intervention period, in the morning before starting and after each component (midday and evening) of the intervention. They will complete a brief ecological momentary assessment (EMA) state measure survey with each blood draw. The evening survey will contain additional questions assessing participation and response to the intervention activities. Participants will provide one saliva sample for genomic analysis. Study staff will be on site to collect samples. Follow-up 1 (7–10 days post intervention): Participants will provide 3 blood samples collected throughout the course of the day, concurrent with brief EMA surveys, collected at home and continue wearing smartwatch. The Follow-up 1 survey will contain assessments of perceived stress, and other key outcomes of interest to researchers. Follow-up 2 (1–3 months post intervention): Participants will complete a similar protocol to the Follow-up 1 Timepoint to assess lasting change in outcomes of interest.
Analytic Approach	Multi-level and mixed effects models to examine effects of the intervention on both perceived stress and changes in multi-omics analytes. exploratory follow-up analyses may explore moderation by demographic and individual difference factors (e.g., sex, STRAIN), as well as time-varying covariance of changes to perceived stress and analytes. Exploratory analyses to identify unique biological responses to different intervention components. Multi-omics: Identify analytes that change in response to the intervention (after false discovery rate/familywise error correction), then conduct integrative enrichment analyses to determine relevant biological and disease pathways. Multi-omic predictive modeling to identify subpopulations that may be more likely to respond overall or respond to specific components of the intervention.
Possible Outcomes	Identify the biological pathways through which the intervention acts to result in reduced stress levels during the intervention, alongside the biological pathways that predict lasting change in stress levels (i.e., at follow-up 2). Determine which analytes are associated with baseline levels of, and changes to, PSS scores across the study. This information can be used to determine biological systems involved in stress processes (e.g., innate immunity), as well as outcomes that might be impacted by stress biology. Determine the key individual differences that impact intervention efficacy and whether these are associated with biological processes as well as determine differential responses to components of the intervention that will enable development of personalized interventions in future studies/therapies (Grant et al., 2022).
Limitations / Considerations	Always use past theoretical research as a guide and consider biological plausibility when conducting exploratory analyses. Achieving adequate power for random assignment may be challenging without a large funding source, thus researchers may need to focus on within-person analyses instead.
Implications	Results will advance understanding of the biological mechanisms associated with changes in perceived stress and advance a precision medicine approach to stress reduction.
Costs/Benefits of Multi-omics (What did multi-omics buy us here?)	By using multi-omics, it is possible to elucidate mechanistic pathways through which the intervention impacted biological processes, perceived stress, and possibly later health, and the timing of changes. A more traditional approach might assess a few analytes before and after the intervention period. Knowing how an intervention impacts a few analytes might lead to a publishable finding that the intervention reduced stress

and this effect was mediated by reductions in IL-6, for example, but will not allow us to answer more nuanced mechanistic questions about the links between IL-6 and stress reduction. A multi-omics approach will enable the identification of shared or subtype specific signatures of IL-6 reduction. In addition, it allows one to assess a more comprehensive picture illuminating mechanisms other than IL-6 that are important in stress-related inflammatory processes and enables the identification of novel analytes and mechanisms that may not have been previously considered.

Similar to the example in Box 1, the additional biological information that multi-omics approaches provide compared to single omes and clinical data alone often enables the development of superior prediction models that can be used to predict responses to treatments and stratify people into different therapeutic interventions. Combining multi-omics data with wearable data may improve predictive power of such models. Wearables provide real-time continuous monitoring of the effect of therapeutic interventions and provide context to biological changes with physiological data.

Box 3.

Multi-Omics Approaches: Resources and Analytic Tools

Description	Tool / Key Reference
Reviews of analysis techniques used in multi-omics studies of psychiatric disorders	→ Amasi-Hartoonian et al., 2022 → Sathyanarayanan et al., 2023
Guides to multi-omics study design, data integration, and data analysis for translational medicine and psychoneuroimmunology research	→ Athieniti & Spyrou, 2023 → Mengelkoch et al., 2023
Catalog to help researchers select social determinants of health measures to include in studies	→ NIH PhenX Toolkit (Hamilton et al., 2011)
Review of unsupervised multi-omics data integration methods	→ Vahabi & Michailidis, 2022
Review of network based integrative multi-omics analysis	→ Agamah et al., 2022
Tools for determining appropriate sample size in multi-omics studies	→ MultiPower/MultiML (Tarazona et al., 2020) → PowerTools (Acharjee et al., 2020)
Platforms that contain common multi-omics data analytic tools for both supervised and unsupervised analytic approaches	→ mixOmics (Cao et al., 2008) → MetaboAnalyst (Pang et al., 2022) → 3omics (Kuo et al., 2013) → PaintOmics (Liu et al., 2022) → OmicsNet2.0 (Zhou et al., 2022) → Mergeomics2.0 (Ding et al., 2021) → TidyMass (Shen et al., 2022)
Tools for integrative multi-omics analyses (e.g., pathway enrichment and overrepresentation analysis)	→ IMPaLA (Kamburov et al., 2011) → clusterProfiler (Yu et al., 2012) → MOFA2 (Argelaguet et al., 2018) → PathwayMultiomics (Odom et al., 2021)

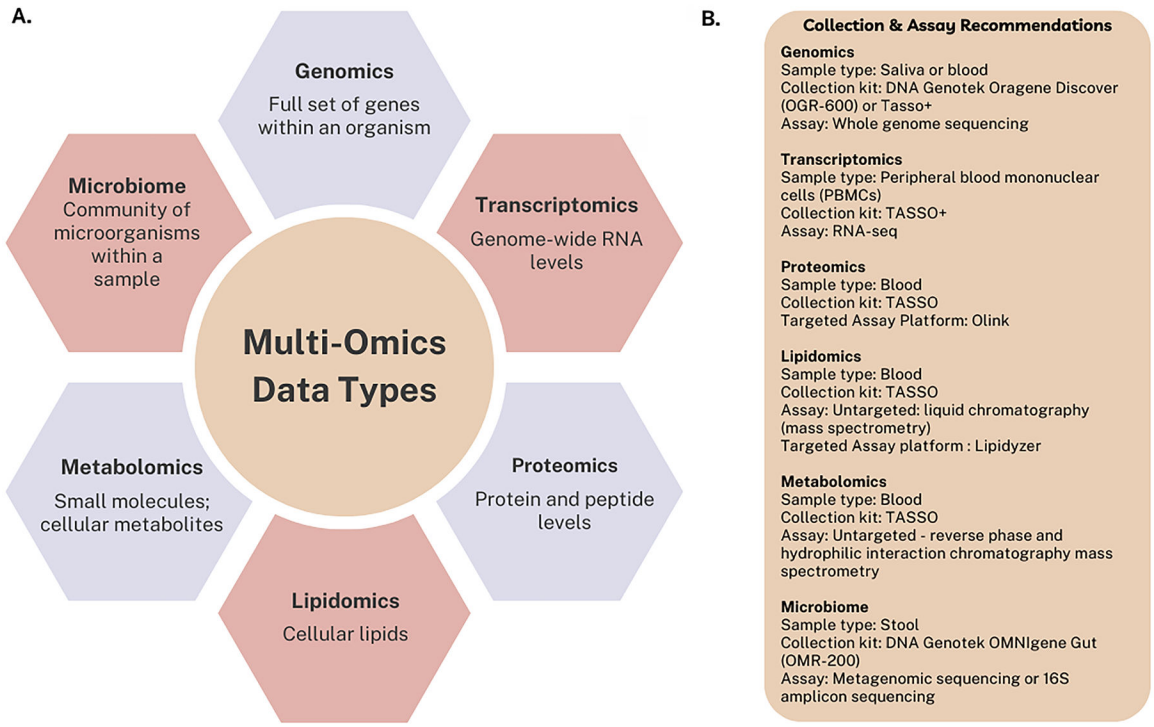

Figure 1.

Multi-Omics Data Types. (a) Common multi-omics data types include genomics (i.e., full set of genes within an organism), transcriptomics (i.e., genome-wide RNA levels), proteomics (i.e., protein and peptide levels), lipidomics (i.e., cellular lipids), metabolomics (i.e., small molecules; cellular metabolites), and microbiome (i.e., community of microorganisms within a sample). (b) Collection and assay recommendations. Note: This is not an exhaustive list of all possible sample types, collection kits, or assay methodologies, but rather, one option for each ome.

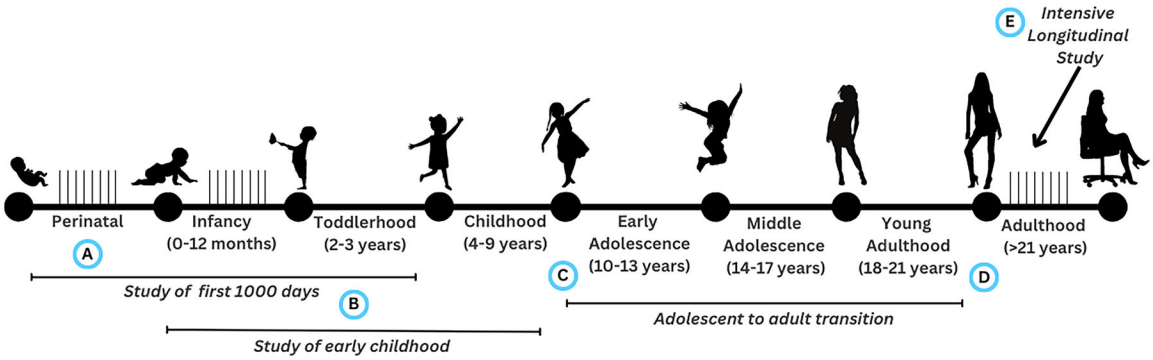

Figure 2.

Longitudinal study design recommendations in stress and multi-omics research. (a) Studies beginning in the perinatal period should examine associations between maternal and child multi-omics and birth outcomes, growth, and cognitive and emotional development, including measures of maternal stress, diet, and social support. Parents should be surveyed for children's adverse childhood experiences (ACEs). Monitoring environmental exposures in the home for two-week periods using exposome monitoring and parental surveys is recommended to give context to multi-omics analyses. Here, researchers have the power to examine trajectories of molecular change across the entire lifespan. (b) Studies of early childhood should pair multi-omics and analyses with developmental milestones of interest, and behavioral measures and tasks. Environmental exposure assessments should also include both home and school monitoring. Both parents and children should be surveyed about the child's ACEs. (c) When examining the transition from adolescence to adulthood, associations between multi-omics and pubertal timing/transition, physical and mental health, and school performance should be assessed. Children can be asked to self-report psychological data, including ACEs. Parental surveys and environmental exposure assessments can be included to add additional context to analyses. (d) In any longitudinal studies occurring in adulthood, researchers should examine the stability of analytes across the study as they relate to stress, health, and disease, including interactions between ACEs and current stress levels on multi-omics and stress-related pathologies. Analyte change in response to experimental (e.g., social evaluation) stressors can be examined to provide insight into how stress response systems function. Researchers may also consider assessing analyte levels before and after immersive interventions to observe the molecular changes that occur during the transition from stress-related dysfunction to health. (e) In intensive longitudinal study designs, stress levels can be tracked multiple times per day, daily, or weekly, providing a higher-resolution assessment of current stress levels as well as the variability in these levels over time. These designs can be cost effective in that high numbers of repeated measures in stress observations can compensate for smaller overall sample size for multi-omics analysis (Moriarity & Slavich, 2023). Although adult populations are easier to recruit for these types of study designs, valuable gains could be made from intensive longitudinal designs which monitor the perinatal or childhood periods as well.