Brain, Behavior, & Immunity - Health 45 (2025) 100977

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Protocol for project MHISS: Mental Health and Immunodynamics of Social Stress

Daniel P. Moriarity [a,*], Andrea C.M. Miller [a], Japneet Kaur [b], Ritika Prasad [c], Matthew B. Figueroa [a], George M. Slavich [a]

[a] Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA
[b] Department of Psychology, York University, Toronto, ON, Canada
[c] School of Professional Studies, Columbia University, New York, NY, USA

ARTICLE INFO

Keywords:
Stress
Depression
Inflammation
Intensive longitudinal data
Mental health
College

ABSTRACT

Background: Growing evidence suggests that immune alterations may mediate the impact of stress on a plethora of negative psychological and somatic health outcomes. In particular, social stress has been demonstrated to be a particularly potent type of stress that modulates immune activity. Typically, this effect has been tested in the lab with acute social stressors. To build upon this research with greater external validity, we used the transition to college campuses for 1st year undergraduates as an ecologically valid social stressor in this novel, intensive longitudinal psychoneuroimmunology study.

Method: This NIMH-funded study collected data from 173 incoming 1st year students at a large public university in California, USA. Eligible participants were recruited using an online screener disseminated by the University registrar's office and had to be 17–19 years old, fluent in English, living on campus, not have self-selected any roommates, and have moved at least 100 miles to campus. Enrolled participants completed a baseline survey, daily self-report measures (3589 reports total), and blood draws every three days for 22 days (656 assayed samples), as well as an additional survey on the 22nd day. The start of the daily surveys was timed so that students' 7th survey was their first full day on campus (i.e., the day after move-in). We also describe sub-studies involving (a) diagnostic interviews at the end of students' 1st academic year, (b) extending the daily surveys to capture a full month for participants with a menstrual cycle, and (c) piloting a college transition resilience program.

Discussion: Consistent with recent calls from the NIMH Director, this study uses the transition to college as an ecologically valid stress paradigm, in combination with novel intensive longitudinal assessment of immunology, to characterize social stress-related changes in biopsychosocial functioning over time. Studies resulting from this project will shed light on the dynamic interplay between key psychoneuroimmunological processes, advance the methodological standards of this field, and help identify intervention opportunities to improve mental health on college campuses and beyond.

1. Background

Stress is one of, if not the most widely studied mechanism driving negative health outcomes, given it is a transdiagnostic predictor of modern-day somatic and mental health disorders, including heart disease (Case and Deaton, 2017) and depression (LeMoult et al., 2020). Importantly, stress is a strong modulator of biological stress responses (Lupien et al., 2009; Shields and Slavich, 2017), positioning it as a focal construct in the field of psychoneuroimmunology. However, the field of stress science in human populations has been restricted by an overreliance on acute social stress tasks that, while extremely dependable in evoking both psychological and biological stress responses, fail to embrace the full complexity of human stressors (Simmons et al., 2021). Given the transdiagnostic importance of stress research, improving public health is contingent on methodologically rigorous studies that capture the nuance of human psychosocial and physiological responses to stress.

The focus on social stress itself is defensible, and arguably necessary, given the breadth of health outcomes that are particularly strongly

* Corresponding author.
E-mail address: dmoriarity@mednet.ucla.edu (D.P. Moriarity).

https://doi.org/10.1016/j.bbih.2025.100977
Received 13 November 2024; Received in revised form 24 February 2025; Accepted 10 March 2025
Available online 12 March 2025

associated with social stress in comparison to other types of stress (Feurer et al., 2017; McRae et al., 2006; Moriarity et al., 2021; Skoluda et al., 2015; Slavich et al., 2009, 2020; Vrshek-Schallhorn et al., 2015). In fact, Social Safety Theory has argued that humans have evolved to be particularly attuned to signals of social threat vs. safety given our highly interconnected nature (Slavich, 2020, 2022; Slavich et al., 2023). Further, the subjective experience and biological impact of our social environment can be amplified by cognitive interpretations of the social world and one's place in them (e.g., whether most people are inherently trustworthy vs. manipulative). However, consistent with calls from the past director of NIMH (Simmons et al., 2021), it is necessary to expand the breadth of stressor paradigms scientists use to more comprehensively develop our ability to foster resilience to the negative (and promote the positive) consequences of stress. Presently, the field of stress research is primarily built upon studies using (a) acute laboratory stressors and/or (b) retrospective accounts of stressors, both of which have value but are also inherently limited by concerns regarding (a) external validity and (b) recall bias, respectively. To complement these approaches, the field is in need of ecologically valid study designs that take advantage of naturally occurring stressors to collect prospective data.

To address this field-wide limitation, we designed Project Mental Health and Immunodynamics of Social Stress (MHISS), which used the transition to college for 1st year undergraduates as a naturally occurring, high intensity stressor that is characterized by the largest social upheaval many of these young students have ever (and likely, will ever) undergo. Consequently, the transition to college for first years promises to be a highly potent, developmentally critical social stressor during adolescence/emerging adulthood. This social-cognitive upheaval is hypothesized to contribute to why college students are nearly twice as likely as their peers to experience certain mental health difficulties including depression (Auerbach et al., 2016a; Burcusa and Iacono, 2007; Wilson and Dumornay, 2022). Increasing relevance to psychoneuroimmunology research, college students are also at higher risk of many communicable illnesses than non-college students (Marshall et al., 2019), likely due in part to close proximity living situations and other lifestyle differences. In addition to addressing a key limitation in the field of stress research, this methodology also enables this study to investigate the established mental health epidemic on college campuses (Auerbach et al., 2016b)—both through empirical studies and strategic partnership with local university administrators to improve the health resources provided to students during new student orientation and beyond.

Beyond the need to develop ecologically valid stress paradigms to increase the tools available to psychoneuroimmunologists, our team has recently highlighted concerns with typical longitudinal designs in our field (Moriarity and Slavich, 2023). Psychoneuroimmunology as a field seeks to characterize the interplay between psychosocial and immunological processes. To date, however, the vast majority of studies have used cross-sectional designs or longitudinal designs with infrequent (or singular) assessment of immune biology (Moriarity and Slavich, 2023). Given the highly dynamic nature of key psychoneuroimmunological processes (e.g., inflammatory activity, stress responses, many types of psychopathological symptoms), higher frequency assessment is necessary to capture the within-person variability that is of causal relevance.

Although intensive longitudinal data (ILD) collection has been increasing in popularity across the psychological sciences (Burke et al., 2017; Dora et al., 2024; Mengelkoch et al., 2023), there has been an understandable dearth of investment in this area for immune-focused studies given the scaling cost and burden (for both participants and research staff). However, physiometric (Gloger et al., 2020; Moriarity and Alloy, 2021; Segerstrom, 2020) evidence from salivary (Shields et al., 2019), urinary (Seizer and Schubert, 2024), and blood-based (Koelman et al., 2019) immune assessments consistently highlight the highly dynamic nature of many key immune measures, indicating that standard longitudinal designs do not suffice to extract mechanistic inferences for psychoneuroimmunological hypotheses. As discussed in greater detail in Moriarity and Slavich (2023), pairing data collection frequency to the temporal dynamics of the variables of interest is key to (a) isolate causally relevant within-person variability, (b) determine "optimal time lags" to use in future research (Dormann and Griffin, 2015), and (c) account for non-ergodicity (i.e., the degree to which an individual's specific effects differ from those that exist on average across a sample; Fisher et al., 2018; Molenaar, 2004). As such, it is imperative to invest in datasets which evaluate the cost-benefit analysis of intensive longitudinal immune assessments—a core motivation behind Project MHISS.

1.1. The present study

The goal of this protocol paper is to enhance the transparency of future empirical studies from this project by ensuring all methodological details are available in an open-access journal and to demonstrate the feasibility of these methods. In sum, the goals of Project MHISS are both methodological and applied in nature. First, it will contribute to the diversification of stressor paradigms by establishing the transition to college as an ecologically valid, intensive stressor. Second, it will evaluate the methodological value of immune assessments taken multiple times per week during an acutely stressful life event. Third, it will use intensive longitudinal biopsychosocial data to test the dynamic interplay between various types of stress (e.g., interpersonal, goal-oriented), social experiences (e.g., loneliness, trust), emotion regulation traits (e.g., rumination, cognitive reappraisal), behavioral tendencies (e.g., seeking social support, seeking distraction), and mental health (e.g., depression, anxiety) during a period characterized by risk for anxiety, mood psychopathology, and problematic substance use. Fourth, and more specifically, it will directly test key features of Social Safety Theory (Slavich, 2020) using social and non-social stressors, subjective social experiences such as loneliness and trust, and cognitive questionnaires with both social and non-social facets. Fifth, it will seek to identify key phases of risk that might be useful for college administrators to plan the implementation of support services for students. Lastly, the final year piloted a resiliency program to support a healthy transition to college for incoming undergraduates.

2. Method

2.1. Participants

Participants are undergraduate students at a large public university in California, USA. Participants aged 17–19 years at the time of screening were recruited via electronic screeners delivered by the local Office of Admissions. To participate, participants must have reported fluency in English, be living on campus, have university assigned roommates, and be moving at least 100 miles to campus. In addition, participants during the first two years of data collection had to be comfortable drawing their own blood microsamples and not have current severe immunological diseases or be using strong immune-modulating drugs. The need for informed consent was waived by the institution's Institutional Review Board in favor of an information sheet describing the study procedures along with risk/benefits.

Demographic descriptives for all participants included in the dataset can be found in Table 1 and Table 2. In total, data were collected from 173 unique individuals resulting in a total of 163 baseline assessments,

Table 1
Total sample demographics—continuous variables.

Characteristic	Mean	Median	SD	Range
Age	18.17 years	18 years	.40 years	17–19 years
Subjective SES	6.45	7.00	1.68	1–10

Note: *SD* = Standard deviation, SES = Socioeconomic status.

Table 2
Total sample demographics—categorical variables.

Characteristic	Number (%)
Sex at birth	
Female	133 (76.9 %)
Male	40 (23.1 %)
Gender	
Genderfluid	1 (.6 %)
Gender non-binary	2 (1.2 %)
Genderqueer	1 (.6 %)
Man	41 (23.7 %)
Two spirit	1 (.6 %)
Woman	120 (69.4 %)
Not listed or prefer to self-describe	1 (.6 %)
I feel that multiple identities better describe the way in which I identify	6 (3.5 %)
Sexuality	
Asexual	2 (1.2 %)
Bisexual	28 (16.2 %)
Heterosexual	93 (53.8 %)
Lesbian or gay	9 (5.2 %)
Mostly heterosexual	11 (6.4 %)
Queer	11 (6.4 %)
Questioning	3 (1.7 %)
Pansexual	3 (1.7 %)
Demisexual	2 (1.2 %)
I feel that multiple identities better describe the way in which I identify	3 (1.7 %)
I do not use a label	8 (4.6 %)
Race	
American Indian, Native American, Alaska Native, or Indigenous	1 (.6 %)
Black of African American	12 (6.9 %)
East Asian	46 (26.6 %)
Hispanic or Latina/e/o/x	36 (20.8 %)
Middle Eastern or North African	3 (1.7 %)
Native Hawaiian or Pacific Islander	5 (2.9 %)
South Asian	27 (15.6 %)
White	78 (45.1 %)
Not listed or prefer to self-describe	5 (2.9 %)
Prefer not to say	3 (1.7 %)
Family Income	
More than $200,000	56 (32.4 %)
$100,000-$200,000	44 (25.4 %)
$50,000-$100,000	22 (12.7 %)
$25,000-$50,000	22 (12.7 %)
Less than $25,000	8 (4.6 %)
Prefer not to say	21 (14.1 %)

3589 daily assessments, 656 assayed blood samples (only blood samples from participants who completed the ILD protocol were assayed to balance cost vs. analytic utility), 154 end-of-ILD protocol assessments, and 32 optional end-of-academic year follow-ups. Recruitment flowchart can be found in Fig. 1. In total, there were 153 study completers (see additional criteria for completion in the Procedures section below). Several individuals withdrew after the first day after only completing either the (a) daily assessment or (b) baseline assessment, hence the discrepancy between the number of individuals included in the dataset and the baseline assessments. Of note, compliance rates were incredibly high amongst study completers: 98 % for daily self-report surveys (3297/3366 possible surveys for 153 study completers, not including MHISS-fem [described below] or surveys from participants who dropped out/were removed due to non-compliance for other study components) and 95 % for blood draws (656/688 possible blood draws across 86 study completers in the two years that collected blood samples).

2.2. Procedure

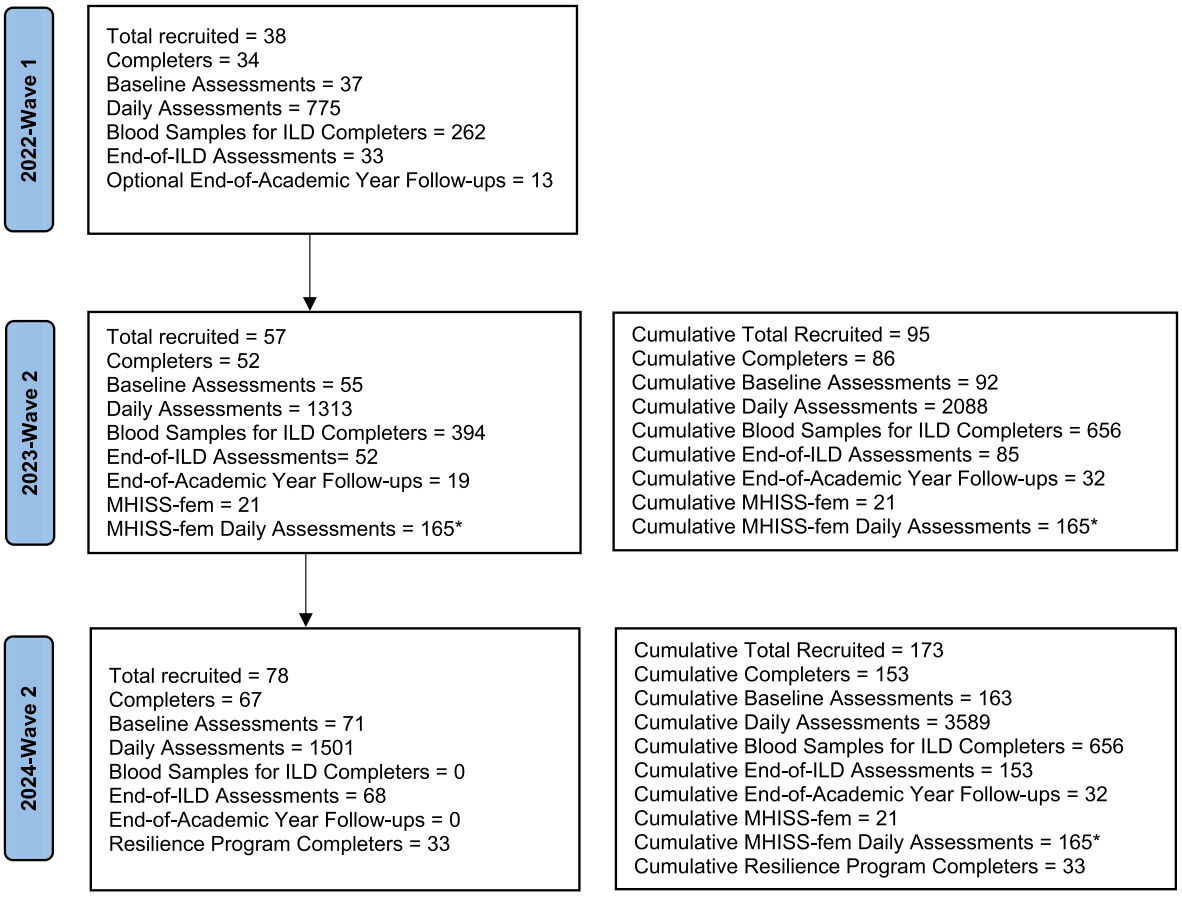
Primary protocol. Data collection involved an initial online screener followed by a 22-day ILD protocol that included (a) a baseline survey, (b) daily surveys, and (c) an end-of-ILD assessment on the final day of the ILD protocol (see Fig. 2 for Study Timeline and differences between waves). The start of the daily surveys was timed so that students' 7th survey was their first full day on campus (i.e., the day after move-in). Participants needed to complete >70 % of the daily surveys (16/22) and both the baseline and end-of-ILD surveys to complete the study and receive compensation ($60 in Years 1 + 2; $35 in Year 3 due to the lack of blood samples). Participants who completed 90 % of the daily surveys (20/22) were eligible for increased compensation ($20 in Years 1 + 2; $15 in Year 3 due to lack of blood samples). In Years 1 + 2, 75 % of blood draws (6/8) were also necessary for any compensation. Participants could earn an additional $5 for completing the optional diagnostic interview at the end of the academic year. Participants in MHISS-fem (described below) received an additional $1 per daily survey over 8 days, $2 for reporting next menstrual date, and $5 for completing 7/8 possible surveys. Compensation was completed via gift card.

As an attention check, each type of survey also included several items designed to test whether participants carefully read and answered the questions. Attention checks were included in all three types of surveys. To ensure careful responding, the attention checks in the daily surveys were changed approximately once per week. Multiple incorrect attention checks in a given survey rendered that survey invalid. Participants were excluded from the study if the baseline or end-of-ILD survey was deemed invalid (as they were only provided once) or if it dropped the participant below 16 valid daily surveys.

Additionally, during the first two waves of data collection, self-administered blood microsamples were collected every 3 days (Days 1, 4, 7, 10, 13, 16, 19, 22). ILD self-report questionnaires were supplemented with additional surveys about recent substance use and changes to medical status (e.g., chronic illnesses, infections, viruses, changes to medication) on blood sampling days. Participants were instructed to complete both the daily self-report surveys and blood draws between 8:00 a.m. and 11:00 a.m. local time to control for diurnal variation. Participants were provided training videos and given the opportunity to ask questions via e-mail, phone, or Zoom during blood sampling to maximize comfort and adherence. The timing of the blood draw was verified through an image upload at the end of the daily survey. Samples of whole capillary blood were collected via lancet puncture in the arm. Samples were dried and shipped overnight to a laboratory where they were aliquoted and frozen before analysis. The dried blood pods were collected individually into 2 ml microtubes upon arrival to the lab, labelled and stored at −80C until subjected to downstream analyses. Samples were analyzed in duplicate for C-reactive protein and triplicate for interferon-γ, interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17A, and tumor necrosis factor-α using Meso Scale Discovery S-PLEX Proinflammatory Panel 1 (human) Kits.

Secondary protocols: The second year of data collection also featured an optional sub-study, MHISS-fem, which extended the ILD self-report protocol by 8 days for participants with menstrual cycles. Inclusion/exclusion criteria were identical to what was described above (i.e., was consistent with the rest of the second year of data collection). The third year of the study did not include blood assessments, but did pilot a college resilience transition program with participants randomized to the program or treatment-as-usual (i.e., standard student orientation resources). Inclusion/exclusion criteria for this substudy were identical to previous years except participants were not excluded for medical status because the blood samples were not being collected. The resiliency program was added to test how self-instructed, flexible introduction of standard psychotherapy skills might influence stress and mental health outcomes during the college transition. This program was completed approximately 2 weeks prior to the start of data collection and consisted of 12 short modules focused on cognitive, emotional, and behavioral responses to stress. Each module consisted of a short video of a presentation highlighting key concepts and skills. The total duration of the videos was 1 hour and 10 minutes. Duration viewing was used as a validity check to ensure that each video was watched to completion. Recruited participants who did not complete the full duration of all videos before the beginning of the study were excluded.

Finally, in the first 2 years, there was an optional online, diagnostic



Note: *MHISS-fem daily assessments included in daily assessment counts.

Fig. 1. Recruitment flowchart.
Note: *MHISS-fem daily assessments included in daily assessment counts.

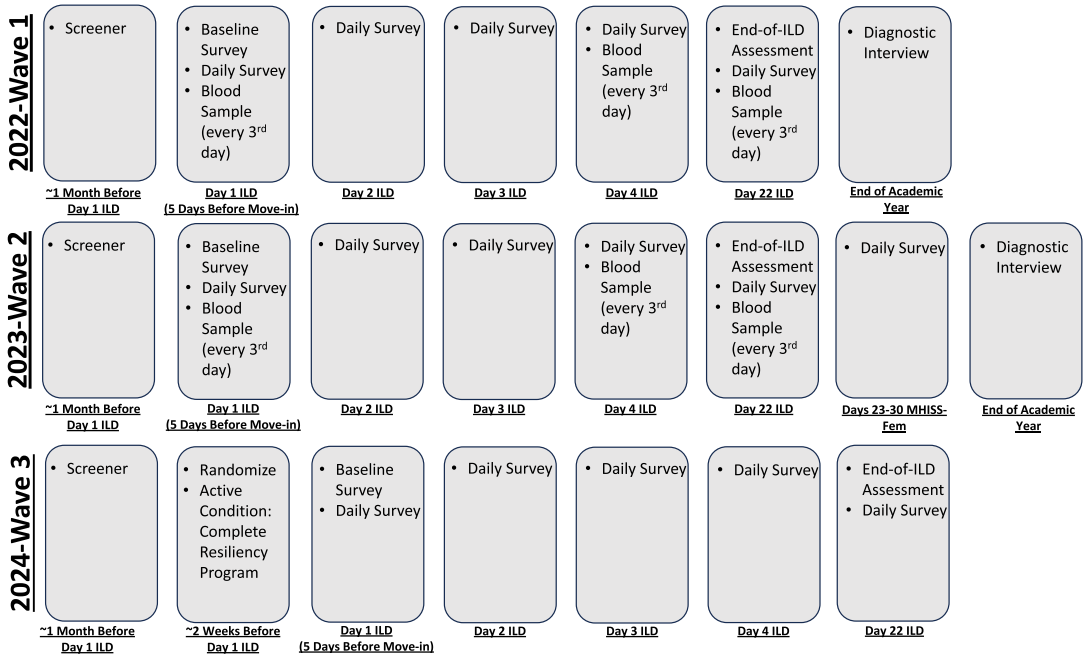


Fig. 2. Study timeline.
Note: ILD = Intensive longitudinal data.

Table 3
Assessment timetable.

Measures	Screener	Baseline	22 Days of ILD	End of ILD	End of 1st Year
Self-Report Measures					
Demographics	X				
Medical Status		X	X		
Sleep Survey			X		
Cognitive Emotion Regulation Questionnaire		X		X	
Greek Life Assessment				X	
Sensitivity to Punishment and Reward Questionnaire		X			
Behavioral Emotion Regulation Questionnaire		X			
Emotion Reactivity Scale		X			
Berlin Social Support Scale		X		X	
Behavioral Inhibition System/ Behavioral Activation System Scale (including sexuality subscale)		X			
Everyday Discrimination Scale		X		X	
Rumination on Positive Affect Scale		X			
Ruminative Responses Scale		X			
Connor-Davidson Reactivity Scale		X			
Positive Valence Systems Scale		X		X	
Dysfunctional Attitudes Scale		X			
Altman Self-Rating Mania Scale		X		X	
Sexual History		X		X	
Adverse Childhood Experiences		X			
Emotion Regulation Questionnaire		X			
Test of Negative Social Exchange		X			
Perceived Devaluation Discrimination Scale				X	
Blood Assessment Feedback				X	
Substance Use			X		
Adolescent Stress and Adversity Inventory			X		
Inventory of Depression and Anxiety Symptoms-II			X		
Modified International Physical Activity Questionnaire			X		
Perceived Threat and Perceived Neglect Scale			X		
Perceived Stress Scale			X		
Brief State Rumination Inventory			X		
Patient-Reported Outcomes Measurement Information System- Anxiety Short Form			X		
Perceived Relationship Quality Component Inventory			X		
UCLA Loneliness Survey			X		
Blood assessment validation image (every 3rd day)			X		
Blood samples (every 3rd day)			X		
Composite International Diagnostic Interview—Depression Module					X

Note: ILD = Intensive longitudinal data. Please note that not all measures were given to all participants. Some measures were added for portions of the study based on current research assistants' interests.

interview for participants at the end of their 1st academic year to screen for incidence of depression while on campus. A timetable of all assessments is shown in Table 3.

3. Discussion

Project MHISS was designed to gain new insights into the interplay between stress, the immune system, and health outcomes in emerging adults, while also highlighting methodologies necessary to advance these areas of work. Methodologically, it used the transition to college dorms for 1st year undergraduates as an ecologically valid, immersive stressor and will evaluate the utility of this paradigm in stress research and psychoneuroimmunology. Therefore, this project contributes to the diversification of the stress paradigms available to researchers to better understand the complexity and nuances of human stress responses (Simmons et al., 2021). This paradigm is also extremely well-suited for testing key hypotheses posited by Social Safety Theory, given the massive social upheaval experienced by first-year students moving far from home into college dorms (Slavich, 2020, 2022; Slavich et al., 2023).

Additionally, inspired by the low temporal stability of immune proteins (Koelman et al., 2019; Seizer and Schubert, 2024; Shields et al., 2019), Project MHISS featured high frequency blood microsampling (once every 3 days). Critically, the high compliance rate observed in study completers (95 %) demonstrates the feasibility of this approach from both data collection and participant burden perspectives. Further, by assaying for 10 different immune proteins, Project MHISS is well-positioned to make novel contributions to the physiometric understanding of immune processes over time, while also giving a more fine-grained view of the interplay between key psychoneuroimmunological processes (e.g., stress, inflammation, depression symptoms). However, given the novelty of this design, it is important to emphasize that the first studies published from this data to evaluate the merits of this data collection strategy will be highly exploratory and require both replication and expansion to other samples, frequencies, stressors, and biomarker panels.

Beyond its applied and methodological contributions, Project MHISS has the potential to reduce the public health burden of the mental health epidemic in college students (Auerbach et al., 2016b) by identifying key periods of risk during the transition to college (e.g., pre-move in vs. a few weeks post-move in) that can guide deployment of support services by university administrators. In support of this goal, the last year of this study featured an RCT for a resiliency program. Finally, Project MHISS is also more racially and ethnically diverse than the majority of psychoneuroimmunology research, and included expansive assessments of gender and sexuality—key attributes to ensure the growth of an equitable and generalizable field of psychoneuroimmunology as well as the development of college resiliency programs that will support diverse student populations.

CRediT authorship contribution statement

Daniel P. Moriarity: Writing – review & editing, Writing – original draft, Visualization, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Andrea C.M. Miller:** Writing – review & editing, Project administration, Methodology, Investigation, Conceptualization. **Japneet Kaur:** Writing – review & editing, Project administration, Investigation. **Ritika Prasad:** Writing – review & editing, Project administration, Investigation. **Matthew B. Figueroa:** Writing – review & editing, Project administration, Investigation. **George M. Slavich:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Ethics approval and consent to participate

This study was reviewed and approved by the Institutional Review Board at the University of California, Los Angeles.

Consent for publication

Not applicable.

Funding

Daniel P. Moriarity was supported by National Research Service Award F32 MH130149 and grant #OPR21101 from the California Governor's Office of Planning and Research/California Initiative to Advance Precision Medicine. George M. Slavich was supported by grant #OPR21101 from the California Governor's Office of Planning and Research/California Initiative to Advance Precision Medicine.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Daniel Moriarity reports financial support was provided by the National Institute of Mental Health. George Slavich reports financial support was provided by the California Governor's Office of Planning and Research. The others authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

Data availability

No data were used in the preperation of this article.

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