Susceptibility to Stress and Nature Exposure: Unveiling the Integrative Model of Environmental Sensitivity

By

Aaron M. Eisen, MS

A Dissertation

Presented to Oregon Health & Science University

School of Nursing

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

March 28, 2025

Approval Page

APPROVED:

Hector A. Olvera-Alvarez, PhD, PE, Dissertation Chair

Nathan F. Dieckmann, PhD, Committee Member

Quin E. Denfeld, PhD, RN, FAHA, Committee Member

Ellen L. Tilden, PhD, CNM, FACNM, Committee Member

Susan Bakewell-Sachs, PhD, RN, FAAN, Dean, School of Nursing

Acknowledgment of Financial Support

This program of research was supported, in part, by the JPB Environmental Health Fellowship from the JPB Foundation, administered by the Harvard T.H. Chan School of Public Health; the Hoffman Program for Chemicals and Health at the Harvard T.H. Chan School of Public Health; the National Institute on Minority Health and Health Disparities (NIMHD; Grant: 5U54MD007592), a component of the National Institutes of Health (NIH); and the Achievement Rewards for College Scientists (ARCS) Scholar Award. The funding entities had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscripts; the content is solely the responsibility of the author.

Acknowledgments

This dissertation would not have been possible without the unwavering support of my chair, Dr. Hector Olvera-Alvarez, whose mentorship has profoundly shaped my development as a scholar. I am especially grateful to my committee members and manuscript co-authors for their renowned expertise, which has been instrumental in refining the intellectual quality and methodological rigor of this work. I also wish to acknowledge all the mentors who have guided me along this journey, as well as the encouragement of my family and friends who anchored me through it. This dissertation is dedicated to the memory of Florence and Raymond Caine, my grandparents, who always believed in me.

Abstract

Background

Emerging epidemiological evidence indicates that groups in low socioeconomic positions exhibit more pronounced health benefits from nature exposure (e.g., contact with natural green spaces) compared to more privileged groups. This implies that increasing access to nature for disadvantaged communities could be a strategic approach to attenuate health disparities by alleviating the risks of chronic stressors among groups who are the most susceptible to stress. However, the evidence supporting this possibility is mixed, including reports of null associations, and further research is thus needed to better understand the causal mechanisms underpinning this phenomenon. Establishing these mechanisms could ultimately reveal more effective pathways for addressing health disparities, as nature-based interventions offer a promising approach: they are passive, promoting health without requiring behavioral change; they are sustainable, typically with low maintenance costs; and they can be implemented through public health policy to create lasting impacts.

Objective

The objective of this program of research was to uncover potential causal mechanisms underpinning epidemiological evidence that groups in lower versus higher socioeconomic positions exhibit more pronounced health benefits from nature exposure.

Framework

To guide this inquiry, we developed the Integrative Model of Environmental Sensitivity, a theoretical framework for synthesizing knowledge from disparate literatures to better understand how individual differences in environmental sensitivity could be leveraged to reduce disparities in health across socioeconomic gradients. Central to this framework are two overarching ideas: (susceptibility to stress) groups in lower socioeconomic positions often face higher exposure to persistent psychosocial stressors in early life, which in turn could induce a lifelong susceptibility to stress through various neurobiological pathways; (environmental sensitivity) susceptibility to stress, traditionally understood as heightened

reactivity to stressors, could also encompass enhanced responsivity to health-protective exposures, inducing greater risks in adverse environments, but also greater benefits in protective environments. Put together, these ideas provide a plausible mechanistic explanation as to why groups in lower versus higher socioeconomic positions could derive greater benefits from the health-protective effects of nature exposure.

Methods

Based on our framework, we operationalized environmental sensitivity across three levels of analysis: a pro-inflammatory immune state as a neurobiological correlate of susceptibility to stress; early life stress as a causal antecedent of susceptibility to stress; and socioeconomic status as the broader context through which social and health relationships are shaped, serving as an upstream facilitator of susceptibility to stress. The first aim was to establish experimental evidence that a pro-inflammatory state could be associated with greater recovery from an acute stressor in a nature versus office environment. The second aim was to extrapolate this experimental evidence into a real-world paradigm using an observational design to demonstrate that early life stress could be associated with better health among residents of greener neighborhoods. The third aim was to integrate the broader context of socioeconomic status into this real-world paradigm to demonstrate that residential nature exposure could be associated with better health among groups with higher lifetime exposure to stressors related to the social determinants of health.

Results

In the first study, we found that participants with a pro-inflammatory state exhibited greater recovery from an acute stressor in a nature versus office environment, relative to less susceptible participants. This evidence broadly elucidates a physiological mechanism through which groups with high exposure to early-life stressors could derive greater health benefits from nature exposure. In the second study, we found that participants with higher exposure to early-life stressors exhibited more pronounced cardiometabolic benefits when living in greener neighborhoods, relative to those with moderate exposures. This evidence reinforces the role of early life stress as a facilitator of the mechanistic pathway through

which groups in low socioeconomic positions could derive greater health benefits from nature exposure. In the third study, we found that participants in lower socioeconomic positions reported the highest exposure to early-life stressors and also exhibited more pronounced cardiometabolic benefits when living in greener neighborhoods, relative to those in moderate positions. This evidence reinforces the role of low socioeconomic status as an upstream facilitator of early life stress and in turn, the physiological mechanism that could promote greater health benefits from nature exposure.

Discussion

Overall, our findings contribute to growing evidence and further support the idea that increasing access to nature within disadvantaged neighborhoods could be an effective strategy to reduce disparities in health across socioeconomic gradients. Specifically, our findings further underscore the importance of integrating protective physical environments into public health strategies, especially for groups in low socioeconomic positions with a history of early-life stressor exposure, who are particularly susceptible to health risks but also might stand to experience the greatest health benefits from nature exposure.

Conclusion

Looking forward, future research in line with the Integrative Model of Environmental Sensitivity could lead to a better understanding of how the total environment could be harnessed to more effectively reduce disparities in health among vulnerable populations. As the evidence supporting this theoretical framework continues to expand, it could inform more targeted interventions that leverage individual differences in environmental sensitivity to promote health equity, ultimately providing more nuanced, strategic, and socioeconomically attuned approaches to public health.

Table of Contents

Page

Approval Page ii

Financial Support iii

Acknowledgments iv

Abstract v

Chapter One 1

Chapter Two 38

Chapter Three 88

Chapter Four 128

Chapter Five 171

The sections of this dissertation are arranged in the following manner. In Chapter One, I develop the Integrative Model of Environmental Sensitivity to guide my inquiry into a significant gap in the literature. In Chapters Two – Four, I systematically examine this framework across three levels of analysis. In Chapter Five, I synthesize the evidence across these studies, highlight key implications, and provide directions for future research. References and supporting information are provided in their respective chapters, and lists of tables and figures are provided after the title page for each data-based manuscript.

Chapter One

Emerging epidemiological evidence indicates that groups in low socioeconomic positions exhibit more pronounced health benefits from nature exposure compared to more privileged groups. This implies that increasing access to nature for socially disadvantaged communities could be a strategic approach to reduce disparities in health across socioeconomic gradients. However, the evidence supporting this possibility is mixed, including reports of null associations, and further investigation is thus needed to better understand the mechanisms underpinning this phenomenon. Establishing these mechanisms could ultimately reveal more effective strategies for addressing health disparities, as nature-based interventions offer a promising approach: they are passive, promoting health without requiring behavioral change; they are sustainable, often with low maintenance costs; and they can be implemented through public health policy to create lasting impacts.

[1] Significance

It is well-established that contact with nature (natural green spaces) is associated with a broad range of physical and mental health benefits [1–4]. For instance, studies have shown that nature exposure in residential settings reduces the risk of cardiovascular disease [5], metabolic disorders [6], mental health disorders [7], respiratory disease [8], immunological disorders [9], neurological disorders [10], and all-cause mortality [11]. Studies have also shown that residential nature exposure improves cognition and behavioral regulation [12], sleep quality and circadian function [13], happiness and social connectedness [14], and general well-being and life satisfaction [15]. The broad diversity of these benefits implicates a multiplicity of mechanistic pathways, including stress reduction [16], attention restoration [17], increased physical activity [18], improved air quality [19], more opportunities for socialization [20], enhanced immune function [21], exposure to medicinal phytoncides [22], and local temperature regulation [23].

Importantly, emerging epidemiological evidence indicates that nature exposure has the potential to attenuate health disparities, with stronger health-protective effects observed

in lower versus higher income neighborhoods. In England, a study on the population below retirement age (n = 40,813,236) found that the disparity gap for all-cause mortality and deaths from circulatory disease between the highest and lowest income groups was 26% – 30% smaller in the greenest neighborhoods [24]. In Scotland, a study on the population below retirement age (n = 5,404,700) found that the disparity gap for premature mortality between the highest and lowest income groups was 40% smaller in the greenest neighborhoods [25]. In Europe, a secondary analysis of the European Quality of Life Survey (n = 21,294) found that the disparity gap for mental well-being between the highest and lowest income groups was 40% smaller in the greenest neighborhoods [26]. In the United States, two studies on Medicare beneficiaries in Miami-Dade County, Florida (n = 249,405) found that the disparity gap for chronic conditions (hypertension, diabetes, hyperlipidemia, depression, and dementia) between the highest and lowest income groups was 13% – 17% smaller in the greenest neighborhoods [27,28]. In China, a secondary analysis of the 33 Chinese Community Health Study (n = 2,154) found that the disparity gap for kidney failure between the highest and lowest income groups was 9% smaller in the greenest neighborhoods [29].

However, there have also been reports of mixed and null associations. In Latin America, a secondary analysis of the Urban Health in Latin America Study (n = 152,773,086) found that the magnitude of cardiovascular disease mortality reduction by educational attainment was 5% larger in neighborhoods with medium-high versus low greenness [30]. In South Africa, a secondary analysis of the South African National Income Dynamics Study (n = 11,156) found that residing in greener neighborhoods was associated with a 2% lower incidence of depression among middle versus low-income groups [31]. In Australia, two secondary analyses of the Longitudinal Study of Australian Children (n = 10,090) found no effect modification for neighborhood greenness on the disparity gap for parent-reported child health [32] or maternal body mass index [33].

Given the mixed evidence in the literature, it is clear that further investigation is needed to better understand this phenomenon, which could lead to more effective strategies for addressing health disparities. Although the potential implications of this evidence are

promising, the causal mechanisms underpinning this phenomenon remain unknown. Developing theoretical frameworks and establishing experimental evidence could provide insight into these mechanisms, helping to address ambiguities in the literature and further supporting the idea that increasing access to nature for socially disadvantaged communities could be a strategic approach to reduce disparities in health across socioeconomic gradients. Therefore, the overarching objective of this program of research was to identify and examine potential causal mechanisms underpinning this phenomenon.

[2] Background

One potential causal mechanism underpinning this phenomenon is outlined by integrating two overarching ideas. The first idea is that groups in low socioeconomic positions, compared to more privileged groups, often face higher exposure to persistent psychosocial stressors in early life [34–37], which can induce a lifelong susceptibility to stress through various neurobiological pathways (i.e., Biological Embedding Model [38–41]). The second idea is that susceptibility to stress could reflect increased sensitivity to both adverse (risk-promoting) and protective (benefit-enhancing) environmental conditions (i.e., Differential Susceptibility Hypothesis [42–45]). Put together, these ideas suggest that increased environmental sensitivity induced by early life stress could provide a mechanistic explanation as to why groups in lower versus higher socioeconomic positions could derive greater benefits from the health-protective effects of nature exposure.

[2.1] Biological Embedding Model

It is well-established that groups in low socioeconomic positions, compared to more privileged groups, face social inequities that obstruct and compromise experiences with the social determinants of health [46,47]. This represents at least one prominent pathway through which groups in low socioeconomic positions are burdened with high exposure to stressors across the lifespan, and particularly during childhood [48–51]. For instance, evidence indicates that children living in poverty have a five-fold risk of being exposed to psychosocial stressors compared to their more advantaged counterparts [52]. It is also

well-established that early life stress is associated with the leading causes of morbidity and mortality, including cardiovascular disease, respiratory disease, kidney disease, mental health disorders, metabolic disorders, stroke, and cancer [53–56]. The Centers for Disease Control (CDC) recognizes this association as a preventable public health crisis and has estimated that early life stress could account for 13% of the prevalence of coronary heart disease, the leading cause of death in the United States [57].

The robust association between early life stress and negative health outcomes across the lifespan raises important questions. How do adverse experiences become physically embedded under the skin of the developing child? What causes these changes to persist throughout the life course? Through what mechanisms do these changes robustly increase morbidity and mortality? For over two decades, biomedical and behavioral scientists across various disciplines sought to answer these questions, which ultimately led to the paradigm of biological embedding, a set of integrative and heuristic frameworks to explain the plethora of negative outcomes associated with early life stress [38–41]. Biological embedding occurs "when experience gets under the skin and alters human biological and developmental processes; when systematic differences in experience in different social environments in society lead to systematically different biological and developmental states; when these differences are stable and long term; and finally, when they have the capacity to influence health, well-being, learning, or behavior over the life course" [38].

In short, it is well-established that early life stress can induce developmental alterations that exert enduring effects, even decades later, across numerous neurobiological systems (e.g., central nervous system, autonomic nervous system, immune system, cardiovascular system, endocrine system [58–61]). Together, these neurobiological systems engage in multidirectional transactions throughout the lifespan, persistently amplifying cross-talk that increases reactivity to stressors (e.g., Neuroimmune Network Hypothesis [62], Social Signal Transduction Theory of Depression [63], Cumulative Risk Model [64], Toxic Stress [65], Allostatic Load Model [66]).

For instance, mounting evidence indicates that early life stress sensitizes cortico-amygdala circuits with increased vigilance and threat processing, amplifying innate immune re-

sponses and facilitating the development of a chronic pro-inflammatory state ("brain to immune traffic" [62]). This amplified immune response also induces neuro-inflammation that has been shown to further sensitize cortico-amygdala circuits with increased vigilance and threat processing ("immune to brain traffic" [62]) in a lifelong and self-perpetuating cycle. Neuro-inflammation has also been shown to reduce cortico-basal ganglia reward sensitivity, eliciting profound changes in health behaviors and executive functioning [62]. These changes facilitate increased engagement with high-risk behaviors (e.g., tobacco, alcohol, and substance use, physical inactivity, high-fat diets; Reward Deficiency Model of Addiction [67]) that in turn, further propagate inflammation [62].

The plethora of negative health outcomes associated with early life stress underscores a complex etiology of person x environment interactions. Yet, it is clear that chronic inflammation could be a common soil that helps to fertilize the development and progression of many of them [68]. For instance, through sensitizing cortico-amygdala circuits with increased vigilance and threat processing, chronic inflammation also sensitizes the sympathetic-adrenal-medullary (SAM) axis and the hypothalamic-pituitary-adrenal (HPA) axis to be more reactive in response to stressors [69], which is associated with an increased risk of cardiovascular disease, metabolic disorders, mental health disorders, and all-cause mortality [70]. Chronic inflammation itself also causes significant cellular and tissue damage across neurobiological systems and is associated with an increased risk of cardiovascular disease, respiratory disease, kidney disease, cancer, and other chronic inflammatory conditions (e.g., insulin-dependent diabetes, inflammatory bowel disease, multiple sclerosis, rheumatoid arthritis [71]). Further, by reducing cortico-basal ganglia reward sensitivity, chronic inflammation also induces anhedonia [72] and can facilitate increased engagement with high-risk behaviors [69], increasing the risk of various mental and physical health disorders [67]. Importantly, this list is not exhaustive, but rather highlights some of the most well-established pathways through which early life stress increases morbidity and mortality across the lifespan.

Based on this evidence, the prevailing perspective in the biological embedding literature is that while biological responses to stressors are often beneficial in the short term (facilitating

immediate adaptive responses), persistent activation of the stress response system is toxic and maladaptive in the long term [62–66]. The biological embedding of early life stress causes disruptions in the brain, resulting in the dysregulation of physiological mediators (e.g., autonomic, endocrine, immune, metabolic) that are the precursors of later impairments in behavior and the mechanisms of chronic stress-related diseases [65]. Allostatic load is often the term used to describe the wear and tear resulting from repeated allostatic adjustments (adaptations to stressors), which increases the risk of negative outcomes as a person ages [66]. From this perspective, there is an optimal level of stress responsivity, with either persistent hyper-activation or hypo-activation of these physiological mediators representing dysfunctional deviations from the norm [73]. This implies that children reared in supportive environments (with appropriate challenges) undergo normal development, while children reared in adverse environments are at risk for developmental dysregulation [62–66].

Given that groups in low socioeconomic positions, compared to more privileged groups, often face higher exposure to persistent psychosocial stressors across the lifespan (e.g., poor housing conditions, neighborhood deprivation, food insecurities, barriers to healthcare, racism and discrimination, poor air and water quality [48–51]) and are more susceptible to the health risks of chronic stress (heightened neurobiological reactivity to stressors [62–66]), early life stress could be a key pathway through which socioeconomic status becomes biologically embedded, altering how individuals experience and respond to environmental exposures across the lifespan and contributing to health disparities [74–77].

Building on this foundation, the following operational definitions were used to guide the current program of research: *socioeconomic status* is defined as the position of an individual in their society which is determined by both social and economic factors that impact exposure to and experiences with psychosocial stressors; *early life stress* is defined as persistent exposure to psychosocial stressors during childhood, with ranging degrees of perceived severity, that induce neurobiological responses and could promote developmental alterations over time; *susceptibility to stress* is defined as heightened neurobiological reactivity to stressors, which could be a function of early life exposures.

[2.2] Differential Susceptibility Hypothesis

While biomedical and behavioral scientists of the biological embedding literature sought to answer the question of "how adverse experiences become physically embedded under the skin of the developing child", evolutionary biologists and developmental psychologists from a different field of literature sought to answer a different question: "why should childhood experiences alter later development and influence health and well-being over the lifespan?" For well over two decades, this field has recognized that developmental strategies that promote success in some environments could lead to failure in others and therefore, a single best approach for development is unlikely to exist (for a comprehensive synthesis, see West-Eberhard, 2003 [78]). This perspective challenges the prevailing notion that early life stress derails normal development; rather, stressful and supportive environments were a part of the human experience throughout our evolutionary history, meaning that our developmental systems have been shaped by natural selection to respond to a range of environmental conditions [42–45]. When children are reared in stressful environments, it might not disturb, but rather redirect childhood development toward strategies that are adaptive in adverse environments; and by contrast, when children are reared in well-resourced and supportive environments, it might redirect childhood development toward strategies that are adaptive in these contexts, at least within the range encountered during evolution [79–82].

Diverging from the maladaptive connotation of biological embedding, this evolutionary-developmental perspective posits that humans undergo conditional adaptations to environmental influences: "evolved plasticity mechanisms that detect and respond to specific features of childhood environments, features that have proven reliable over evolutionary time in predicting the nature of the physical and social world into which children will mature, and entrain developmental pathways that reliably matched those features during a species' natural selective history" [79]. From this perspective, early life stress and adversity serve a dual function, working as cues for plasticity mechanisms and modulating the sensitivity of these mechanisms over time [83–86]. The idea that some individuals are more sensitive to adverse exposures is not novel, as demonstrated by the concept of

susceptibility to stress [62–66]. Yet, the biological embedding literature focuses exclusively on maladaptive outcomes and lacks a functional model of individual differences that accounts for why these differences would evolve and be maintained by natural selection.

For over two decades, efforts to develop such a model ultimately gave rise to the differential susceptibility literature, a set of heuristic frameworks to explain individual differences in susceptibility to environmental influences [42–45]. According to these frameworks, the same mechanisms that determine susceptibility to chronic stress and adversity might also confer enhanced responsivity to the positive, supportive, and protective aspects of the environment [79–82]. In other words, individuals who are susceptible to stress might respond to their environmental conditions in a "for better and for worse" manner and have a wider range of reaction norms that cover the full gamut of environmental exposures, whereas individuals who are less susceptible might have a much narrower range of reaction norms, responding less towards both adverse (risk-promoting) and supportive (benefit-enhancing) environmental conditions [87–90] (for an interpretation based on reaction norms, see Manuck, 2009 [91]).

[2.2.1] Biological Sensitivity to Context Theory

One of the core concepts of the differential susceptibility literature is biological sensitivity to context, a conditional adaptation model of developmental variation in the stress response system based on two propositions [79,80]. The first proposition is that the stress response system is a complex and integrated consort of neurobiological responses (e.g., autonomic, neuroendocrine, neuroimmune, cardiometabolic) designed to prepare humans for challenges and threats, but also functions to increase susceptibility to social resources and supportive factors in the ambient environment. This dual function emphasizes the need to conceptualize stress reactivity more broadly as heightened neurobiological sensitivity to context. The second proposition is that the stress response system operates as a mechanism of conditional adaptation, encoding information about levels of adversity versus support in the early-life environment; this information is then used to

regulate the activation thresholds and response magnitudes of the stress response system to match those specific environmental conditions.

Based on mounting evidence that early life stress increases stress reactivity [62–66] and growing evidence that heightened stress reactivity enhances sensitivity to supportive conditions [92–95], these propositions posit a u-shaped association between early-life adversity versus support and biological sensitivity to context: (1) exposure to high adversity and low support upregulates biological sensitivity to context, increasing the capacity and tendency of an individual to identify and respond to external challenges and threats; (2) exposure to high support and low adversity also upregulates biological sensitivity to context, increasing susceptibility to social resources and supportive factors in the ambient environment; (3) and by contrast, relatively moderate exposures in either direction downregulate biological sensitivity to context, maximizing adaptive fitness in environments that are not particularly adverse or supportive, as experienced by the vast majority of individuals [79,80]. Because biological sensitivity to context has associated costs (increased risk of negative outcomes under adverse conditions), it would not be adaptive for the majority of individuals who are reared in normative environments. Rather, lower levels of biological sensitivity to context would facilitate the best outcomes in these environments, buffering individuals against the risks of chronic stressors in a world that is not particularly adverse or threatening, but also not consistently safe or supportive.

[2.2.2] Adaptive Calibration Model

Another core concept of the differential susceptibility literature is adaptive calibration, a model that extends and refines the assumptions of biological sensitivity to context into the broader evolutionary framework of Life History Theory [81,82]. Although this re-analysis supported a number of refinements (e.g., sex differences, switch points, life stages), the most notable contribution was highlighting that adverse and supportive rearing environments might induce different adaptive phenotypes of biological sensitivity to context [96–99]. In short, Life History Theory in evolutionary biology is used to explain coordinated patterns of human development, encompassing growth, survival, and reproduction

over the life course [100–103]. Maximizing adaptive fitness within specific environmental contexts necessitates inherent trade-offs in these developmental investments, characterized as slower versus faster life history strategies [104]. Assuming that basic bioenergetic resources are met, slower life history strategies are the product of supportive rearing environments and are oriented towards future outcomes, including long-term health and well-being. By contrast, faster life history strategies are the product of adverse rearing environments and are oriented towards immediate outcomes, including survival under threatening conditions experienced throughout our evolutionary history (e.g., predatory threats, hostile conspecifics), prompting developmental trade-offs that are often detrimental for long-term health and well-being [81,82] (e.g., susceptibility to stress [62–66]).

For instance, one mechanism through which early life stress could promote a faster life history strategy is through the adaptive calibration of the immune system (e.g., Neuroimmune Network Hypothesis [62]). As noted before, early life stress sensitizes cortico-amygdala circuits with increased vigilance and threat processing, facilitating the development of a pro-inflammatory state ("brain to immune traffic") that further sensitizes cortico-amygdala circuits with increased vigilance and threat processing ("immune to brain traffic") in a life-long and self-sustaining cycle. Importantly, increased vigilance to threats would be a remarkably adaptive trait in adverse environments, increasing the capacity and tendency of an individual to identify and respond to physical challenges and threats, while the amplified inflammatory response would also protect them against infection from their frequent engagement in fight or flight behaviors [62,63]. However, this would often be at the cost of their long-term health and well-being due to heightened allostatic load [66], a very costly but incredibly adaptive developmental strategy in environments where immediate survival is in question [84–86].

In support of differential susceptibility, emerging experimental evidence has shown that a pro-inflammatory immune state also enhances sensitivity to supportive social conditions [105]. Consistent with the concept of susceptibility to stress, participants exposed to an in-vivo inflammatory challenge (low-dose endotoxin; $n = 61$) demonstrated increased neural activity in threat-processing regions (bilateral amygdala and dorsal anterior cingulate

cortex) when receiving negative versus neutral social feedback about their performance on an audio-recorded interview, relative to participants who were given a placebo (n = 54). But also consistent with the concept of differential susceptibility, the same participants who received the endotoxin also demonstrated heightened neural activity in reward-processing regions (ventral striatum and ventromedial prefrontal cortex) when receiving positive versus neutral social feedback about their performance on the interview, relative to participants who were given the placebo. Together, these findings reveal that inflammation can increase neural sensitivity to both negative and positive social feedback, which would also represent another remarkably adaptive trait under adverse conditions, especially given the historical implications that social conflict, rejection, and isolation had for physical danger, along with the implications that social support and organization had for security [106].

[2.2.3] Differential Susceptibility Theory

Another core concept of the differential susceptibility literature is the theory of differential susceptibility [88,89], a model that extends the concept of conditional adaptation to consider the impact of nature (genetics) versus nurture (environmental exposures) on plasticity mechanisms [107]. Although developmental plasticity is adaptive in the sense that it matches specific phenotypes to environmental conditions, incorrect predictions can result in mismatched phenotypes that reduce rather than enhance fitness [108]. Therefore, it is suspected that natural selection has maintained genes for both "conditional" (plastic) and "alternative" (non-plastic) developmental strategies as a form of insurance against mismatched phenotypes [109]. From this perspective, the biological function of differential susceptibility is to reduce the costs of developmental plasticity by making some individuals resistant to environmental influences [110]. However, this model was later expanded to include a prenatal programming hypothesis, suggesting that prenatal exposures (e.g., maternal stress hormones) can activate or suppress genes for conditional developmental strategies through epigenetic modifications [111]. In support of this hypothesis, animal models have shown that prenatal stress can increase susceptibility to the negative effects of adverse rearing environments, but also to the beneficial effects of supportive rearing environments [112].

[2.2.4] Differential Susceptibility Hypothesis

Collectively, the evolutionary-inspired arguments of the Biological Sensitivity to Context Theory [79,80], the Adaptive Calibration Model [81,82], and the Differential Susceptibility Theory [88,89] converge on the Differential Susceptibility Hypothesis, that individuals who are more susceptible to the negative outcomes of adverse (risk-promoting) environmental conditions are also more susceptible to the positive outcomes of supportive (benefit-enhancing) environmental conditions [42–45]. Within this field of literature, susceptibility to the environment is grounded in neurobiology and characterized as heightened stress reactivity (e.g., autonomic, neuroendocrine, neuroimmune, cardiometabolic), representing a sustained developmental alteration enabled by early-life exposures [83–86].

Importantly, this conceptualization of susceptibility does not negate but rather incorporates and extends the concept of susceptibility within the biological embedding literature [38–41]. Both fields emphasize that early life stress can induce a lifelong susceptibility to stress, which in turn increases the risk of negative outcomes under adverse environmental conditions. However, the biological embedding literature focuses exclusively on negative outcomes and makes no assumptions about whether or to what extent susceptibility to stress could also moderate the positive outcomes of supportive environmental conditions [62–66]. The consequence has been an imbalanced approach to research, yielding significantly more knowledge about dysfunction rather than adaptive function, making it challenging to attain a full account of the subject matter. Through shifting the emphasis on dysregulation to conditional adaptation, the differential susceptibility literature advances the crucial argument that what is currently recognized as susceptibility to stress could instead reflect increased sensitivity to both adverse and supportive environmental conditions.

Over the past two decades, the differential susceptibility paradigm has cultivated a very active area of research focused on disentangling person x environment interactions across three levels of analysis: genetic, physiological, and behavioral markers of differential susceptibility (for a cumulative synthesis, see Boyce, 2016 [42]). Physiological markers comprise a necessary link between genes and behavior, whereby genetic markers operate through physiological processes and behavioral markers are the consequence of these

processes [42–45]. Accordingly, whatever the level of analysis employed, neurobiological susceptibility to environmental influences represents the fundamental construct of interest.

Studies of genetic markers have identified candidate genes involved in serotonergic signaling (e.g., 5-HTTLPR, 5-HTR2A, THP-1 [113–115]), dopaminergic signaling (e.g., DRD4, DRD2, COMT [116–118]), and other neuro-pathways (e.g., MAOA, CRHR1, OXTR, BDNF [119]). Studies of physiological markers have centered on the stress response system, including autonomic (e.g., PEP, HRV, RSA, EDA, sAA [92,120–123]) and neuro-endocrine (e.g., CORT, ACTH, CRH [95,124,125]) reactivity. Studies of behavioral markers have identified candidate traits among both children (e.g., negative emotionality, difficult temperament, impulsivity [126]) and adults (e.g., sensory processing sensitivity, personality characteristics, negative affect [127]).

As a culmination of this work, a seminal review of 56 studies encompassing thousands of participants (n = 22,686; age 18+ [56%]) demonstrated that individuals who were susceptible to stress (across these biobehavioral markers) also exhibited greater health benefits under supportive social conditions (e.g., positive life events, social support, quality relationships, better access to the social determinants of health), as compared to individuals who were less susceptible [128]. Overall, these findings support the argument that many of the susceptibility factors identified in the biological embedding literature might instead operate as differential susceptibility factors.

Building on this foundation, the following operational definitions were used to guide the current program of research: an *environmental factor* is defined as a specific exposure that influences health or well-being, with a valence ranging from a "stressor" (a stimulus that causes stress) to a "protective factor" (a stimulus that protects against stressors); an *environmental condition* is defined as the ratio of environmental factors at a given place and time, with a valence ranging from "adverse" (an elevated ratio of stressors to protective factors, i.e., risk-promoting) to "protective" (an elevated ratio of protective factors to stressors, i.e., benefit-enhancing); (3) the *total environment* is defined as the external socioemotional and physicochemical world: the sum of all environmental conditions that an individual is exposed to across their lifespan; (4) *environmental sensitivity* is defined

as heightened neurobiological responsivity to the health influences of both adverse and protective environmental conditions, which could be a result of early-life exposures.

[3] Theoretical Framework

Incorporating the concept of differential susceptibility into the biological embedding literature could necessitate a significant shift in how susceptibility is conceptualized in public health research. Traditionally, susceptibility is often understood as a heightened sensitivity (a neurobiological predisposition) to the health risks of adverse environments and is observed more consistently among vulnerable groups (those with a higher risk of being exposed to chronic stressors). However, the differential susceptibility literature offers a more nuanced understanding: that the same neurobiological mechanisms that increase sensitivity to adverse environments could also enhance sensitivity to protective environments. Taken together, this alternative perspective suggests that early life stress might be better understood as not merely increasing susceptibility to stress, but as cultivating a broader form of environmental sensitivity.

This understanding could have widespread and far-reaching implications for public health research, particularly in elucidating the differential impacts of social and physical environmental factors across diverse populations and socioeconomic gradients to inform targeted interventions. To help facilitate this process, the principal investigator and co-investigators of this program of research developed a theoretical framework to better understand how individual differences in environmental sensitivity could be leveraged to reduce disparities in health across socioeconomic gradients. Based on the interconnections between the biological embedding and differential susceptibility literatures, this framework is grounded on two overarching ideas: (susceptibility to stress) groups in low socioeconomic positions, compared to more privileged groups, often face higher exposure to persistent psychosocial stressors in early life, which can induce a lifelong susceptibility to stress through various neurobiological pathways; (environmental sensitivity) susceptibility to stress, traditionally understood as a heightened reactivity to stressors, could also encompass enhanced respon-

sivity to health-protective exposures, inducing greater risks in adverse environments, but also greater benefits in protective environments.

Importantly, this framework warrants investigation into the idea that early life stress could be at least one mechanism underlying epidemiological evidence that nature exposure has the potential to attenuate health disparities, with stronger health-protective effects observed in lower versus higher income neighborhoods [24–29]. Specifically, it is plausible that increased environmental sensitivity induced by early life stress could provide a physiological pathway for groups in lower versus higher socioeconomic positions to derive greater health benefits from residential nature exposure. However, the literature supporting this framework has centered on social environments, and further research is needed to reveal whether or to what extent early life stress could also promote greater benefits from protective physical environments such as nature.

Establishing this evidence could ultimately reveal more effective strategies for addressing health disparities, as nature-based interventions offer a promising approach [129–132]. For instance, incorporating nature into residential settings is typically a safe, feasible, sustainable, and cost-effective intervention target [133–136] with potential as a complementary health approach that (1) could be installed as a passive intervention, promoting health without requiring behavioral change or administration by trained personnel; (2) could be a long-term intervention, promoting generational health with relatively low maintenance costs; (3) could provide multiple co-benefits, including more opportunities for exercise and socialization; and (4) could be implemented through public health policy to create large-scale impacts (for an excellent summary, see Frumkin et al. 2017 [4]).

There is also an extensive field of literature on the health-protective effects of natural versus urban environments, dating back to the earliest civilizations [137]. Over the past century, this field has been refined and numerous theoretical frameworks have been advanced based on evolutionary perspectives (e.g., Arousal Theory [138], Prospect-Refuge and Habitat Theory [139], Savanna Hypothesis [140], Forest Hypothesis [141], Biocultural Theory [142], Biophilia Hypothesis [143], Stress Reduction Theory [144], Attention Restoration Theory [145], Fractal Pattern Theory [146]). Even though these frameworks differ in

important respects, they converge on the fundamental premise that humans share an innate psycho-physiological affinity to natural features that maintained safety and nourishment throughout our evolutionary history. Due to these connections, many types of nature exposure can have a positive effect on physical and mental health, subjective well-being, and cognitive function relative to urban settings [1–4].

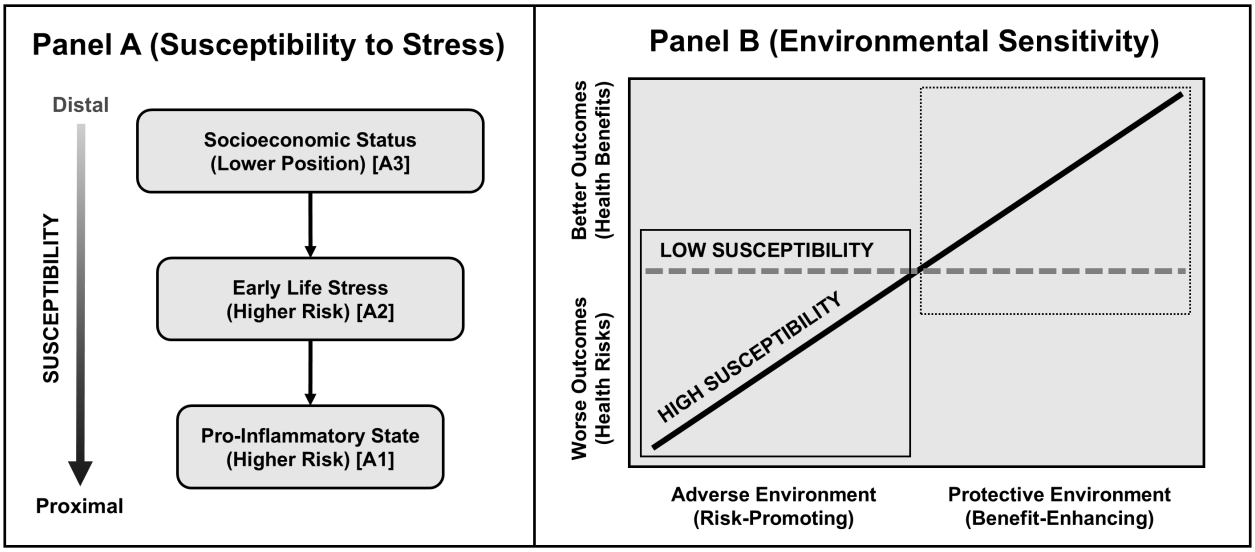
Embedding this evolutionary perspective into our theoretical framework implies that the strength of this affinity and the magnitude of its positive effects would be more pronounced among groups in lower versus higher socioeconomic positions with higher exposure to early-life stressors. Considering that a pro-inflammatory immune state is a central mechanism underpinning the association between early life stress and negative health outcomes under adverse conditions (e.g., Neuroimmune Network Hypothesis [62,147–150]), we expect it could also be a central mechanism enhancing positive outcomes under protective conditions. In this regard, a pro-inflammatory state could be a particularly relevant indicator of environmental sensitivity, given its proximal position on the causal pathway between early life stress and morbidity and mortality. Yet, to our knowledge, no studies have investigated whether early life stress or its neuroimmune correlates could be associated with greater health benefits from nature exposure. Therefore, the objective of this program of research was to provide initial insight into these associations to determine if there is sufficient evidence that warrants further investigation.

[4] Specific Aims

Overtly, this program of research sought to address the question of whether increased environmental sensitivity induced by early life stress could be at least one mechanism underlying epidemiological observations that groups in lower versus higher socioeconomic positions exhibit greater health benefits from nature exposure. Based on our theoretical framework, environmental sensitivity was operationalized across three levels of analysis: a pro-inflammatory immune state as a physiological manifestation of susceptibility to stress; early life stress as a causal antecedent of susceptibility to stress; and socioeconomic status as the broader context through which social and health relationships are shaped, serving

as an upstream facilitator of susceptibility to stress. Our specific aims were addressed in a three-paper series with a focus on each level of analysis using a bottom-up approach to provide a systematic examination of environmental sensitivity, progressively building from physiological mechanisms to broader societal contexts (see Fig 1).

Figure 1. Theoretical Framework & Specific Aims



Susceptibility to Stress: groups in low socioeconomic positions, compared to more privileged groups, often face higher exposure to persistent psychosocial stressors in early life, which can induce a lifelong susceptibility to stress through various neurobiological pathways, including a pro-inflammatory immune state; **Environmental Sensitivity**: susceptibility to stress, traditionally understood as a heightened reactivity to stressors, could also encompass enhanced responsivity to health-protective exposures, inducing greater risks in adverse environments, but also greater benefits in protective environments.

The first aim was to establish experimental evidence that a pro-inflammatory immune state could be associated with greater autonomic recovery from an acute psychosocial stressor in a nature versus office (control) environment. This aim centered on stress recovery as chronic stress is one of the most well-established mechanisms underpinning health disparities [74,75] and can effectively be mitigated by nature exposure [151,152]. Attainment of this aim could broadly elucidate a physiological mechanism through which groups with high exposure to early-life stressors could derive greater health benefits from nature exposure.

The second aim was to extrapolate this experimental evidence into a real-world paradigm using an observational design to demonstrate that early life stress could be associated

with better health among residents of greener neighborhoods. Cardiometabolic health was selected as the outcome of interest as cardiovascular disease and metabolic disorders are well-documented drivers of health disparities [153,154] and represent a class of conditions particularly responsive to the health-protective effects of nature exposure [155,156]. Attainment of this aim could reinforce the role of early life stress as a facilitator of the mechanistic pathway through which groups in low socioeconomic positions could derive greater health benefits from nature exposure.

The third aim was to integrate the broader context of socioeconomic status into this real-world paradigm to demonstrate that residential nature exposure could be associated with better health among groups with higher lifetime exposure to stressors related to the social determinants of health. Latent classes were used to validate expected groups and test for predicted associations based on low socioeconomic status, including higher rates of physical and mental health issues [74,75] and stronger health-protective effects among residents of greener neighborhoods [24–29]. Attainment of this aim could reinforce low socioeconomic status as an upstream facilitator of early life stress and in turn, the physiological mechanism that could promote greater health benefits from nature exposure.

[5] Conclusion

Although the attainment of these aims would provide relatively modest evidence, intended to encourage further investigation, contextualizing this evidence into our theoretical framework could have widespread and far-reaching implications for public health research. Specifically, this could further support an alternative conceptualization of "susceptibility" as increased "environmental sensitivity", conveying that individuals who are more susceptible to the risks of adverse environments might also be more receptive to the benefits of protective ones. This could also further support the evidence base for differential susceptibility by extending this concept to protective physical environments, opening another avenue of integration with public health research. A large-scale adoption of differential susceptibility to the total environment could provide opportunities for more effective interventions

through altering and improving physical environments with the intention of promoting positive well-being outcomes, which has been less of a focus in public health research.

Ultimately, future research in line with this theoretical framework could lead to a greater understanding of the ways in which nature-based interventions could be leveraged to reduce disparities in health among vulnerable groups. As the evidence base for this framework expands, we could more effectively identify and target mechanisms of health risks and benefits among susceptible groups and tailor public health interventions, taking into account individual differences in environmental sensitivity to develop more nuanced, strategic, and socioeconomically attuned approaches for addressing health disparities.

References

1. Hartig T, Mitchell R, de Vries S, Frumkin H. Nature and health. Annu Rev Public Health. 2014;35: 207–28. doi:10.1146/annurev-publhealth-032013-182443

2. James P, Banay RF, Hart JE, Laden F. A review of the health benefits of greenness. Curr Epidemiol Rep. 2015;2: 131–42. doi:10.1007/s40471-015-0043-7

3. Jimenez MP, DeVille NV, Elliott EG, Schiff JE, Wilt GE, Hart JE, et al. Associations between nature exposure and health: a review of the evidence. Int J Environ Res Public Health. 2021;18: 4790. doi:10.3390/ijerph18094790

4. Frumkin H, Bratman GN, Breslow SJ, Cochran B, Kahn PH, Lawler JJ, et al. Nature contact and human health: a research agenda. Environ Health Perspect. 2017;125: 075001. doi:10.1289/EHP1663

5. Liu X-X, Ma X-L, Huang W-Z, Luo Y-N, He C-J, Zhong X-M, et al. Green space and cardiovascular disease: a systematic review with meta-analysis. Environ Pollut. 2022;301: 118990. doi:10.1016/j.envpol.2022.118990

6. Ccami-Bernal F, Soriano-Moreno DR, Fernandez-Guzman D, Tuco KG, Castro-Díaz SD, Esparza-Varas AL, et al. Green space exposure and type 2 diabetes mellitus incidence: a systematic review. Health Place. 2023;82: 103045. doi:10.1016/j.healthplace.2023.103045

7. Liu Z, Chen X, Cui H, Ma Y, Gao N, Li X, et al. Green space exposure on depression and anxiety outcomes: a meta-analysis. Environ Res. 2023;231: 116303. doi:10.1016/j.envres.2023.116303

8. Tang M, Liu W, Li H, Li F. Greenness and chronic respiratory health issues: a systematic review and meta-analysis. Front Public Health. 2023;11: 1279322. doi:10.3389/fpubh.2023.1279322

9. Andersen L, Corazon SS, Stigsdotter UK. Nature exposure and its effects on immune system functioning: a systematic review. Int J Environ Res Public Health. 2021;18: 1416. doi:10.3390/ijerph18041416

10. Hu X, Wang J, Yang T, Jin J, Zeng Q, Aboubakri O, et al. Role of residential greenspace in the trajectory of major neurological disorders: a longitudinal study in UK Biobank. Sci Total Environ. 2024;912: 168967. doi:10.1016/j.scitotenv.2023.168967

11. Rojas-Rueda D, Nieuwenhuijsen MJ, Gascon M, Perez-Leon D, Mudu P. Green spaces and mortality: a systematic review and meta-analysis of cohort studies. Lancet Planet Health. 2019;3: 469–77. doi:10.1016/S2542-5196(19)30215-3

12. Bratman GN, Hamilton JP, Daily GC. The impacts of nature experience on human cognitive function and mental health. Ann N Y Acad Sci. 2012;1249: 118–36. doi:10.1111/j.1749-6632.2011.06400.x

13. Shin JC, Parab KV, An R, Grigsby-Toussaint DS. Greenspace exposure and sleep: a systematic review. Environ Res. 2020;182: 109081. doi:10.1016/j.envres.2019.109081

14. Arbuthnott KD. Nature exposure and social health: prosocial behavior, social cohesion, and effect pathways. J Environ Psychol. 2023;90: 102109. doi:10.1016/j.jenvp.2023.102109

15. Biedenweg K, Scott RP, Scott TA. How does engaging with nature relate to life satisfaction? Demonstrating the link between environment-specific social experiences and life satisfaction. J Environ Psychol. 2017;50: 112–24. doi:10.1016/j.jenvp.2017.02.002

16. Roe JJ, Thompson CW, Aspinall PA, Brewer MJ, Duff EI, Miller D, et al. Green space and stress: evidence from cortisol measures in deprived urban communities. Int J Environ Res Public Health. 2013;10: 4086–103. doi:10.3390/ijerph10094086

17. Ohly H, White MP, Wheeler BW, Bethel A, Ukoumunne OC, Nikolaou V, et al. Attention restoration theory: a systematic review of the attention restoration potential of exposure to natural environments. J Toxicol Environ Health B. 2016;19: 305–43. doi:10.1080/10937404.2016.1196155

18. Rodriguez-Villamizar LA, Hellemans K, Jerrett M, Su J, Sandler DP, Villeneuve PJ. Neighborhood greenness and participation in specific types of recreational physical

activities in the Sister Study. Environ Res. 2024;243: 117785. doi:10.1016/j.envres.2023.117785

19. Nowak DJ, Hirabayashi S, Bodine A, Greenfield E. Tree and forest effects on air quality and human health in the United States. Environ Pollut. 2014;193: 119–29. doi:10.1016/j.envpol.2014.05.028

20. Maas J, van Dillen SME, Verheij RA, Groenewegen PP. Social contacts as a possible mechanism behind the relation between green space and health. Health Place. 2009;15: 586–95. doi:10.1016/j.healthplace.2008.09.006

21. Kuo M. How might contact with nature promote human health? Promising mechanisms and a possible central pathway. Front Psychol. 2015;6: 1093. doi:10.3389/fpsyg.2015.01093

22. Li Q, Nakadai A, Matsushima H, Miyazaki Y, Krensky AM, Kawada T, et al. Phytoncides (wood essential oils) induce human natural killer cell activity. Immunopharmacol Immunotoxicol. 2006;28: 319–33. doi:10.1080/08923970600809439

23. Huang H, Lu Z, Fan X, Zhai W, Zhang L, Xu D, et al. Urban heatwave, green spaces, and mental health: a review based on environmental health risk assessment framework. Sci Total Environ. 2024;948: 174816. doi:10.1016/j.scitotenv.2024.174816

24. Mitchell R, Popham F. Effect of exposure to natural environment on health inequalities: an observational population study. Lancet. 2008;372: 1655–60. doi:10.1016/S0140-6736(08)61689-X

25. Nicholls N, Caryl F, Olsen JR, Mitchell R. Neighbourhood natural space and the narrowing of socioeconomic inequality in years of life lost: a cross-sectional ecological analysis of the Scottish Burden of Disease. J Epidemiol Community Health. 2022;76: 976–83. doi:10.1136/jech-2022-219111

26. Mitchell RJ, Richardson EA, Shortt NK, Pearce JR. Neighborhood environments and socioeconomic inequalities in mental well-being. Am J Prev Med. 2015;49: 80–4. doi:10.1016/j.amepre.2015.01.017

27. Brown SC, Lombard J, Wang K, Byrne MM, Toro M, Plater-Zyberk E, et al. Neighborhood greenness and chronic health conditions in Medicare beneficiaries. Am J Prev Med. 2016;51: 78–89. doi:10.1016/j.amepre.2016.02.008

28. Brown SC, Perrino T, Lombard J, Wang K, Toro M, Rundek T, et al. Health disparities in the relationship of neighborhood greenness to mental health outcomes in 249,405 U.S. Medicare beneficiaries. Int J Environ Res Public Health. 2018;15: 430. doi:10.3390/ijerph15030430

29. Wang R, Dong G, Cao M, Zhou Y, Dong G-H. Exploring "equigenesis" in the associations between green space and kidney health among middle-aged and older adults using street view data. Innov Aging. 2024;8: igad130. doi:10.1093/geroni/igad130

30. Moran MR, Bilal U, Dronova I, Ju Y, Gouveia N, Caiaffa WT, et al. The equigenic effect of greenness on the association between education with life expectancy and mortality in 28 large Latin American cities. Health Place. 2021;72: 102703. doi:10.1016/j.healthplace.2021.102703

31. Tomita A, Vandormael AM, Cuadros D, Di Minin E, Heikinheimo V, Tanser F, et al. Green environment and incident depression in South Africa: a geospatial analysis and mental health implications in a resource-limited setting. Lancet Planet Health. 2017;1: e152–e162. doi:10.1016/S2542-5196(17)30063-3

32. Feng X, Astell-Burt T. Do greener areas promote more equitable child health? Health Place. 2017;46: 267–73. doi:10.1016/j.healthplace.2017.05.006

33. Astell-Burt T, Feng X. Does the potential benefit of neighbourhood green space for body mass index depend upon socioeconomic circumstances and local built and transport environments? A test of the 'equigenesis' hypothesis in Australia. J Transp Health. 2017;5: S40. doi:10.1016/j.jth.2017.05.327

34. Evans GW, Kantrowitz E. Socioeconomic status and health: the potential role of environmental risk exposure. Annu Rev Public Health. 2002;23: 303–31. doi:10.1146/annurev.publhealth.23.112001.112349

35. Evans GW. The environment of childhood poverty. Am Psychol. 2004;59: 77–92. doi:10.1037/0003-066X.59.2.77

36. Evans GW, Gonnella C, Marcynyszyn LA, Gentile L, Salpekar N. The role of chaos in poverty and children's socioemotional adjustment. Psychol Sci. 2005;16: 560–5. doi:10.1111/j.0956-7976.2005.01575.x

37. Evans GW, Kim P. Childhood poverty, chronic stress, self-regulation, and coping. Child Dev Perspect. 2013;7: 43–8. doi:10.1111/cdep.12013

38. Hertzman C. Putting the concept of biological embedding in historical perspective. Proc Natl Acad Sci U S A. 2012;109 Suppl 2: 17160–7. doi:10.1073/pnas.1202203109

39. Hertzman C, Boyce T. How experience gets under the skin to create gradients in developmental health. Annu Rev Public Health. 2010;31: 329–47. doi:10.1146/annurev.publhealth.012809.103538

40. McEwen BS. Brain on stress: how the social environment gets under the skin. Proc Natl Acad Sci U S A. 2012;109 Suppl 2: 17180–5. doi:10.1073/pnas.1121254109

41. Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol Behav. 2012;106: 29–39. doi:10.1016/j.physbeh.2011.08.019

42. Boyce WT. Differential susceptibility of the developing brain to contextual adversity and stress. Neuropsychopharmacology. 2016;41: 142–62. doi:10.1038/npp.2015.294

43. Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, van Ijzendoorn MH. Differential susceptibility to the environment: an evolutionary--neurodevelopmental theory. Dev Psychopathol. 2011;23: 7–28. doi:10.1017/S0954579410000611

44. Ellis BJ, Del Giudice M. Beyond allostatic load: rethinking the role of stress in regulating human development. Dev Psychopathol. 2014;26: 1–20. doi:10.1017/S0954579413000849

45. Belsky J, Pluess M. Beyond risk, resilience, and dysregulation: phenotypic plasticity and human development. Dev Psychopathol. 2013;25: 1243–61. doi:10.1017/S095457941300059X

46. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on Community-Based Solutions to Promote Health Equity in the United States. *Communities in Action: Pathways to Health Equity*. Washington (DC): National Academies Press; 2017. pp. 99–184.

47. National Academies of Sciences, Engineering, and Medicine; National Academy of Medicine; Committee on the Future of Nursing 2020–2030. *The Future of Nursing 2020-2030: Charting a Path to Achieve Health Equity*. Washington (DC): National Academies Press; 2021. pp. 38–51.

48. Evans GW, Kim P. Multiple risk exposure as a potential explanatory mechanism for the socioeconomic status–health gradient. Ann N Y Acad Sci. 2010;1186: 174–89. doi:10.1111/j.1749-6632.2009.05336.x

49. Evans GW, Schamberg MA. Childhood poverty, chronic stress, and adult working memory. Proc Natl Acad Sci U S A. 2009;106: 6545–9. doi:10.1073/pnas.0811910106

50. Wells NM, Evans GW, Beavis A, Ong AD. Early childhood poverty, cumulative risk exposure, and body mass index trajectories through young adulthood. Am J Public Health. 2010;100: 2507–12. doi:10.2105/AJPH.2009.184291

51. Evans GW, Kim P. Childhood poverty and young adults' allostatic load: the mediating role of childhood cumulative risk exposure. Psychol Sci. 2012;23: 979–83. doi:10.1177/0956797612441218

52. US Department of Health and Human Services. *Fourth National Incidence Study of Child Abuse and Neglect (NIS-4): Report to Congress, Executive Summary*. 2019 Apr 29 [cited 2025 Mar 21]. Available from: https://acf.gov/opre/report/fourth-national-incidence-study-child-abuse-and-neglect-nis-4-report-congress-executive

53. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998;14: 245–58. doi:10.1016/S0749-3797(98)00017-8

54. Merrick MT, Ford DC, Ports KA, Guinn AS, Chen J, Klevens J, et al. Vital signs: estimated proportion of adult health problems attributable to adverse childhood experiences and implications for prevention – 25 states, 2015-2017. MMWR Morb Mortal Wkly Rep. 2019;68: 999–1005. doi:10.15585/mmwr.mm6844e1

55. Jones CM, Merrick MT, Houry DE. Identifying and preventing adverse childhood experiences: implications for clinical practice. JAMA. 2020;323: 25–6. doi:10.1001/jama.2019.18499

56. Centers for Disease Control and Prevention. Preventing adverse childhood experiences. 2021 Aug 23 [cited 2025 Mar 21]. Available from: https://www.cdc.gov/vitalsigns/aces/index.html

57. Gervin DW, Holland KM, Ottley PG, Holmes GM, Niolon PH, Mercy JA. Centers for Disease Control and Prevention investments in adverse childhood experience prevention efforts. Am J Prev Med. 2022;62: S1–S5. doi:10.1016/j.amepre.2021.11.014

58. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. JAMA. 2009;301: 2252–9. doi:10.1001/jama.2009.754

59. Taylor SE. Mechanisms linking early life stress to adult health outcomes. Proc Natl Acad Sci U S A. 2010;107: 8507–12. doi:10.1073/pnas.1003890107

60. Berens AE, Jensen SKG, Nelson CA. Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. BMC Med. 2017;15: 135. doi:10.1186/s12916-017-0895-4

61. Agorastos A, Pervanidou P, Chrousos GP, Baker DG. Developmental trajectories of early life stress and trauma: a narrative review on neurobiological aspects beyond stress system dysregulation. Front Psychiatry. 2019;10: 118. doi:10.3389/fpsyt.2019.00118

62. Nusslock R, Miller GE. Early-life adversity and physical and emotional health across the lifespan: a neuroimmune network hypothesis. Biol Psychiatry. 2016;80: 23–32. doi:10.1016/j.biopsych.2015.05.017

63. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull. 2014;140: 774–815. doi:10.1037/a0035302

64. Evans GW, Li D, Whipple SS. Cumulative risk and child development. Psychol Bull. 2013;139: 1342–96. doi:10.1037/a0031808

65. Shonkoff JP, Garner AS; Committee on Psychosocial Aspects of Child and Family Health; Committee on Early Childhood, Adoption, and Dependent Care; Section on Developmental and Behavioral Pediatrics. The lifelong effects of early childhood adversity and toxic stress. Pediatrics. 2012;129: 232–46. doi:10.1542/peds.2011-2663

66. McEwen BS, Stellar E. Stress and the individual: mechanisms leading to disease. Arch Intern Med. 1993;153: 2093–101.

67. Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, et al. Reward deficiency syndrome: a biogenetic model for the diagnosis and treatment of impulsive, addictive, and compulsive behaviors. J Psychoactive Drugs. 2000;32 Suppl: 1–112. doi:10.1080/02791072.2000.10736099

68. Danese A, Lewis SJ. Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma? Neuropsychopharmacology. 2017;42: 99–114. doi:10.1038/npp.2016.198

69. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol Bull. 2011;137: 959–97. doi:10.1037/a0024768

70. Juster R-P, McEwen BS, Lupien SJ. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci Biobehav Rev. 2010;35: 2–16. doi:10.1016/j.neubiorev.2009.10.002

71. Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, et al. Chronic inflammation in the etiology of disease across the life span. Nat Med. 2019;25: 1822–32. doi:10.1038/s41591-019-0675-0

72. Eisenberger NI, Berkman ET, Inagaki TK, Rameson LT, Mashal NM, Irwin MR. Inflammation-induced anhedonia: endotoxin reduces ventral striatum responses to reward. Biol Psychiatry. 2010;68: 748–54. doi:10.1016/j.biopsych.2010.06.010

73. Sapolsky RM. Stress and the brain: individual variability and the inverted-U. Nat Neurosci. 2015;18: 1344–46. doi:10.1038/nn.4109

74. Kim P, Evans GW, Chen E, Miller G, Seeman T. How socioeconomic disadvantages get under the skin and into the brain to influence health development across the lifespan. In: Halfon N, Forrest CB, Lerner RM, Faustman EM, editors. *Handbook of Life Course Health Development*. Cham (CH): Springer; 2018. doi:10.1007/978-3-319-47143-3_19

75. Evans GW, Chen E, Miller G, Seeman T. How poverty gets under the skin: a life course perspective. In: King RB, Maholmes V, editors. *The Oxford Handbook of Poverty and Child Development*. New York: Oxford University Press; 2012. pp. 13–36.

76. Kim P, Evans GW, Angstadt M, Ho SS, Sripada CS, Swain JE, et al. Effects of childhood poverty and chronic stress on emotion regulatory brain function in adulthood. Proc Natl Acad Sci U S A. 2013;110: 18442–7. doi:10.1073/pnas.1308240110

77. Sripada RK, Swain JE, Evans GW, Welsh RC, Liberzon I. Childhood poverty and stress reactivity are associated with aberrant functional connectivity in default mode network. Neuropsychopharmacology. 2014;39: 2244–51. doi:10.1038/npp.2014.75

78. West-Eberhard MJ. *Developmental Plasticity and Evolution*. New York: Oxford University Press; 2003.

79. Boyce WT, Ellis BJ. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. Dev Psychopathol. 2005;17: 271–301. doi:10.1017/S0954579405050145

80. Ellis BJ, Essex MJ, Boyce WT. Biological sensitivity to context: II. Empirical explorations of an evolutionary-developmental theory. Dev Psychopathol. 2005;17: 303–28. doi:10.1017/S0954579405050157

81. Del Giudice M, Ellis BJ, Shirtcliff EA. The Adaptive Calibration Model of stress responsivity. Neurosci Biobehav Rev. 2011;35: 1562–92. doi:10.1016/j.neubiorev.2010.11.007

82. Ellis BJ, Oldehinkel AJ, Nederhof E. The Adaptive Calibration Model of stress responsivity: an empirical test in the Tracking Adolescents' Individual Lives Survey study. Dev Psychopathol. 2017;29: 1001–21. doi:10.1017/S0954579416000985

83. Ellis BJ, Jackson JJ, Boyce WT. The stress response systems: universality and adaptive individual differences. Dev Rev. 2006;26: 175–212. doi:10.1016/j.dr.2006.02.004

84. Ellis BJ, Del Giudice M, Shirtcliff EA. Beyond allostatic load: the stress response system as a mechanism of conditional adaptation. In: Beauchaine TP, Hinshaw SP, editors. *Child and Adolescent Psychopathology*. 2nd ed. Hoboken: Wiley; 2013. pp. 251–84.

85. Ellis BJ, Del Giudice M. Developmental adaptation to stress: an evolutionary perspective. Annu Rev Psychol. 2019;70: 111–39. doi:10.1146/annurev-psych-122216-011732

86. Ellis BJ, Sheridan MA, Belsky J, McLaughlin KA. Why and how does early adversity influence development? Toward an integrated model of dimensions of environmental experience. Dev Psychopathol. 2022;34: 447–71. doi:10.1017/S0954579421001838

87. Bakermans-Kranenburg MJ, van Ijzendoorn MH. Research review: genetic vulnerability or differential susceptibility in child development: the case of attachment. J Child Psychol Psychiatry. 2007;48: 1160–73. doi:10.1111/j.1469-7610.2007.01801.x

88. Belsky J, Bakermans-Kranenburg MJ, van IJzendoorn MH. For better and for worse: differential susceptibility to environmental influences. Curr Dir Psychol Sci. 2007;16: 300–4. doi:10.1111/j.1467-8721.2007.00525.x

89. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? Mol Psychiatry. 2009;14: 746–54. doi:10.1038/mp.2009.44

90. Belsky J. Differential susceptibility to environmental influences. Int J Child Care Educ Policy. 2013;7: 15–31. doi:10.1007/2288-6729-7-2-15

91. Manuck SB. The reaction norm in gene-environment interaction. Mol Psychiatry. 2009;15: 881–2. doi:10.1038/mp.2009.139

92. Boyce WT, Chesney M, Alkon A, Tschann JM, Adams S, Chesterman B, et al. Psychobiologic reactivity to stress and childhood respiratory illnesses: results of two prospective studies. Psychosom Med. 1995;57: 411–22. doi:10.1097/00006842-199509000-00001

93. Ellis BJ, Shirtcliff EA, Boyce WT, Deardorff J, Essex MJ. Quality of early family relationships and the timing and tempo of puberty: effects depend on biological sensitivity to context. Dev Psychopathol. 2011;23: 85–99. doi:10.1017/S0954579410000660

94. Essex MJ, Armstrong JM, Burk LR, Goldsmith HH, Boyce WT. Biological sensitivity to context moderates the effects of the early teacher-child relationship on the development of mental health by adolescence. Dev Psychopathol. 2011;23: 149–61. doi:10.1017/S0954579410000702

95. Obradović J, Bush NR, Stamperdahl J, Adler NE, Boyce WT. Biological sensitivity to context: the interactive effects of stress reactivity and family adversity on socio-emotional behavior and school readiness. Child Dev. 2010;81: 270–89. doi:10.1111/j.1467-8624.2009.01394.x

96. Del Giudice M, Belsky J. The development of life history strategies: toward a multi-stage theory. In: Buss DM, Hawley PH, editors. *The Evolution of Personality and Individual Differences*. Oxford: Oxford University Press; 2011. pp. 154–76.

97. Ellis BJ, Bjorklund DF. Beyond mental health: an evolutionary analysis of development under risky and supportive environmental conditions. Dev Psychol. 2012;48: 591–97. doi:10.1037/a0027651

98. Del Giudice M. Early stress and human behavioral development: emerging evolutionary perspectives. J Dev Orig Health Dis. 2014;5: 270–80. doi:10.1017/S2040174414000257

99. Ellis BJ, Giudice MD, Shirtcliff EA. The Adaptive Calibration Model of stress responsivity: concepts, findings, and implications for developmental psychopathology. In: Beauchaine TP, Hinshaw SP, editors. *Child and Adolescent Psychopathology*. 3rd ed. Hoboken: Wiley; 2017. pp. 237–76.

100. Hill K. Life History Theory and evolutionary anthropology. Evol Anthropol. 1993;2: 78–88. doi:10.1002/evan.1360020303

101. McNamara JM, Houston AI. State-dependent life histories. Nature. 1996;380: 215–21. doi:10.1038/380215a0

102. Penke L. Bridging the gap between modern evolutionary psychology and the study of individual differences. In: Buss DM, Hawley PH, editors. *The Evolution of Personality and Individual Differences*. New York: Oxford University Press; 2010.

103. Del Giudice M, Kaplan HS, Gangestad SW. Life History Theory and evolutionary psychology. In: Buss DM, editor. *The Handbook of Evolutionary Psychology*. 2nd ed. Hoboken: Wiley; 2015. pp. 88–114.

104. Ellis BJ, Figueredo AJ, Brumbach BH, Schlomer GL. The impact of harsh versus unpredictable environments on the evolution and development of life history strategies. Hum Nat. 2009;20: 204–68. doi:10.1007/s12110-009-9063-7

105. Muscatell KA, Moieni M, Inagaki TK, Dutcher JM, Jevtic I, Breen EC, et al. Exposure to an inflammatory challenge enhances neural sensitivity to negative and positive social feedback. Brain Behav Immun. 2016;57: 21–9. doi:10.1016/j.bbi.2016.03.022

106. Slavich GM, Cole SW. The emerging field of human social genomics. Clin Psychol Sci. 2013;1: 331–48. doi:10.1177/2167702613478594

107. Belsky J, Pluess M. The nature (and nurture?) of plasticity in early human development. Perspect Psychol Sci. 2009;4: 345–51. doi:10.1111/j.1745-6924.2009.01136.x

108. Belsky J, Pluess M. Differential susceptibility to environmental influences. In: Cicchetti D, editor. *Developmental Psychopathology: Developmental Neuroscience*. 3rd ed. Hoboken: Wiley; 2016. pp. 59–106.

109. Belsky J. Conditional and alternative reproductive strategies: individual differences in susceptibility to rearing experiences. In: Rodgers J, Rowe D, Miller W, editors. *Genetic Influences on Human Fertility and Sexuality*. Boston: Kluwer; 2000. pp. 127–46.

110. Belsky J. Differential susceptibility to rearing influence: an evolutionary hypothesis and some evidence. In: Ellis BJ, Bjorklund DF, editors. *Origins of the Social Mind: Evolutionary Psychology and Child Development*. New York: Guilford Press; 2005. pp. 139–63.

111. Hartman S, Belsky J, Pluess M. Prenatal programming of environmental sensitivity. Transl Psychiatry. 2023;13: 1–10. doi:10.1038/s41398-023-02461-y

112. Hartman S, Freeman SM, Bales KL, Belsky J. Prenatal stress as a risk- and an opportunity-factor. Psychol Sci. 2018;29: 572–80. doi:10.1177/0956797617739983

113. Manuck SB, Flory JD, Ferrell RE, Muldoon MF. Socio-economic status covaries with central nervous system serotonergic responsivity as a function of allelic variation in the serotonin transporter gene-linked polymorphic region. Psychoneuroendocrinology. 2004;29: 651–68. doi:10.1016/S0306-4530(03)00094-5

114. Jokela M, Keltikangas-Järvinen L, Kivimäki M, Puttonen S, Elovainio M, Rontu R, et al. Serotonin receptor 2A gene and the influence of childhood maternal nurturance on adulthood depressive symptoms. Arch Gen Psychiatry. 2007;64: 356–60. doi:10.1001/archpsyc.64.3.356

115. Jokela M, Räikkönen K, Lehtimäki T, Rontu R, Keltikangas-Järvinen L. Tryptophan hydroxylase 1 gene (TPH1) moderates the influence of social support on depressive symptoms in adults. J Affect Disord. 2007;100: 191–97. doi:10.1016/j.jad.2006.10.016

116. Bakermans-Kranenburg MJ, van IJzendoorn MH, Pijlman FTA, Mesman J, Juffer F. Experimental evidence for differential susceptibility: dopamine D4 receptor

polymorphism (DRD4 VNTR) moderates intervention effects on toddlers' externalizing behavior in a randomized controlled trial. Dev Psychol. 2008;44: 293–300. doi:10.1037/0012-1649.44.1.293

117. Keltikangas-Järvinen L, Elovainio M, Kivimäki M, Raitakari OT, Viikari JSA, Lehtimäki T. Dopamine receptor D2 gene Taq1A (C32806T) polymorphism modifies the relationship between birth weight and educational attainment in adulthood: 21-year follow-up of the Cardiovascular Risk in Young Finns study. Pediatrics. 2007;120: 756–61. doi:10.1542/peds.2007-0073

118. van IJzendoorn MH, Bakermans-Kranenburg MJ, Mesman J. Dopamine system genes associated with parenting in the context of daily hassles. Genes Brain Behav. 2008;7: 403–10. doi:10.1111/j.1601-183X.2007.00362.x

119. Moore SR, Depue RA. Neurobehavioral foundation of environmental reactivity. Psychol Bull. 2016;142: 107–64. doi:10.1037/bul0000028

120. Gannon L, Banks J, Shelton D, Luchetta T. The mediating effects of psychophysiological reactivity and recovery on the relationship between environmental stress and illness. J Psychosom Res. 1989;33: 167–75. doi:10.1016/0022-3999(89)90044-5

121. El-Sheikh M, Harger J, Whitson SM. Exposure to interparental conflict and children's adjustment and physical health: the moderating role of vagal tone. Child Dev. 2001;72: 1617–36. doi:10.1111/1467-8624.00369

122. El-Sheikh M, Keller PS, Erath SA. Marital conflict and risk for child maladjustment over time: skin conductance level reactivity as a vulnerability factor. J Abnorm Child Psychol. 2007;35: 715–27. doi:10.1007/s10802-007-9127-2

123. Obradović J, Bush NR, Boyce WT. The interactive effect of marital conflict and stress reactivity on externalizing and internalizing symptoms: the role of laboratory stressors. Dev Psychopathol. 2011;23: 101–14. doi:10.1017/S0954579410000672

124. Rudolph KD, Troop-Gordon W, Granger DA. Peer victimization and aggression: moderation by individual differences in salivary cortisol and alpha-amylase. J Abnorm Child Psychol. 2010;38: 843–56. doi:10.1007/s10802-010-9412-3

125. Bolten M, Nast I, Skrundz M, Stadler C, Hellhammer DH, Meinlschmidt G. Prenatal programming of emotion regulation: neonatal reactivity as a differential susceptibility factor moderating the outcome of prenatal cortisol levels. J Psychosom Res. 2013;75: 351–57. doi:10.1016/j.jpsychores.2013.04.014

126. Slagt M, Dubas JS, Deković M, van Aken MAG. Differences in sensitivity to parenting depending on child temperament: a meta-analysis. Psychol Bull. 2016;142: 1068–1110. doi:10.1037/bul0000061

127. Aron EN, Aron A, Jagiellowicz J. Sensory processing sensitivity: a review in the light of the evolution of biological responsivity. Pers Soc Psychol Rev. 2012;16: 262–82. doi:10.1177/1088868311434213

128. Belsky J, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. Psychol Bull. 2009;135: 885–908. doi:10.1037/a0017376

129. Hartig T. Green space, psychological restoration, and health inequality. Lancet. 2008;372: 1614–15. doi:10.1016/S0140-6736(08)61669-4

130. Craig JM, Prescott SL. Planning ahead: the mental health value of natural environments. Lancet Planet Health. 2017;1: e128–e129. doi:10.1016/S2542-5196(17)30068-2

131. Badland H, Pearce J. Liveable for whom? Prospects of urban liveability to address health inequities. Soc Sci Med. 2019;232: 94–105. doi:10.1016/j.socscimed.2019.05.001

132. Xian Z, Nakaya T, Liu K, Zhao B, Zhang J, Zhang J, et al. The effects of neighbourhood green spaces on mental health of disadvantaged groups: a systematic review. Humanit Soc Sci Commun. 2024;11: 1–19. doi:10.1057/s41599-024-02970-1

133. Wolf KL, Measells MK, Grado SC, Robbins AST. Economic values of metro nature health benefits: a life course approach. Urban For Urban Green. 2015;14: 694–701. doi:10.1016/j.ufug.2015.06.009

134. Brochu P, Jimenez MP, James P, Kinney PL, Lane K. Benefits of increasing greenness on all-cause mortality in the largest metropolitan areas of the United States within the past two decades. Front Public Health. 2022;10: 841936. doi:10.3389/fpubh.2022.841936

135. Buckley RC, Chauvenet ALM. Economic value of nature via healthcare savings and productivity increases. Biol Conserv. 2022;272: 109665. doi:10.1016/j.biocon.2022.109665

136. Wilson J, Xiao X. The economic value of health benefits associated with urban park investment. Int J Environ Res Public Health. 2023;20: 4815. doi:10.3390/ijerph20064815

137. Glacken CJ. *Traces on the Rhodian Shore: Nature and Culture in Western Thought from Ancient Times to the End of the Eighteenth Century*. Berkeley: University of California Press; 1967.

138. Berlyne DE. *Aesthetics and Psychobiology*. New York: Appleton-Century-Crofts; 1971.

139. Appleton J. *The Experience of Landscape*. London: Wiley; 1975.

140. Orians GH. Habitat selection: general theory and applications to human behavior. In: Lockard JS, editor. *The Evolution of Human Social Behavior*. Amsterdam: Elsevier; 1980. pp. 49–63.

141. Potts R. Environmental hypotheses of hominin evolution. Am J Phys Anthropol. 1998;107: 93–136. doi:10.1002/(SICI)1096-8644(1998)107:27+¡93::AID-AJPA5¿3.0.CO;2-X

142. Kellert SR. The biological basis for human values of nature. In: Kellert SR, Wilson EO, editors. *The Biophilia Hypothesis*. Washington (DC): Island Press; 1993. pp. 42–69.

143. Wilson EO. *Biophilia: The Human Bond with Other Species*. Cambridge (MA): Harvard University Press; 1984.

144. Ulrich RS. Aesthetic and affective response to natural environment. In: Altman I, Wohlwill JF, editors. *Behavior and the Natural Environment*. New York: Plenum Press; 1983. pp. 85–125.

145. Kaplan R, Kaplan S. *The Experience of Nature: A Psychological Perspective*. New York: Cambridge University Press; 1989.

146. Hagerhall CM, Purcell T, Taylor R. Fractal dimension of landscape silhouette outlines as a predictor of landscape preference. J Environ Psychol. 2004;24: 247–55. doi:10.1016/j.jenvp.2003.12.004

147. Miller G, Chen E. Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolescence. Psychosom Med. 2007;69: 402–9. doi:10.1097/PSY.0b013e318068fcf9

148. Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, et al. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc Natl Acad Sci U S A. 2009;106: 14716–21. doi:10.1073/pnas.0902971106

149. Miller GE, Chen E. Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. Psychol Sci. 2010;21: 848–56. doi:10.1177/0956797610370161

150. Ehrlich KB, Ross KM, Chen E, Miller GE. Testing the biological embedding hypothesis: is early life adversity associated with a later proinflammatory phenotype? Dev Psychopathol. 2016;28: 1273–83. doi:10.1017/S0954579416000845

151. Ward Thompson C, Roe J, Aspinall P, Mitchell R, Clow A, Miller D. More green space is linked to less stress in deprived communities: evidence from salivary cortisol patterns. Landsc Urban Plan. 2012;105: 221–29. doi:10.1016/j.landurbplan.2011.12.015

152. Ward Thompson C, Aspinall P, Roe J, Robertson L, Miller D. Mitigating stress and supporting health in deprived urban communities: the importance of green space and the social environment. Int J Environ Res Public Health. 2016;13: 440. doi:10.3390/ijerph13040440

153. Hostinar CE, Ross KM, Chen E, Miller GE. Early-life socioeconomic disadvantage and metabolic health disparities. Psychosom Med. 2017;79: 514–23. doi:10.1097/PSY.0000000000000455

154. Hamad R, Penko J, Kazi DS, Coxson P, Guzman D, Wei PC, et al. Association of low socioeconomic status with premature coronary heart disease in US adults. JAMA Cardiol. 2020;5: 899–908. doi:10.1001/jamacardio.2020.1458

155. Yeager RA, Smith TR, Bhatnagar A. Green environments and cardiovascular health. Trends Cardiovasc Med. 2020;30: 241–46. doi:10.1016/j.tcm.2019.06.005

156. Keith RJ, Hart JL, Bhatnagar A. Greenspaces and cardiovascular health. Circ Res. 2024;134: 1179–96. doi:10.1161/CIRCRESAHA.124.323583

Chapter Two

Title & Authorship

Susceptibility to stress and nature exposure: Unveiling differential susceptibility to physical environments; a randomized controlled trial

Aaron M. Eisen[1], Gregory N. Bratman[2,3,4], Hector A. Olvera-Alvarez[1]

[1]School of Nursing, Oregon Health & Science University, Portland, OR

[2]School of Environmental and Forest Sciences, University of Washington, Seattle, WA

[3]Department of Psychology, University of Washington, Seattle, WA

[4]Department of Environmental and Occupational Health Sciences, University of Washington, Seattle, WA

Funding Acknowledgments

This research was financially supported by the JPB Environmental Health Fellowship from the JPB Foundation, administered by the Harvard T.H. Chan School of Public Health [to Hector A. Olvera-Alvarez and Gregory N. Bratman]; Grant 5U54MD007592 from the National Institute on Minority Health and Health Disparities (NIMHD), a component of the National Institutes of Health (NIH) [to Hector A. Olvera-Alvarez]; Aaron M. Eisen was an ARCS Foundation Scholar. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of this manuscript.

Citation: PLOS ONE

Eisen AM, Bratman GN, Olvera-Alvarez HA. Susceptibility to stress and nature exposure: Unveiling differential susceptibility to physical environments; a randomized controlled trial. 2025. PLoS One 19: e0301473. doi:10.1371/journal.pone.0301473

Directory of Tables & Figures

List of Tables

Table	Name	Page
1	Participant Characteristics	**57**
S1	Bivariate Correlations (Susceptibility Indicators)	**83**
S2	Bivariate Correlations (Baseline Autonomic Metrics)	**83**

List of Figures

Figure	Title	Page
1	Theoretical Framework	**47**
2	Flow Diagram of the Exposure Experiment	**50**
3	Virtual Reality Environments	**52**
4	Forest Plots of Standardized Effects (Continuous Interaction Terms)	**59**
5	Interaction Plots: Susceptibility by Condition on Autonomic Activation	**60**
S1	Cardiovascular Arousal and Recovery (Autonomic Activation)	**84**
S2	Nature Exposure and Stress Recovery (Autonomic Activation)	**85**
S3	Interaction Plots: Maximum Information	**86**
S4	Forest Plots of Standardized Effects (Binary Interaction Terms)	**87**

Abstract

Background

Emerging epidemiological evidence indicates that nature exposure could be associated with greater health benefits among groups in lower versus higher socioeconomic positions. One possible mechanism underpinning this evidence is described by our framework: (susceptibility) individuals in low socioeconomic positions often face higher exposure to persistent psychosocial stressors in early life, which can induce a pro-inflammatory immune state as a lifelong susceptibility to stress; (differential susceptibility) susceptible individuals are more sensitive to the health risks of adverse (risk-promoting) environments, but also to the health benefits of protective (benefit-enhancing) environments.

Objective

Experimental investigation of a pro-inflammatory immune state as a mechanism facilitating better stress recovery from nature exposure.

Methods

We determined differences in stress recovery (via heart rate variability) caused by exposure to a nature or office environment in virtual reality (10 min) after an acute stressor among 64 healthy college-age males with varying levels of susceptibility (socioeconomic status, early life stress, and a pro-inflammatory state [inflammatory reactivity and glucocorticoid resistance to an in vitro bacterial challenge]).

Results

Findings for inflammatory reactivity and glucocorticoid resistance were modest but consistently trended towards better recovery in the nature condition. Differences in recovery were not observed for socioeconomic status or early life stress.

Discussion

Among healthy college-age males, we observed expected trends according to their differential susceptibility when assessed as inflammatory reactivity and glucocorticoid resistance,

suggesting these biological correlates of susceptibility to stress could be more proximal indicators than self-reported assessments of socioeconomic status and early life stress. If future research in more diverse populations aligns with these trends, this could support an alternative conceptualization of susceptibility as increased environmental sensitivity, reflecting heightened responses to adverse but also protective environmental conditions. With this knowledge, future investigators could examine how individual differences in environmental sensitivity could provide an opportunity for those who are the most susceptible to experience the greatest benefits from nature exposure.

[1] Introduction

Emerging epidemiological evidence indicates that nature exposure (e.g., contact with natural green spaces) could be associated with better health among groups in low socioeconomic positions to a greater degree than among more privileged groups [1–4]. This implies that nature exposure within urban settings could potentially attenuate the adverse effects of chronic stress on health with the greatest impact among individuals who are the most susceptible to life stressors [5–7]. However, the evidence supporting this possibility primarily comes from cross-sectional and observational studies, including reports of null associations [8–10]. Further investigation is necessary to better understand this phenomenon, especially through experimental paradigms that could provide insight into potential causal mechanisms. Establishing experimental evidence could further support the idea that nature-based interventions (e.g., increasing access to urban parks) could help curb disparities in health across socioeconomic conditions.

One possible mechanism underpinning this phenomenon is outlined by integrating three overarching ideas: (1) individuals in low socioeconomic conditions often face higher exposure to persistent psychosocial stressors in early life, which can induce a lifelong susceptibility to stress through various neurobiological pathways; (2) nature exposure protects against the adverse health effects of stress; (3) susceptibility to stress could reflect increased sensitivity to environmental conditions, inducing greater benefits from the health-protective effects of nature exposure among individuals in lower versus higher socioeconomic positions.

[1.1] Early Life Stress

Evidence demonstrates that individuals in low socioeconomic positions, compared to more privileged groups, often face higher exposure to persistent psychosocial stressors in early life [11–15]. Evidence also demonstrates that early life stress can produce a lifelong susceptibility to stress through various neurobiological pathways (i.e., Biological Embedding Model [16–26]). One of the most well-established pathways consists of early life stress inducing a pro-inflammatory immune state, observed as heightened neuroimmune reac-

tivity to psychological (e.g., social) and biological (e.g., bacterial) stressors combined with resistance to anti-inflammatory signals (i.e., Neuroimmune Network Hypothesis [27,28]).

In short, when the amygdala activates in response to perceived threats, the sympathetic-adrenal-medullary (SAM) axis engages within seconds to trigger the sympathetic nervous system, sending a cascade of messengers (e.g., catecholamines) that are received by monocytes as pro-inflammatory signals [29]. Minutes later, the hypothalamic-pituitary-adrenal (HPA) axis engages, sending another cascade of messengers (e.g., glucocorticoids) that are received by monocytes as anti-inflammatory signals [29]. Importantly, early life stress has been shown to increase monocyte sensitivity to pro-inflammatory signals, but also decrease monocyte sensitivity to anti-inflammatory signals, leading to a pro-inflammatory immune state which persists throughout adulthood ("brain to immune traffic" [27,28]). Consequentially, this pro-inflammatory state induces neuroinflammation which has also been shown to elevate amygdala reactivity to perceived threats in a self-sustaining cycle ("immune to brain traffic" [27,28]).

As an example of this pro-inflammatory state, experimental evidence has shown that early life stress is associated with increased monocyte production of pro-inflammatory cytokines (e.g., interleukin-6; IL-6) among healthy adults in response to psychosocial stressors [30,31]. Other evidence has shown that early life stress is associated with increased monocyte production of pro-inflammatory cytokines (e.g., IL-6) and resistance to glucocorticoids (e.g., cortisol) among healthy adults in response to in vitro bacterial challenges [32-34]. Importantly, evidence also indicates that higher socioeconomic status during adulthood is unable to reverse these developmental alterations [32,35].

Together, these findings suggest that early life stress becomes biologically embedded through a pro-inflammatory state that, when combined with persistent exposure to stressors, could result in chronic inflammation and consequently heighten the risk of developing the diseases of aging [27,28]. This risk is particularly elevated among individuals in low socioeconomic positions, who are more likely to experience early life stress, current life stressors, and health disparities across these diseases [32,35]. In this context, a pro-inflammatory state could represent a more sensitive and relevant indi-

cator as a biological correlate of susceptibility to stress (proximal; shorter pathway between indicators and outcomes), compared to self-report assessments of socioeconomic status and early life stress (distal; longer pathway between indicators and outcomes that in turn, increases the risk of unmeasured confounders).

[1.2] Nature Exposure

Psychoevolutionary theories posit that many types of nature exposure are health-protective relative to exposure to urban settings, as human beings share an innate physiological affinity to natural features that afforded safety and nourishment throughout our evolutionary history [36–39]. Due to these connections, nature exposure can have a positive effect on health through stress-related mechanisms, including better stress recovery (e.g., see Roger Ulrich's Stress Reduction Theory [40-41]). This idea is supported by experimental evidence of increased parasympathetic activation and reduced sympathetic activation within natural versus urban settings following sympathetic arousal induced by an acute psychosocial stressor [41–46].

For instance, Ulrich et al. (1991) found that healthy participants exposed to videos of natural versus urban environments demonstrated increased parasympathetic activation (e.g., pulse transit time) and reduced sympathetic activation (e.g., muscle tension, skin conductance), following sympathetic arousal induced by an acute psychosocial stressor (a video depicting graphic injuries in a woodworking shop) [41]. More recent studies have also reported similar findings, where healthy participants exposed to a natural versus indoor office environment in virtual reality demonstrated increased parasympathetic and reduced sympathetic activation (e.g., heart rate variability; HRV), following sympathetic arousal induced by an acute psychosocial stressor (Trier Social Stress Test; TSST) [45,46].

Therefore, better stress recovery (increased parasympathetic activation and reduced sympathetic activation following an acute stressor) is one plausible mechanism underpinning the health-protective effects of nature exposure [41,47,48]. More specifically, evidence supports the idea that incorporating nature into residential settings buffers against the effects of chronic stress [49–51] and reduces the risk of various stress-related diseases

[52–55], as exemplified by the aforementioned epidemiological evidence [1–4]. In the present study, we centered our interpretations on cardiovascular disease given the direct and observable link between autonomic activation and cardiovascular physiology, as evidenced by changes in heart rate, pulse, and blood pressure.

[1.3] Differential Susceptibility

We propose that individuals in lower versus higher socioeconomic positions could experience greater cardiovascular benefits from nature exposure due to increased sensitivity to environmental conditions as a function of susceptibility to stress. In this context, a pro-inflammatory immune state induced by early life stress could heighten the effects of various environmental conditions. Although research has primarily centered on the negative effects of adverse (risk-promoting) environments, growing evidence indicates a link to better outcomes within protective (benefit-enhancing) environments. This idea is grounded within evolutionary-developmental theories [56–59] which converge on the Differential Susceptibility Hypothesis: that susceptible individuals are more sensitive to risks of adverse environments, but are also more sensitive to the benefits of protective environments, relative to less susceptible individuals [59].

In support of this hypothesis, a seminal review of fifty-six studies encompassing thousands of participants (n = 22,686) demonstrated that individuals who were susceptible to stress (using an extensive range of behavioral, physiological, and genetic indicators) also exhibited greater physical and mental health benefits in response to protective social conditions (e.g., positive feedback, social support) relative to less susceptible individuals [60]. Emerging evidence also indicates differential susceptibility could be relevant for the specific susceptibility indicators employed in the present study, including socioeconomic status, early life stress, and a pro-inflammatory state.

For instance, regarding socioeconomic status, a landmark study on the population of England below the age of retirement (n = 40,813,236) found that the cardiovascular disparity gap between the highest and lowest income groups was 30% smaller in the greenest neighborhoods [1]. Regarding early life stress, a national longitudinal survey of individuals

in the United States (n = 34,458) provided evidence that adults with adverse childhood experiences had greater decreases in transdiagnostic psychopathological factors following annual reductions in current life stress compared to adults without adverse childhood experiences [61]. Regarding a pro-inflammatory state, experimental evidence has shown that healthy participants (n = 61) exposed to an in vivo inflammatory challenge (low-dose endotoxin) demonstrated heightened neural activity in reward processing regions (ventral striatum and ventromedial prefrontal cortex) when receiving positive versus neutral social feedback about their performance on an audio-recorded interview, relative to participants who were given a placebo (n = 57 [62]).

Throughout this body of evidence, a trend emerges in which susceptible individuals exhibit better outcomes in protective environments relative to less susceptible individuals. In other words, susceptible individuals tend to exhibit greater sensitivity to both adverse and protective environmental influences than their less susceptible counterparts, who appear to exhibit relatively moderate effects from their environment [59].

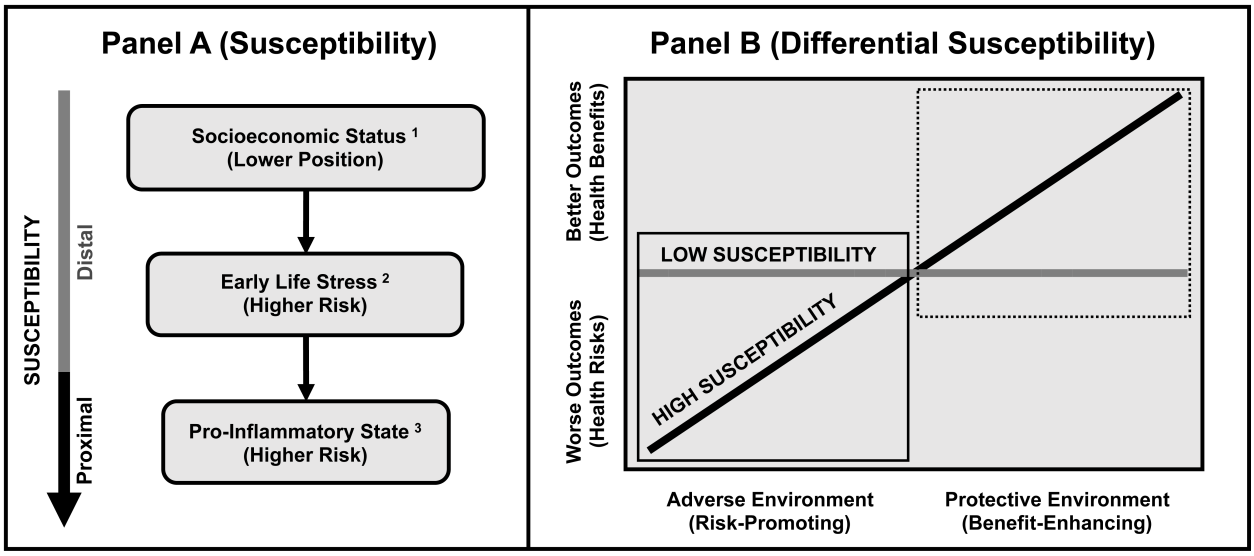
[1.4] Present Study

Embedding this theory into our framework (see Fig 1) implies that individuals in lower versus higher socioeconomic positions are more likely to exhibit greater cardiovascular risks in adverse environments, but also greater cardiovascular benefits in protective environments [59]. Specifically, we expect that individuals in lower socioeconomic positions are more likely to experience: early life stress; a pro-inflammatory immune state induced by early life stress; and enhanced sensitivity to the cardiovascular benefits of natural environments as a function of susceptibility to stress. Considering that a pro-inflammatory state is a key mechanism driving the association between early life stress and negative outcomes under adverse conditions [27,28], we expect that it could also be a key mechanism leading to positive outcomes under protective conditions.

Put together, the aforementioned evidence supports the possibility that individuals with a pro-inflammatory immune state could derive greater cardiovascular benefits from the stress-buffering effects of nature. However, to our knowledge, this mechanism has never

been explored in an experimental paradigm. The purpose of this investigation was to: (1) posit a theoretical framework to highlight potential mechanisms underpinning differential susceptibility to natural environments, and (2) provide initial insight into the hypothesized associations to determine if there is sufficient evidence that supports more comprehensive investigations in larger and more diverse samples.

Figure 1. Theoretical Framework



Emerging epidemiological evidence indicates that nature exposure could be associated with greater health benefits among groups in lower versus higher socioeconomic positions. One possible mechanism underpinning this evidence is described by our theoretical framework. **Susceptibility:** individuals in lower socioeconomic positions often face higher exposure early-life stressors, which can induce a lifelong susceptibility to stress through various neurobiological pathways, including a pro-inflammatory immune state. **Differential Susceptibility:** susceptible individuals are more sensitive to the health risks of adverse environments (e.g., worse recovery from stress), but are also more sensitive to the health benefits of protective environments (e.g., better recovery from stress), relative to less susceptible individuals.

(1) *Socioeconomic Status* is defined as the position of an individual in their society which is determined by both social and economic factors that impact exposure to and experiences with psychosocial stressors [63]. (2) *Early Life Stress* is defined as persistent exposure to psychosocial stressors during childhood, with ranging degrees of perceived severity, that induce neurobiological responses and could promote developmental alterations over time [64]. (3) A *Pro-Inflammatory Immune State* is defined as heightened neuroimmune reactivity to psychological (e.g., social) and biological (e.g., bacterial) stressors combined with resistance to anti-inflammatory signals [27,28]. Panel B was adapted from "For Better and For Worse: Differential Susceptibility to Environmental Influences" by Jay Belsky, Marian J. Bakermans-Kranenburg, and Marinus H. van IJzendoorn, 2007, Current Directions in Psychological Science, 16(6), 300-304. Copyright 2007 by the Association for Psychological Science. Adapted with permission.

In this controlled experimental study, we determined differences in stress recovery caused by exposure to either a nature environment (a local public park) or a comparator environment (indoor office setting) following exposure to an acute psychosocial stressor (Trier Social Stress Test) among healthy participants with varying levels of susceptibility. The environmental exposures were conducted using virtual reality as immersive modalities have been shown to induce responses comparable to real-world exposures [65,66] and offer several key advantages, including the mitigation of confounding factors (e.g., exercise, socialization [52]), isolation of sensory effects (e.g., visual, auditory [65]), and greater control over the exposure (e.g., presence of humans, weather [66]). Stress recovery was operationalized by indicators of autonomic activation (heart rate variability [67]) as the homeostasis of this nervous system indicates neuro-cardiac interactions in response to environmental conditions [68,69], responds rapidly to acute exposures [69,70], and is robustly associated with cardiovascular health [67–74].

We also tested distal and proximal indicators of susceptibility in the context of our theoretical framework (see Fig 1). Distal indicators included socioeconomic status (subjective social status) and early life stress (adverse childhood experiences), while proximal indicators included two immunological assessments of monocytes to index a pro-inflammatory state (increased inflammatory reactivity and glucocorticoid resistance in response to an in vitro bacterial challenge). We hypothesized that susceptible participants would exhibit greater autonomic recovery from the acute psychosocial stressor (increased parasympathetic and reduced sympathetic activation) when exposed to the nature versus office environment, relative to less susceptible participants.

[2] Materials & Methods

[2.1] Participants

We recruited male students (n = 64), 18 – 30 years of age, from a Texas university using local advertisements between April 1st and July 31st, 2019. Participants were fluent English speakers, non-smokers, non-drug users, not diagnosed with or taking medication for

chronic illness (diabetes, cardiovascular disease, metabolic syndrome, epilepsy, seizures, and asthma), and without a history of sleep problems; who were not night-shift workers and were naïve to our stressor. We recruited young adults to focus this stage of research on a healthier sample, as with age comes the development of aging-related health states that might confound the analyses. We also recruited exclusively young males (sex assigned at birth) to minimize variability in our outcome (stress recovery) that was not attributed to the experimental conditions or susceptibility indicators [75]. This was based on prior research showing that males demonstrate less variability than females in response to the same psychosocial stressor that was used in this investigation [76–78]. For instance, the literature supporting this stressor has provided evidence that hormonal fluctuations associated with menstrual cycles (e.g., estradiol, progesterone) and altered diurnal neuroendocrine rhythms associated with oral contraceptive use increase the variability of stress responses among females [79]. All participants provided written informed consent and were compensated with 40 USD for completing the experiment. This study was approved by the Institutional Review Board at the University of Texas at El Paso (1385515-3).

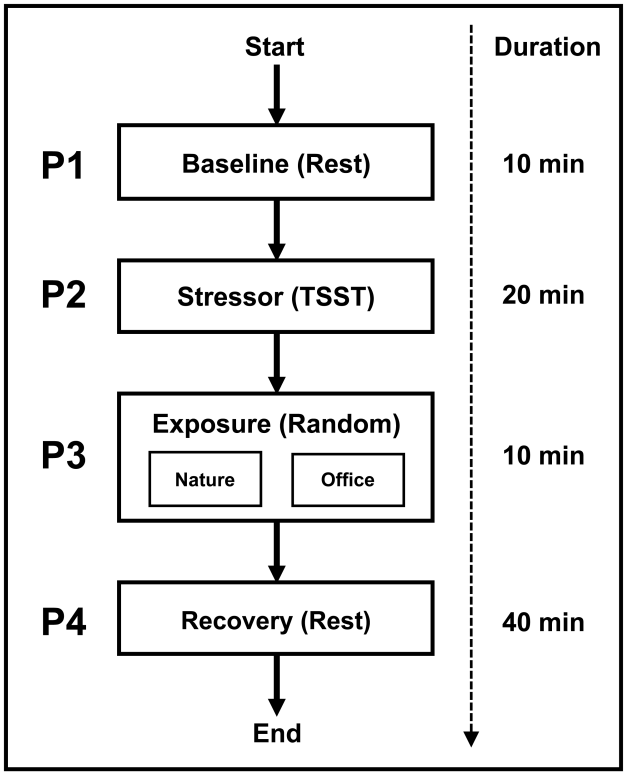
[2.2] Study Design

We used a between-group design to compare the effects of the nature versus indoor office environment on stress recovery from an acute psychosocial stressor, with a focus on the modifying effects of susceptibility to stress. We did this by having participants experience the psychosocial stressor, followed by a 10-min exposure to a randomly assigned environment (nature or office) delivered using virtual reality, and subsequently a 40-min recovery period. Changes in stress recovery were observed throughout the experiment (see Fig 2) and indexed using autonomic activation (heart rate variability). We then examined changes in autonomic activation as a function of the interaction between the environmental conditions and susceptibility to stress, represented as both distal indicators (socioeconomic status and early life stress) and proximal indicators (inflammatory reactivity and glucocorticoid resistance).

[2.3] Procedure

During an initial visit to the laboratory, participants underwent a health screening to determine the following exclusion criteria: body mass index $\geq$25 kg/m^2, waist circumference $\geq$40 inches, blood pressure $\geq$140/90 mmHg, fasting glucose $\geq$100 mg/dL, and moderate or worse depressive severity (PHQ-9 score $\geq$10 [80]). Participants then completed self-report questionnaires as measures of socioeconomic status and early life stress. Finally, all participants were exposed to a 5-min 360º VR video of Zion National Park, minimizing the potential for a "novelty" effect during the exposure experiment for those who had never experienced virtual reality [81]. Participants who passed the health screening were scheduled for the experiment (see Fig 2) on a separate day and at a standardized time (9:00am or 2:00pm, within three days of the initial visit) to mitigate circadian effects [82].

Figure 2. Flow Diagram of the Exposure Experiment



Stress recovery was assessed using heart rate variability to index changes in autonomic activation (sympathetic and parasympathetic) from baseline to the recovery period. Socioeconomic status (MacArthur Scale of Subjective Social Status) and early life stress (Adverse Childhood Experience Questionnaire) were measured during an initial visit to the laboratory within three days of the exposure experiment. Inflammatory reactivity and glucocorticoid resistance (in response to the in vitro bacterial challenge) were assessed before the start of the exposure experiment.

[2.3.1] Baseline

Upon arrival at the laboratory on the day of the exposure experiment, participants rested in an examination room for 15 min and then provided a blood sample for the bioassay of inflammatory reactivity and glucocorticoid resistance. Subsequently, participants attached three wireless electrodes to their abdomen and below their collarbone and reclined on an examination table for 10 min to complete the baseline assessment. The electrodes were connected wirelessly to a computer and remained on the participant for the duration of the experiment.

[2.3.2] Stressor

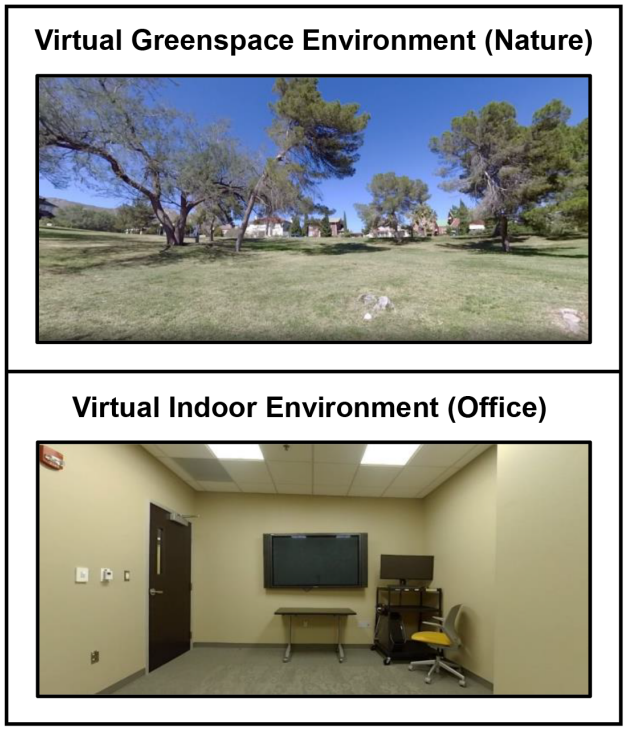
Participants were then taken to an office space devoid of natural elements to experience a variation of the Trier Social Stress Test which has been shown to effectively simulate stressful situations in the real world [76,83,84]. The stressor exposure was coordinated by a female experimenter and performed in front of a male judge with two tasks: a public speaking task (why you would be the best candidate for your "dream job" during a mock job interview) and a mental arithmetic task (rapid and accurate serial subtraction). To increase the efficacy of the stressor, participants were informed that video monitoring was being conducted for the speech task and misinformed that the participant with the highest score on the mental arithmetic task would receive an additional incentive worth 30 USD. When participants stopped before the time allocated for the speech task, they were prompted to continue, with a 10-second pause on subsequent prompts. For the mental arithmetic task, when participants answered incorrectly, a buzzer was sounded and they were prompted to restart from the beginning of the task. The stressor lasted for 20 min with four 5-min blocks (instructions, preparation, speech task, and mental arithmetic task).

[2.3.3] Exposure

Participants were then exposed to one of two randomly assigned immersive virtual reality environments, including a nature setting (a local public park with distant houses) or an indoor office setting (the same office used for the experiment, but in virtual reality).

Images of these environments are presented in Fig 3. A technician conducted the random assignment, blinding the experimenter to the condition group of the participant. The virtual exposures were delivered using a commercial headset (VIVE Pro™, HTC Corporation, Taoyuan, Taiwan) and consisted of 360° videos, recorded using an 8k 360° camera (Insta360 Pro™, Insta360.Inc, Shenzhen, Hong Kong).

Figure 3. Virtual Reality Environments



Equirectangular depictions of the 360-degree 8k stationary recordings delivered in virtual reality using a commercial headset after participants experienced the acute stressor. The virtual greenspace environment (nature) was recorded at a public park within the same county as the university where the exposure experiment was conducted. The virtual indoor environment (office) was recorded at the same office used for the experiment. Participants were seated in a chair for the duration of the exposure (10 min).

We selected a public park in the same county as the university as this was a natural landscape that was familiar and accessible to the participants, concordant with epidemiological evidence that observed the effects of nature in residential settings [1–4]. We avoided settings with humans or animals, tall grass or dense tree cover, substantial landscape features or significant inclines, and recorded the setting in mid-spring under direct sunlight. We also used the office environment as the reference condition for our analyses as this was the physical location of the participants during the virtual exposures, ensuring that the participants in the office condition did not experience a change of setting. This was done to minimize the impact of this condition, avoiding confounders that could be introduced by exposing participants to a different setting than their current location, while

also accounting for any effects of wearing the headset. Participants were seated in a chair in the middle of the office for the duration of the 10-min exposure. The length of this exposure was expected to induce a measurable effect based on other studies observing effects with even shorter periods [45,46,85–87].

[2.3.4] Recovery

Subsequently, participants remained in the office for 40 min while resting in a chair for the duration of the recovery period. This length was selected to ensure data were collected for at least 70 min after the initiation of the stressor, which is a sufficient amount of time to capture autonomic recovery via heart rate variability based on prior literature [84,88]. After this recovery period, participants were taken back to the examination room and the electrodes were removed. Participants were then debriefed which marked the end of the exposure experiment.

[2.4] Stress Recovery

Stress recovery was assessed using heart rate variability to index changes in autonomic activation throughout the experiment. Data were collected using BIOPAC MP150 for Windows and AcqKnowledge data acquisition software (Biopac Systems Inc., Santa Barbara, CA). Raw signals were filtered through a BIOPAC ECG100C bioamplifier with a sampling frequency of 1 kHz and set to record heart rate (HR) from 40 – 180 beats per minute. Data were broken up into four segments corresponding to the study periods (baseline, stressor, exposure, and recovery; see Fig 2).

Time, frequency, and non-linear domain metrics were analyzed using Kubios software (3.4.3 [89]), using an automatic correction algorithm for artifacts [90]. Time domain analyses included the root mean square of successive RR interval differences (RMSSD) which reflects vagal-mediated changes in beat-to-beat variance [69]. Frequency analyses included low frequency (LF: 0.04 to 0.15 Hz) and high frequency (HF: 0.15 to 0.4 Hz) metrics to calculate the LF/HF ratio which reflects sympathovagal balance [69] and was expressed in power bands of normalized units. Non-linear analyses used return maps (plotting

every interval against the prior interval) to estimate the width of the eclipse (SD1) which reflects vagal-mediated changes in beat-to-beat variance [69], and the length of the eclipse (SD2) which reflects sympathovagal balance [69]. Distinct sympathetic (SNS) and parasympathetic (PNS) tone indexes were then estimated as a composite of time domain (e.g., HR intervals, RR intervals) and non-linear domain (e.g., SD2, SD1) metrics [89]. While these indices are relatively novel in research applications, evidence has demonstrated they provide highly reliable assessments of the corresponding branch of the autonomic nervous system [91–94]. Cleaned data were log-transformed to normalize model residuals and correct for skewed distributions. These metrics were then separated into two profiles to index higher sympathetic (LF/HF, SNS, HR↑) or parasympathetic activation (RMSSD, PNS, HR↓) across the study periods.

[2.5] Stress Susceptibility

[2.5.1] Distal Indicators

Perceived socioeconomic status was measured using the MacArthur Scale of Subjective Social Status [95] which evaluates subjective social standing, reflecting impressions of current circumstances, background characteristics, and future opportunities. Scores are represented on a 10-point scale with higher scores reflecting higher socioeconomic status.

Early life stress was measured using the Adverse Childhood Experience Questionnaire [96] which includes 10 self-report items on experiences of childhood abuse (emotional, physical, and sexual), neglect (emotional and physical), and household dysfunction (divorce, maternal violence, substance abuse, mental illness, and incarceration). Each endorsement is scored as one point with the total score representing the sum of these endorsements.

[2.5.2] Proximal Indicators

Bioassays of serum drawn before the baseline assessment were used to assess inflammatory reactivity and glucocorticoid resistance as proximal indicators of susceptibility to stress. Inflammatory reactivity was assessed by the quantity of IL-6 produced by monocytes from

an in vitro exposure to lipopolysaccharide bacteria. Glucocorticoid resistance was assessed by the sensitivity of monocytes to dexamethasone; the quantity of dexamethasone needed to reduce 50% of IL-6 produced (IC50) from the same lipopolysaccharide exposure.

We used the protocol validated by Miller et al [33,34,97] to assess these indicators using monocyte-corrected values (correcting for the absolute number of monocytes in circulation to account for cellular disparities). Concentrations of IL-6 in supernatants were measured in duplicate using the MILLIPLEX MAP Human High Sensitivity Cytokine panel (catalog # HSCYTMAG-60SK) from MilliporeSigma Corp. (Burlington, MA) and analyzed on a Luminex 200 analyzer running xPONENT® (3.1) software (Luminex Corp., Austin, TX). IL-6 concentrations were reported as pg/mL (detection limit: 0.11 pg/mL). Controls were within the expected range (inter-assay CV: 6.17%). IC50 calculations were performed using GraphPad Prism software (9.1.1; San Diego, CA). Data were log-transformed to normalize model residuals and correct for skewed distributions. Larger values were indicative of higher inflammatory reactivity and glucocorticoid resistance in response to the in vitro bacterial challenge.

[2.6] Data Analysis

First, we confirmed that the stressor induced cardiovascular arousal (increased sympathetic and reduced parasympathetic activation during the stressor period, relative to the baseline period) and that stress recovery was captured following the stressor (increased parasympathetic and reduced sympathetic activation during the exposure and recovery periods, relative to the stressor period) using linear mixed effect models with random intercepts and restricted maximum likelihood estimation to explore the main effect of time for each autonomic metric. This was accomplished using pairwise contrasts with corrections for multiple comparisons (Tukey's HSD). Second, we tested if the nature condition was associated with better stress recovery relative to the office condition also using mixed effect models, but with an interaction term (Time x Condition) for each autonomic metric. In these models, the office condition was used as a reference for the pairwise contrasts.

Our hypothesis was tested using a series of linear regression models, with one sequence per autonomic metric (outcome), to test the unique effect of each susceptibility indicator (socioeconomic status, early life stress, inflammatory reactivity, and glucocorticoid resistance), independently, conserving statistical power. These models used assessments during the recovery period, where the greatest differences between conditions were observed across all autonomic metrics. Each model included the corresponding assessment of the autonomic metric at baseline (to explore changes over time and account for individual differences), two main effects (condition group and susceptibility indicator), and an interaction term (Susceptibility x Condition) to test our hypothesis that the slope of the linear relationship between the susceptibility indicator and autonomic metric differed between the nature and office (reference) conditions. Susceptibility indicators were centered to aid in interpretations and all assumptions for linear regression were confirmed before interpreting our results. We also tested the sensitivity of the effects across all models using binary representations of the susceptibility indicators (delineated by the median).

Although we utilized alphas (0.05 level) to report significant findings, we focused our interpretations on forest plots (standardized coefficients and confidence intervals) that were used to infer directional trends and relative effect sizes across all models, regardless of statistical significance. Data were analyzed using R (3.6.3) with the *lmerTest* package for mixed effect models, the *emmeans* package for contrasts, the *effectsize* package for standardized coefficients, and the *ggplot2* package for generating plots.

[3] Results

As expected from randomization, no significant differences in participant demographics, health status, susceptibility indicators, or autonomic metrics at baseline were noted across the condition groups (see Table 1). Bivariate correlations for the susceptibility indicators (S1 Table) and autonomic metrics (S2 Table) are provided in the supplemental materials.

Table 1. Participant Characteristics

Characteristic	M ± SD or N (%)			*p*
	Total ($n = 64$)	**Office ($n = 32$)**	**Nature ($n = 32$)**	
Demographics				
Age (Years)	22.70 ± 3.35	22.16 ± 3.21	23.25 ± 3.44	.19
Hispanic or Latino	53 (82.8%)	25 (78.1%)	28 (87.5%)	.51
White[1]	55 (85.9%)	26 (81.3%)	29 (90.6%)	.47
Health Status				
BMI (kg/m^2)	24.32 ± 3.27	24.50 ± 3.81	24.14 ± 2.67	.66
SBP (mmHg)	121.67 ± 10.24	122.56 ± 10.91	120.78 ± 9.62	.49
DBP (mmHg)	73.27 ± 7.69	72.88 ± 7.90	73.66 ± 7.59	.69
Pulse (per min)	61.73 ± 8.89	62.50 ± 9.34	60.97 ± 8.49	.50
Depressive Symptoms[2]	3.53 ± 2.81	3.66 ± 2.62	3.41 ± 3.02	.72
Sleep Duration (Hours)[3]	6.93 ± 0.83	7.00 ± 0.94	6.86 ± 0.70	.51
Sleep Quality[4]	2.38 ± 0.75	2.53 ± 0.72	2.22 ± 0.75	.09
Physical Activity[5]	22.32 ± 15.45	22.31 ± 18.26	22.33 ± 12.38	.99
Susceptibility				
Socioeconomic Status[6]	4.00 ± 1.75	3.97 ± 1.75	4.03 ± 1.77	.89
Early Life Stress[7]	1.56 ± 1.71	1.59 ± 1.97	1.53 ± 1.44	.89
Inflammatory Reactivity[8]	1.17 ± 0.41	1.15 ± 0.43	1.19 ± 0.39	.68
Glucocorticoid Resistance[8]	2.02 ± 0.19	2.02 ± 0.19	2.03 ± 0.19	.90
Autonomic Activation (Baseline)				
RMSSD (ms)	73.84 ± 45.66	69.98 ± 32.13	77.70 ± 56.34	.50
PNS (nu)[9]	1.29 ± 1.59	1.19 ± 1.34	1.38 ± 1.82	.62
LF/HF (nu)	1.01 ± 0.86	0.90 ± 0.57	1.30 ± 1.08	.28
SNS (nu)[9]	−0.74 ± 0.85	−0.72 ± 0.95	−0.76 ± 0.76	.86
HR (bpm)	61.04 ± 8.10	60.95 ± 8.35	61.13 ± 7.97	.93

P-values represent between-group differences using t-tests or chi-square tests for the corresponding characteristic. (1) Black: n = 5, Asian: n = 2, Native American: n = 1, Pacific Islander: n = 1. (2) Patient Health Questionnaire. (3) Past month average sleep duration; (4) Past month average sleep quality, from 1 "very good" to 5 "very bad". (5) Past month days x hours of exercise. (6) MacArthur Scale of Subjective Social Status; (7) Adverse Childhood Experience Questionnaire; (8) In vitro bacterial challenge; (9) Composite of time and non-linear domain metrics.

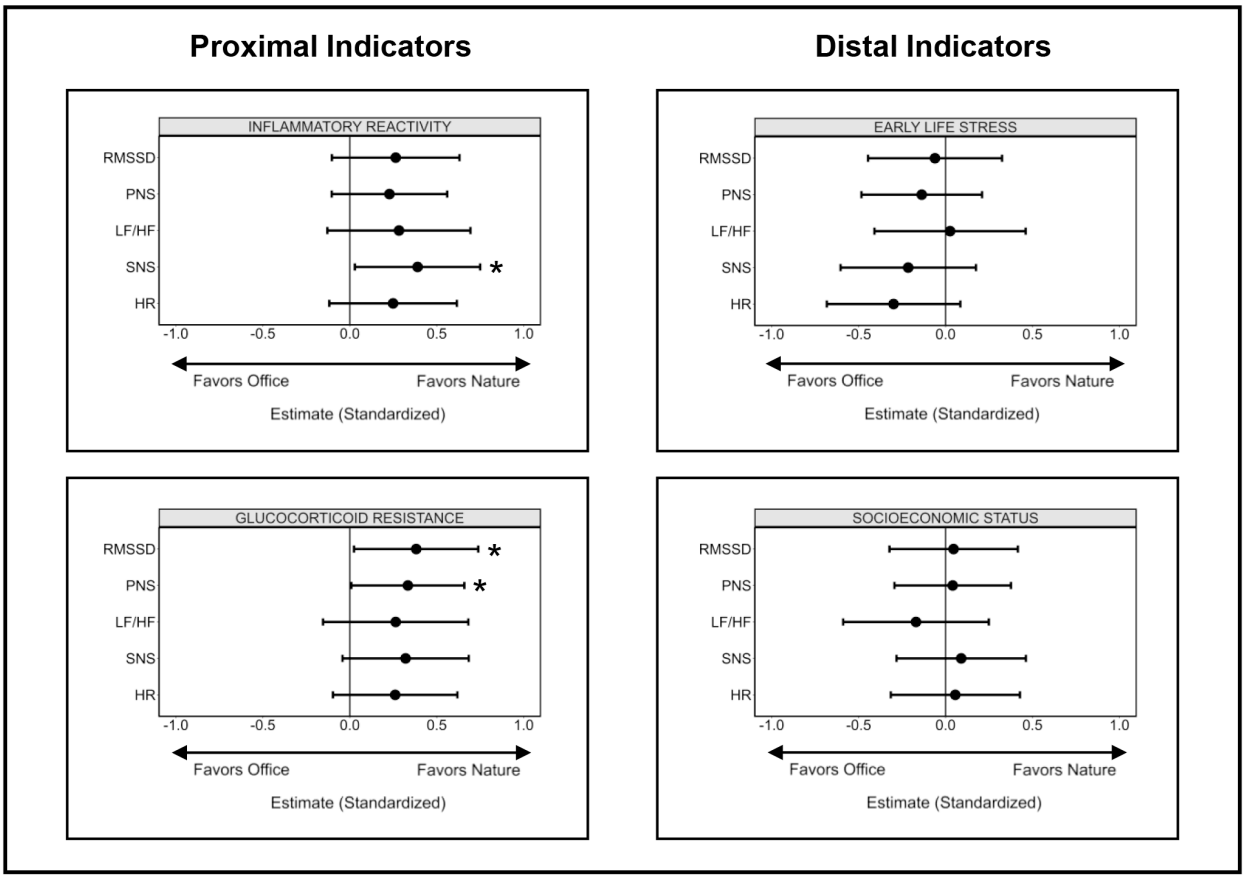
The stressor induced observable cardiovascular arousal as evidenced by significant differences in autonomic activation between the baseline and stressor periods, with higher arousal observed during the stressor period (increased sympathetic and reduced parasympathetic activation, relative to the baseline period; see the S1 Fig). We also observed clear indications of stress recovery following the stressor, as evidenced by significant differences between the stressor and subsequent periods, trending towards lower arousal over time (increased parasympathetic and reduced sympathetic activation, relative to the stressor period; see the S1 Fig).

Significant between-group differences were not observed during the baseline period (p = .71 – .93), the stressor period (p = .74 – .99), the exposure period (p = .42 – .99), or the recovery period (p = .26 – .60), indicating similar levels of stress reactivity and recovery across the condition groups. However, non-significant trends were consistently in the direction of better stress recovery for participants in the nature versus office condition during both post-stressor periods (see the S2 Fig), with the largest between-group differences observed during the recovery period.

[3.1] Modifying Effects of Susceptibility on Stress Recovery

We then tested our interaction terms (Susceptibility x Condition) and interpreted global trends across all models regardless of statistical significance using forest plots with standardized coefficients and confidence intervals (see Fig 4). Modest trends were observed among the interaction effects during the recovery period for the pro-inflammatory indicators; higher inflammatory reactivity and glucocorticoid resistance consistently trended in the direction of better stress recovery (increased parasympathetic and reduced sympathetic activation) in the nature condition versus office condition across all models. However, these same trends were not observed for socioeconomic status or early life stress which showed no discernible trends among the interaction effects with the condition groups on stress recovery.

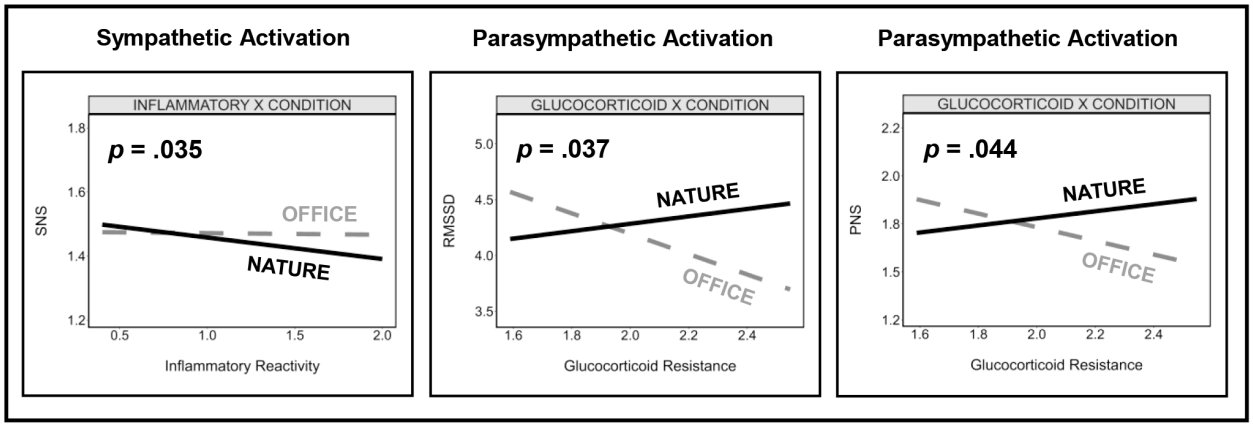
Figure 4. Forest Plots of Standardized Effects (Continuous Interaction Terms)



Forest plots visualizing interaction terms (standardized coefficients and confidence intervals [95%]) across all linear regression models. Within these plots, all models were specified so that among participants with higher susceptibility (continuous), positive interaction terms indicate better stress recovery (increased parasympathetic and reduced sympathetic activation) in the nature condition while negative terms indicate better stress recovery in the office condition. Interaction terms at zero indicate no differences in the association between susceptibility and stress recovery by condition group. *$p < .05$

To better understand the characteristics of these trends, we then generated plots for our significant interaction terms (see Fig 5; S3 Fig). Specifically, inflammatory reactivity was associated with greater reductions in sympathetic activation for participants in the nature versus office condition during the recovery period (SNS: β = -0.390, 95% CI [-0.750, -0.029], p = .035), and glucocorticoid resistance was associated with greater increases in parasympathetic activation for participants in the nature versus office condition during the recovery period (RMSSD: β = 0.382, 95% CI [0.024, 0.739], p = .037; PNS: β = 0.334 95% CI [0.009, 0.659], p = .044).

Figure 5. Interaction Plots: Susceptibility by Condition on Autonomic Activation



Interaction plots visualizing the effect (slope) of susceptibility (inflammatory reactivity or glucocorticoid resistance) on stress recovery (autonomic activation) by condition group (nature [solid black line] versus office [dashed gray line]). Y-axes present sympathetic or parasympathetic activation using fitted values (unstandardized) from the corresponding regression model (baseline adjusted metric of autonomic activity [log] during the recovery period [40 min]). X-axes present susceptibility indicators using log-values. P-values (beta weights) represent the interaction term.

The direction of these significant interactions indicates that the effect (slope) of a pro-inflammatory state on autonomic activation differs between the environmental conditions. Specifically, a pro-inflammatory state was associated with better recovery in the nature versus office environment (increased parasympathetic and reduced sympathetic activation), following sympathetic arousal induced by the stressor. The direction of the simple slopes for each condition suggests a pro-inflammatory state had a positive trend on stress recovery in the nature condition (SNS: β = -0.335, 95% CI [-0.586, -0.083], p = .010; RMSSD: β = 0.134, 95% CI [-0.117, 0.385], p = .290; PNS: β = 0.186, 95% CI [-0.043, 0.414], p = 0.110) but a negative trend on stress recovery in the office condition (SNS: β = 0.055, 95% CI [-0.202, 0.311], p = .671; RMSSD: β = -0.248, 95% CI [-0.502, 0.007], p = .056; PNS: β = -0.148, 95% CI [-0.381, 0.084], p = .206), although these trends were modest and mostly non-significant.

[3.2] Sensitivity Analyses

Sensitivity analyses using binary indicators suggested these trends were fairly consistent across continuous and binary representations of susceptibility. Specifically, these binary analyses again revealed no discernible trends for socioeconomic status or early life

stress while inflammatory reactivity and glucocorticoid resistance consistently trended towards better stress recovery in the nature condition and worse recovery in the office condition (see the S4 Fig). It is also of note that binary trends for inflammatory reactivity and glucocorticoid resistance were larger and mostly significant relative to continuous trends (modest and mostly non-significant).

[4] Discussion

In this experimental study among healthy college-age males, we observed partial support for our hypothesis that susceptible participants would exhibit greater autonomic recovery from an acute psychosocial stressor in a nature versus office environment, relative to less susceptible participants. Specifically, we found that participants with higher inflammatory reactivity and glucocorticoid resistance exhibited greater increases in parasympathetic activation and greater reductions in sympathetic activation when exposed to a virtual nature versus office environment, relative to participants with lower inflammatory reactivity and glucocorticoid resistance. However, no differences in autonomic recovery were found among participants in lower versus higher socioeconomic positions or among participants with higher versus lower exposure to early-life stressors.

While the conclusions that can be drawn from this evidence are tentative, overall our findings support the need for further research in larger and more diverse samples, especially considering that we observed expected trends for inflammatory reactivity and glucocorticoid resistance following just a 10-min virtual reality exposure in a small sample of college-age males. As the evidence supporting our framework was derived from more representative samples, including females and older adults, it is plausible these trends could be supported in larger and more generalizable studies. In the following sections, we discuss some potential implications if future research using broader and more diverse samples aligns with our findings.

[4.1] Theoretical Implications

Our findings only supported certain aspects of our framework (see Fig 1) where we expected that participants in lower versus higher socioeconomic positions would exhibit greater cardiovascular benefits from the health-protective effects of nature exposure, possibly as a function of a pro-inflammatory immune state induced by early life stress. Specifically, our findings support the possibility that increased inflammatory reactivity and glucocorticoid resistance could be associated with greater autonomic recovery from nature exposure. However, our findings did not support this possibility for lower socioeconomic status or higher early-life stressor exposure.

These null associations were surprising as our expectations were based on large-scale population-based studies in Europe and North America, which have consistently shown that individuals living in socioeconomically deprived neighborhoods exhibit greater cardiovascular benefits from the health-protective effects of nature exposure [1–4]. However, it is possible these associations were not replicated in this study due to our small convenience sample of male college students, and a relative lack of variability in our sample regarding socioeconomic status and early life stress. This might also explain why we did not observe significant associations between our susceptibility indicators (see the S1 Table) as consistently shown within experimental studies [27,28,30–35].

[4.2] Research Implications

If future research in larger and more diverse populations also provides evidence that a pro-inflammatory immune state enhances sensitivity to the health-protective effects of nature exposure, this could carry substantial implications for public health research. Specifically, this could support an alternative conceptualization of susceptibility, predominantly used to explain the health risks associated with adverse environments, as increased environmental sensitivity, reflecting heightened responsivity to the health influences of both adverse and protective environmental conditions.

This could also strengthen the evidence base for the Differential Susceptibility Hypothesis [59], which has primarily centered on social environments, by demonstrating that susceptible individuals also experience greater health benefits from protective physical environ-

ments. In turn, this could provide opportunities for more effective interventions by altering and improving physical environments with the intention of promoting positive well-being outcomes. This has been less of a focus in public health research, which has predominantly focused on the experiences of susceptible individuals in adverse environments.

Further research could also underscore the importance of reconsidering how susceptibility is indexed in public health research, highlighting the advantages of using proximal indicators (e.g., biological correlates of susceptibility to stress). Traditional self-report measures such as socioeconomic status and early life stress are mechanistically distal from health outcomes, restricting their utility as indicators of susceptibility due to the increased likelihood of confounding and the need to account for counteracting exposures that could be unknown or immeasurable. For instance, not all individuals in low socioeconomic positions with high early-life stressor exposure develop susceptibility to stress due to protective factors (e.g., parental attachment, social support [98,99]). Hence, these measures do not consistently yield biological indicators of susceptibility to stress, limiting their application in the discerning of causal pathways.

In our study, only the pro-inflammatory indicators trended towards better stress recovery in the nature versus office condition. Thus, we encourage further experimental work on these causal pathways to employ assessments of inflammatory reactivity and glucocorticoid resistance, potentially representing objective and sensitive indicators of susceptibility to stress compared to distal indicators such as socioeconomic status and early life stress [100,101]. To this end, if we define "susceptibility" as an increased sensitivity to environmental factors, and "vulnerability" as higher exposure to such factors [102], then socioeconomic status and early life stress arguably serve as better indicators of "vulnerability" than "susceptibility".

Future researchers are also encouraged to examine proximal indicators of susceptibility to stress across other neurobiological systems associated with a pro-inflammatory immune state (e.g., neuroendocrine system, central nervous system, autonomic nervous system, cardiovascular system [27,28]). However, there are some discrepancies in the literature regarding how early life stress alters these systems. For instance, early life stress has

been associated with cortisol hyper-reactivity, but also cortisol hypo-reactivity, with either augmentation leading to negative health outcomes during adulthood [103]. Accounting for the severity level of the early-life stressor exposure might explain some of these discrepancies in the literature, as systematic evidence indicates cortisol hyper-reactivity is associated with childhood adversity while cortisol hypo-reactivity is associated with childhood trauma [23]. Therefore, efforts to better conceptualize and measure the distinction between childhood adversity versus trauma are needed to disentangle the complex influence of early life stress on health and well-being across the lifespan [104].

[4.3] Strengths & Limitations

Overall, we provide modest experimental evidence supporting the possibility that a pro-inflammatory immune state could induce greater cardiovascular benefits from nature exposure. Further, our results are supported by high levels of internal validity due to the blinded experimental design, successful induction of stress during the stressor, and successful capture of stress recovery during the post-stressor periods. We also used stringent inclusion and exclusion criteria [76], advanced algorithms to clean the heart rate variability data [90], strategies to mitigate confounding factors (e.g., novelty effect of virtual reality [81], timing of the exposure experiment for circadian effects [82]), along with analyzing blood samples in duplicate using a validated protocol [33,34,97].

We also used a virtual paradigm to isolate sensory effects (e.g., visual, auditory [65]) and mitigate confounding factors (e.g., exercise, socialization [52]) that might have been encountered in real-world settings. However, while virtual and real-world exposures are comparable [65,66], effect sizes are often attenuated in virtual paradigms [105], suggesting our effect sizes might have been larger had we used a real-world paradigm. Nonetheless, our use of a virtual paradigm also provides implications for simulated nature-based interventions that might be remarkably simple but effective, such as windows with nature views [106] or indoor plants [107,108].

However, the generalizability of our study was limited, warranting caution when interpreting our results from a small sample of male college students who were primarily

Hispanic/Latinx and lived in West Texas. Although we expected our sample to have a distribution across our susceptibility indicators, we observed limited variability in our measures of socioeconomic status and early life stress, potentially contributing to the null results associated with these variables. Consequently, our results may have been underpowered and further research is needed to explore these trends in larger and more diverse samples, including females and older adults, with more variability in terms of socioeconomic status, early life stress, and protective factors.

The use of a current measure of socioeconomic status represents another limitation as evidence indicates that higher socioeconomic status during adulthood is unable to reverse the lifelong effects of early life stress [32,35]. To this end, it is also possible our outcomes could have been influenced by other pathways attributed to childhood socioeconomic status that are independent of early life stress. Further, the measure we used could have oversimplified our assessments and it might have been more informative to use a composite index across a broader range of indicators (e.g., household income, maternal education) to account for the various pathways to which socioeconomic status could influence susceptibility to stress, beyond the psychological aspects of subjective social status. Despite these shortcomings, some evidence indicates subjective assessments provide stronger and more consistent associations with stress-related factors compared to objective scales using earned income, educational attainment, and occupational status [95] which were remarkably homogeneous in our sample of college students, most of whom were in their teens or early twenties. However, future researchers should include more comprehensive measures of different pathways (objective and subjective) in early life.

Using adverse childhood experiences [96] as a proxy for early life stress represents another limitation, as this measure does not account for the perceived severity, timing, duration, or frequency of stressful childhood events [100], protective factors [101], or broader societal contexts as emphasized by the social determinants of health [109]. Future researchers should account for these factors with more comprehensive assessments. Regarding the experimental design, it is also possible the virtual office setting was not a perfectly neutral reference as this was the same room where the participants experienced the stressor.

However, a perfectly neutral environmental condition might be unattainable, and we considered that a change from the same real to virtual office setting would be a good approximation of neutral change compared to a new environment. Further, another benefit of using the same real and virtual office setting was that it accounted for any effects of wearing the headset. However, future researchers should also explore these trends using different comparator environments.

Another concern with our approach is the multiple comparisons problem, as alpha inflation increases the risk of false positives when testing a large number of models without corrections [110]. To address this challenge, we focused our interpretations on directional trends and relative effect sizes across all regression models (hypothesis tests), using forest plots with standardized coefficients and confidence intervals. Further, without pre-established cut-off ranges for our pro-inflammatory indicators, we used a median split relative to the distribution of our sample for the binary representations. There is also controversy in the literature regarding the LF metric, with some authors suggesting it reflects both sympathetic and parasympathetic activation [111]. Yet, evidence indicates this metric solely reflects sympathetic activation when it is expressed in normalized units [88,112]. This is complemented by our results, showing a tight alignment with another metric of sympathetic activation (SNS) from alternative domains (composite of time and non-linear metrics [89]). Despite these limitations, overall, our results were supportive of specific elements of our framework which builds upon evidence derived from larger and more diverse samples.

[4.4] Public Health Implications

Overall, our findings support the value of further investigation into the idea that a pro-inflammatory immune state could be at least one potential mechanism underpinning epidemiological observations that nature exposure is associated with better cardiovascular health among groups in lower versus higher socioeconomic positions [1–4]. However, even if a pro-inflammatory immune state is independent of socioeconomic status in larger and more diverse samples, this could still hold substantial implications for public health.

Specifically, this could further support the idea that incorporating nature into urban settings could be a strategic intervention target to curb the prevalence of cardiovascular

disease, but especially among individuals with a pro-inflammatory state. Importantly, nature in urban settings is typically a safe, feasible, and cost-effective intervention target [113,114] with potential as a complementary health approach that (1) could be installed as a passive intervention; (2) is a long-term intervention, fostering generational health; (3) could provide multiple co-benefits and (4) could be implemented through public health policy [52]. Other helpful nature-based interventions could even be provided using windows with nature views [106] or indoor plants [107,108].

Future research in this area could also support a reconceptualization of susceptibility in public health research, conveying that individuals who are more susceptible to the risks of adverse environments might also be more receptive to the benefits of protective ones. This is underscored by our findings, providing modest support for past evidence that heightened inflammatory reactivity and glucocorticoid resistance might not just be risk factors [27,28] but also resources in protective environments [62]. While this idea is contained within the Differential Susceptibility Hypothesis in developmental psychology [59], we provide modest evidence that these effects might also pertain to protective physical environments, providing another avenue of integration with public health.

Based on our theoretical framework, we also assessed susceptibility across a range of indicators, including socioeconomic status, early life stress, inflammatory reactivity, and glucocorticoid resistance. Overall, our findings suggest that a pro-inflammatory state could be a particularly sensitive indicator of environmental sensitivity as a biological correlate of susceptibility to stress (proximal: direct pathway between the indicator and outcome) relative to self-reported assessments of socioeconomic status and early life stress (distal: indirect pathway between the indicator and the outcome, that in turn increases the risk of unmeasured confounder). For instance, not all adults with high early-life stressor exposure develop susceptibility to stress due to protective factors (e.g., parental attachment, social support [98,99]) that could be unknown or immeasurable. Further validation of proximal indicators in larger and more diverse samples could significantly enhance assessments of susceptibility to environmental health effects in research and clinical settings, promoting prevention efforts for public health approaches centered on reducing the prevalence of cardiovascular disease.

[4.5] Conclusion

Ultimately, future research in line with this theoretical framework could lead to a greater understanding of the ways in which nature-based interventions could be leveraged to reduce disparities in health among vulnerable populations. Specifically, this could further underscore the value of integrating protective environments into public health strategies, especially for individuals with a pro-inflammatory immune state who are particularly susceptible to health risks but also might stand to experience the greatest health benefits from nature exposure. Through the use of proximal indicators, we can more effectively identify potential mechanisms facilitating health risks and benefits among susceptible groups and tailor public health interventions, taking into account individual differences in environmental sensitivity to reduce disparities in health across socioeconomic gradients.

Acknowledgments

The authors thank Diana P. Flores, Ismael Beltran, Marcela Murga, and Alan Medina from the Biobehavioral Research Lab at the School of Nursing, University of Texas at El Paso, for their help in conducting the experiment. G.N. Bratman appreciates support from the Doug Walker Endowed Professorship, Craig McKibben and Sarah Merner, John Miller, and discussions with members of the UW Environment and Well-Being Lab.

References

1. Mitchell R, Popham F. Effect of exposure to natural environment on health inequalities: an observational population study. Lancet. 2008;372:1655-60. doi: 10.1016/S0140-6736(08)61689-X.

2. Mitchell RJ, Richardson EA, Shortt NK, Pearce JR. Neighborhood environments and socioeconomic inequalities in mental well-being. Am J Prev Med. 2015;49:80-4. doi: 10.1016/j.amepre.2015.01.017.

3. Brown SC, Perrino T, Lombard J, Wang K, Toro M, Rundek T, et al. Health disparities in the relationship of neighborhood greenness to mental health outcomes in 249,405 U.S. Medicare beneficiaries. Int J Environ Res Public Health. 2018;15:430. doi: 10.3390/ijerph15030430.

4. Rigolon A, Browning MHEM, McAnirlin O, Yoon HV. Green space and health equity: a systematic review on the potential of green space to reduce health disparities. Int J Environ Res Public Health. 2021;18:2563. doi: 10.3390/ijerph18052563.

5. Badland H, Pearce J. Liveable for whom? Prospects of urban liveability to address health inequities. Soc Sci Med. 2019;232:94-105. doi: 10.1016/j.socscimed.2019.05.001.

6. Craig JM, Prescott SL. Planning ahead: the mental health value of natural environments. Lancet Planet Health. 2017;1:e128-e129. doi: 10.1016/S2542-5196(17)30068-2.

7. Tost H, Reichert M, Braun U, Reinhard I, Peters R, Lautenbach S, et al. Neural correlates of individual differences in affective benefit of real-life urban green space exposure. Nat Neurosci. 2019;22:1389-93. doi: 10.1038/s41593-019-0451-y.

8. Astell-Burt T, Feng X. Does the potential benefit of neighbourhood green space for body mass index depend upon socioeconomic circumstances and local built and transport environments? A test of the 'equigenesis' hypothesis in Australia. J Transp Health. 2017;5:S40. doi: 10.1016/j.jth.2017.05.327.

9. Feng X, Astell-Burt T. Do greener areas promote more equitable child health? Health Place. 2017;46:267-73. doi: 10.1016/j.healthplace.2017.05.006.

10. Tomita A, Vandormael AM, Cuadros D, Di Minin E, Heikinheimo V, Tanser F, et al. Green environment and incident depression in South Africa: a geospatial analysis and mental health implications in a resource-limited setting. Lancet Planet Health. 2017;1:e152-e162. doi: 10.1016/S2542-5196(17)30063-3.

11. Evans GW. The environment of childhood poverty. Am Psychol. 2004;59:77-92. doi: 10.1037/0003-066X.59.2.77.

12. Evans GW, Kim P. Multiple risk exposure as a potential explanatory mechanism for the socioeconomic status–health gradient. Ann N Y Acad Sci. 2010;1186:174-89. doi: 10.1111/j.1749-6632.2009.05336.x.

13. Evans GW, Kim P. Childhood poverty and young adults' allostatic load: the mediating role of childhood cumulative risk exposure. Psychol Sci. 2012;23:979-83. doi: 10.1177/0956797612441218.

14. Evans GW, Kim P. Childhood poverty, chronic stress, self-regulation, and coping. Child Dev Perspect. 2013;7:43-8. doi: 10.1111/cdep.12013.

15. Giano Z, Wheeler DL, Hubach RD. The frequencies and disparities of adverse childhood experiences in the U.S. BMC Public Health. 2020;20:1327. doi: 10.1186/s12889-020-09411-z.

16. Hertzman C, Boyce T. How experience gets under the skin to create gradients in developmental health. Annu Rev Public Health. 2010;31:329-47. doi: 10.1146/annurev.publhealth.012809.103538.

17. Hertzman C. Putting the concept of biological embedding in historical perspective. Proc Natl Acad Sci U S A. 2012;109 Suppl 2:17160-7. doi: 10.1073/pnas.1202203109.

18. Aristizabal MJ, Anreiter I, Halldorsdottir T, Odgers CL, McDade TW, Goldenberg A, et al. Biological embedding of experience: a primer on epigenetics. Proc Natl Acad Sci U S A. 2020;117:23261–9. doi: 10.1073/pnas.1820838116.

19. Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol Behav. 2012;106:29-39. doi: 10.1016/j.physbeh.2011.08.019.

20. Agorastos A, Pervanidou P, Chrousos GP, Baker DG. Developmental trajectories of early life stress and trauma: a narrative review on neurobiological aspects beyond stress system dysregulation. Front Psychiatry. 2019;10:118. doi: 10.3389/fpsyt.2019.00118.

21. Fagundes CP, Glaser R, Kiecolt-Glaser JK. Stressful early life experiences and immune dysregulation across the lifespan. Brain Behav Immun. 2013;27:8-12. doi: 10.1016/j.bbi.2012.06.014.

22. Smith KE, Pollak SD. Early life stress and development: potential mechanisms for adverse outcomes. J Neurodev Disord. 2020;12:34. doi: 10.1186/s11689-020-09337-y.

23. Hosseini-Kamkar N, Lowe C, Morton JB. The differential calibration of the HPA axis as a function of trauma versus adversity: a systematic review and p-curve meta-analyses. Neurosci Biobehav Rev. 2021;127:54-135. doi: 10.1016/j.neubiorev.2021.04.006.

24. Maniam J, Antoniadis C, Morris MJ. Early-life stress, HPA axis adaptation, and mechanisms contributing to later health outcomes. Front Endocrinol (Lausanne). 2014;5:73. doi: 10.3389/fendo.2014.00073.

25. Manyema M, Norris SA, Richter LM. Stress begets stress: the association of adverse childhood experiences with psychological distress in the presence of adult life stress. BMC Public Health. 2018;18:835. doi: 10.1186/s12889-018-5767-0.

26. Taylor SE. Mechanisms linking early life stress to adult health outcomes. Proc Natl Acad Sci U S A. 2010;107:8507-12. doi: 10.1073/pnas.1003890107.

27. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol Bull. 2011;137:959-97. doi: 10.1037/a0024768.

28. Nusslock R, Miller GE. Early-life adversity and physical and emotional health across the lifespan: a neuroimmune network hypothesis. Biol Psychiatry. 2016;80:23-32. doi: 10.1016/j.biopsych.2015.05.017.

29. Godoy LD, Rossignoli MT, Delfino-Pereira P, Garcia-Cairasco N, de Lima Umeoka EH. A comprehensive overview on stress neurobiology: basic concepts and clinical implications. Front Behav Neurosci. 2018;12:127. doi: 10.3389/fnbeh.2018.00127.

30. Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. Neuropsychopharmacology. 2010;35:2617-23. doi: 10.1038/npp.2010.159.

31. Schreier HMC, Kuras YI, McInnis CM, Thoma MV, St Pierre DG, Hanlin L, et al. Childhood physical neglect is associated with exaggerated systemic and intracellular inflammatory responses to repeated psychosocial stress in adulthood. Front Psychiatry. 2020;11:504. doi: 10.3389/fpsyt.2020.00504.

32. Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, et al. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc Natl Acad Sci U S A. 2009;106:14716-21. doi: 10.1073/pnas.0902971106.

33. Miller GE, Chen E. Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. Psychol Sci. 2010;21:848-56. doi: 10.1177/0956797610370161.

34. Ehrlich KB, Ross KM, Chen E, Miller GE. Testing the biological embedding hypothesis: is early life adversity associated with a later proinflammatory phenotype? Dev Psychopathol. 2016;28:1273-83. doi: 10.1017/S0954579416000845.

35. Miller G, Chen E. Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolescence. Psychosom Med. 2007;69(5):402-9. doi: 10.1097/PSY.0b013e318068fcf9.

36. Appleton J. The experience of landscape. London: Wiley; 1975.

37. Driver BL, Greene P. Man's nature: innate determinants of response to natural environments. In: Children, nature, and the urban environment: proceedings of a symposium-fair. Upper Darby (PA): US Department of Agriculture, Forest Service, Northeastern Forest Experiment Station; 1977. pp. 62-70. Report No.: NE-30.

38. Orians GH. Habitat selection: general theory and applications to human behavior. In: Lockard JS, editor. The evolution of human social behavior. Amsterdam: Elsevier; 1980. pp. 49-63.

39. Hartig T, Mang M, Evans GW. Restorative effects of natural environment experiences. Environ Behav. 1991;23:3-26. doi: 10.1177/0013916591231001.

40. Ulrich RS. Aesthetic and affective response to natural environment. In: Altman I, Wohlwill JF, editors. Behavior and the natural environment. New York: Plenum Press; 1983. pp. 85-125.

41. Ulrich RS, Simons RF, Losito BD, Fiorito E, Miles MA, Zelson M. Stress recovery during exposure to natural and urban environments. J Environ Psychol. 1991;11:201-30. doi: 10.1016/S0272-4944(05)80184-7.

42. Parsons R, Tassinary LG, Ulrich RS, Hebl MR, Grossman-Alexander M. The view from the road: implications for stress recovery and immunization. J Environ Psychol. 1998;18:113-40. doi: 10.1006/jevp.1998.0086.

43. Brown DK, Barton JL, Gladwell VF. Viewing nature scenes positively affects recovery of autonomic function following acute-mental stress. Environ Sci Technol. 2013;47:5562-9. doi: 10.1021/es305019p.

44. Anderson AP, Mayer MD, Fellows AM, Cowan DR, Hegel MT, Buckey JC. Relaxation with immersive natural scenes presented using virtual reality. Aerosp Med Hum Perform. 2017;88:520-6. doi: 10.3357/AMHP.4747.2017.

45. Guo LN, Zhao RL, Ren AH, Niu LX, Zhang YL. Stress recovery of campus street trees as visual stimuli on graduate students in autumn. Int J Environ Res Public Health. 2019;17:148. doi: 10.3390/ijerph17010148.

46. Yin J, Yuan J, Arfaei N, Catalano PJ, Allen JG, Spengler JD. Effects of biophilic indoor environment on stress and anxiety recovery: a between-subjects experiment in virtual reality. Environ Int. 2020;136:105427. doi: 10.1016/j.envint.2019.105427.

47. Bratman GN, Hamilton JP, Daily GC. The impacts of nature experience on human cognitive function and mental health. Ann N Y Acad Sci. 2012;1249:118-36. doi: 10.1111/j.1749-6632.2011.06400.x.

48. Bratman GN, Olvera-Alvarez HA, Gross JJ. The affective benefits of nature exposure. Soc Personal Psychol Compass. 2021;15:e12630. doi: 10.1111/spc3.12630.

49. Roe JJ, Ward Thompson C, Aspinall PA, Brewer MJ, Duff EI, Miller D, et al. Green space and stress: evidence from cortisol measures in deprived urban communities. Int J Environ Res Public Health. 2013;10:4086-103. doi: 10.3390/ijerph10094086.

50. Ward Thompson C, Roe J, Aspinall P, Mitchell R, Clow A, Miller D. More green space is linked to less stress in deprived communities: evidence from salivary cortisol patterns. Landsc Urban Plan. 2012;105:221-9. doi: 10.1016/j.landurbplan.2011.12.015.

51. Ward Thompson C, Aspinall P, Roe J, Robertson L, Miller D. Mitigating stress and supporting health in deprived urban communities: the importance of green space and the social environment. Int J Environ Res Public Health. 2016;13:440. doi: 10.3390/ijerph13040440.

52. Frumkin H, Bratman GN, Breslow SJ, Cochran B, Kahn PH Jr, Lawler JJ, et al. Nature contact and human health: a research agenda. Environ Health Perspect. 2017;125:075001. doi: 10.1289/EHP1663.

53. Yeager RA, Smith TR, Bhatnagar A. Green environments and cardiovascular health. Trends Cardiovasc Med. 2020;30:241-6. doi: 10.1016/j.tcm.2019.06.005.

54. Shanahan DF, Bush R, Gaston KJ, Lin BB, Dean J, Barber E, et al. Health benefits from nature experiences depend on dose. Sci Rep. 2016;6:28551. doi: 10.1038/srep28551.

55. Mao G, Cao Y, Wang B, Wang S, Chen Z, Wang J, et al. The salutary influence of forest bathing on elderly patients with chronic heart failure. Int J Environ Res Public Health. 2017;14:368. doi: 10.3390/ijerph14040368.

56. Belsky J, Bakermans-Kranenburg MJ, van Ijzendoorn MH. For better and for worse: differential susceptibility to environmental influences. Curr Dir Psychol. 2007;16:300-4. doi: 10.1111/j.1467-8721.2007.00525.x.

57. Boyce WT, Ellis BJ. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. Dev Psychopathol. 2005;17:271-301. doi: 10.1017/s0954579405050145.

58. Del Giudice M, Ellis BJ, Shirtcliff EA. The Adaptive Calibration Model of stress responsivity. Neurosci Biobehav Rev. 2011;35:1562-92. doi: 10.1016/j.neubiorev.2010.11.007.

59. Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, van Ijzendoorn MH. Differential susceptibility to the environment: an evolutionary–neurodevelopmental theory. Dev Psychopathol. 2011;23:7-28. doi: 10.1017/S0954579410000611.

60. Belsky J, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. Psychol Bull. 2009;135:885-908. doi: 10.1037/a0017376.

61. Albott CS, Forbes MK, Anker JJ. Association of childhood adversity with differential susceptibility of transdiagnostic psychopathology to environmental stress in adulthood. JAMA Netw Open. 2018;1:e185354. doi: 10.1001/jamanetworkopen.2018.5354.

62. Muscatell KA, Moieni M, Inagaki TK, Dutcher JM, Jevtic I, Breen EC, et al. Exposure to an inflammatory challenge enhances neural sensitivity to negative and positive social feedback. Brain Behav Immun. 2016;57:21-9. doi: 10.1016/j.bbi.2016.03.022.

63. American Psychological Association. APA dictionary of psychology: socioeconomic status (SES) [Internet]. American Psychological Association. 2023 [cited 2024 Jan 20]. Available from: https://dictionary.apa.org/socioeconomic-status.

64. McLaughlin KA. Early life stress and psychopathology. In: Harkness K, Hayden EP, editors. The Oxford handbook of stress and mental health. Oxford: Oxford University Press; 2020. pp. 45-74.

65. Browning MHEM, Mimnaugh KJ, van Riper CJ, Laurent HK, LaValle SM. Can simulated nature support mental health? Comparing short, single-doses of 360-degree nature videos in virtual reality with the outdoors. Front Psychol. 2020;10:2667. doi: 10.3389/fpsyg.2019.02667.

66. Yin J, Zhu S, MacNaughton P, Allen JG, Spengler JD. Physiological and cognitive performance of exposure to biophilic indoor environment. Build Environ. 2018;132:255-62. doi: 10.1016/j.buildenv.2018.01.006.

67. Kim HG, Cheon EJ, Bai DS, Lee YH, Koo BH. Stress and heart rate variability: a meta-analysis and review of the literature. Psychiatry Investig. 2018;15:235-45. doi: 10.30773/pi.2017.08.17.

68. Ernst G. Heart-rate variability-more than heart beats? Front Public Health. 2017;5:240. doi: 10.3389/fpubh.2017.00240.

69. Shaffer F, Ginsberg JP. An overview of heart rate variability metrics and norms. Front Public Health. 2017;5:258. doi: 10.3389/fpubh.2017.00258.

70. Boesch M, Sefidan S, Ehlert U, Annen H, Wyss T, Steptoe A, et al. Mood and autonomic responses to repeated exposure to the Trier Social Stress Test for Groups (TSST-G). Psychoneuroendocrinology. 2014;43:41-51. doi: 10.1016/j.psyneuen.2014.02.003.

71. Grassi G, Seravalle G, Mancia G. Sympathetic activation in cardiovascular disease: evidence, clinical impact and therapeutic implications. Eur J Clin Invest. 2015;45:1367-75. doi: 10.1111/eci.12553.

72. Hadaya J, Ardell JL. Autonomic modulation for cardiovascular disease. Front Physiol. 2020;11:617459. doi: 10.3389/fphys.2020.617459.

73. van Bilsen M, Patel HC, Bauersachs J, Böhm M, Borggrefe M, Brutsaert D, et al. The autonomic nervous system as a therapeutic target in heart failure: a scientific position statement from the Translational Research Committee of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2017;19:1361-78. doi: 10.1002/ejhf.921.

74. Zhang DY, Anderson AS. The sympathetic nervous system and heart failure. Cardiol Clin. 2014;32:33-45. doi: 10.1016/j.ccl.2013.09.010.

75. Norton BJ, Strube MJ. Understanding statistical power. J Orthop Sports Phys Ther. 2001;31:307-15. doi: 10.2519/jospt.2001.31.6.307.

76. Allen AP, Kennedy PJ, Dockray S, Cryan JF, Dinan TG, Clarke G. The Trier Social Stress Test: principles and practice. Neurobiol Stress. 2016;6:113-26. doi: 10.1016/j.ynstr.2016.11.001.

77. Helminen EC, Morton ML, Wang Q, Felver JC. A meta-analysis of cortisol reactivity to the Trier Social Stress Test in virtual environments. Psychoneuroendocrinology. 2019;110:104437. doi: 10.1016/j.psyneuen.2019.104437.

78. Liu Q, Zhang W. Sex differences in stress reactivity to the Trier Social Stress Test in virtual reality. Psychol Res Behav Manag. 2020;13:859-69. doi: 10.2147/PRBM.S268039.

79. Narvaez Linares NF, Charron V, Ouimet AJ, Labelle PR, Plamondon H. A systematic review of the Trier Social Stress Test methodology: issues in promoting study comparison and replicable research. Neurobiol Stress. 2020;13:100235. doi: 10.1016/j.ynstr.2020.100235.

80. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606-13. doi: 10.1046/j.1525-1497.2001.016009606.x.

81. Chirico A, Gaggioli A. When virtual feels real: comparing emotional responses and presence in virtual and natural environments. Cyberpsychol Behav Soc Netw. 2019;22:220-6. doi: 10.1089/cyber.2018.0393.

82. Koch CE, Leinweber B, Drengberg BC, Blaum C, Oster H. Interaction between circadian rhythms and stress. Neurobiol Stress. 2016;6:57-67. doi: 10.1016/j.ynstr.2016.09.001.

83. Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test' – a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology. 1993;28:76-81. doi: 10.1159/000119004.

84. Allen AP, Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Biological and psychological markers of stress in humans: focus on the Trier Social Stress Test. Neurosci Biobehav Rev. 2014;38:94-124. doi: 10.1016/j.neubiorev.2013.11.005.

85. Hedblom M, Gunnarsson B, Iravani B, Knez I, Schaefer M, Thorsson P, et al. Reduction of physiological stress by urban green space in a multisensory virtual experiment. Sci rep. 2019;9:10113. doi: 10.1038/s41598-019-46099-7.

86. Jiang B, Li D, Larsen L, Sullivan WC. A dose-response curve describing the relationship between urban tree cover density and self-reported stress recovery. Environ Behav. 2014;48:607-29. doi: 10.1177/0013916514552321.

87. Valtchanov D, Ellard C. Physiological and affective responses to immersion in virtual reality: effects of nature and urban settings. J Cyber Ther Rehabil. 2010;3:359-73.

88. Lackschewitz H, Hüther G, Kröner-Herwig B. Physiological and psychological stress responses in adults with attention-deficit/hyperactivity disorder (ADHD). Psychoneuroendocrinology. 2008;33:612-24. doi: 10.1016/j.psyneuen.2008.01.016.

89. Tarvainen MP, Lipponen J, Niskanen JP, Ranta-Aho P. Kubios HRV Version 3 – user's guide. Kuopio: University of Eastern Finland; 2017.

90. Lipponen JA, Tarvainen MP. A robust algorithm for heart rate variability time series artefact correction using novel beat classification. J Med Eng Technol. 2019;43:173-81. doi: 10.1080/03091902.2019.1640306.

91. Cosmo C, Seligowski AV, Aiken EM, Van't Wout-Frank M, Philip NS. Heart rate variability features as predictors of intermittent theta-burst stimulation response in posttraumatic stress disorder. Neuromodulation. 2022;25:588-95. doi: 10.1111/ner.13529.

92. Lundell RV, Tuominen L, Ojanen T, Parkkola K, Räisänen-Sokolowski A. Diving responses in experienced rebreather divers: short-term heart rate variability in cold water diving. Front Physiol. 2021;12:649319. doi: 10.3389/fphys.2021.649319.

93. Suminar DAA, Basri MI, Tammasse J, Bintang AK, Akbar M. Autonomic dysregulation in acute ischemic stroke patient with insomnia. Med Clín Práct. 2021;4 Suppl 1:100206. doi: 10.1016/j.mcpsp.2021.100206.

94. Sahoo TK, Mahapatra A, Ruban N. Stress index calculation and analysis based on heart rate variability of ECG signal with arrhythmia. In: 2019 innovations in power and advanced computing technologies (i-PACT); 2019 March 22-23; Vellore, India. New York: Institute of Electrical and Electronics Engineers; 2019. pp. 1-7.

95. Adler NE, Epel ES, Castellazzo G, Ickovics JR. Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data in healthy white women. Health Psychol. 2000;19:586-92. doi: 10.1037//0278-6133.19.6.586.

96. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998;14:245-58. doi: 10.1016/s0749-3797(98)00017-8.

97. Miller GE, Rohleder N, Stetler C, Kirschbaum C. Clinical depression and regulation of the inflammatory response during acute stress. Psychosom Med. 2005;67:679-87. doi: 10.1097/01.psy.0000174172.82428.ce.

98. Brinker J, Cheruvu VK. Social and emotional support as a protective factor against current depression among individuals with adverse childhood experiences. Prev Med Rep. 2016;5:127-33. doi: 10.1016/j.pmedr.2016.11.018.

99. Crouch E, Radcliff E, Strompolis M, Srivastav A. Safe, stable, and nurtured: protective factors against poor physical and mental health outcomes following exposure to adverse childhood experiences (ACEs). J Child Adolesc Trauma. 2018;12:165-73. doi: 10.1007/s40653-018-0217-9.

100. Anda RF, Porter LE, Brown DW. Inside the adverse childhood experience score: strengths, limitations, and misapplications. Am J Prev Med. 2020;59:293-95. doi: 10.1016/j.amepre.2020.01.009.

101. McEwen CA, Gregerson SF. A critical assessment of the adverse childhood experiences study at 20 years. Am J Prev Med. 2019;56:790-4. doi: 10.1016/j.amepre.2018.10.016.

102. Olvera-Alvarez HA, Kubzansky LD, Campen MJ, Slavich GM. Early life stress, air pollution, inflammation, and disease: an integrative review and immunologic model of social-environmental adversity and lifespan health. Neurosci Biobehav Rev. 2018;92:226-42. doi: 10.1016/j.neubiorev.2018.06.002.

103. Turner AI, Smyth N, Hall SJ, Torres SJ, Hussein M, Jayasinghe SU, et al. Psychological stress reactivity and future health and disease outcomes: a systematic review of prospective evidence. Psychoneuroendocrinology. 2020;114:104599. doi: 10.1016/j.psyneuen.2020.104599.

104. Krupnik V. Trauma or adversity? Traumatology. 2019;25:256-61. doi: 10.1037/trm0000169.

105. Browning MHEM, Shipley N, McAnirlin O, Becker D, Yu CP, Hartig T, et al. An actual natural setting improves mood better than its virtual counterpart: a meta-analysis of experimental data. Front Psychol. 2020;11:2200. doi: 10.3389/fpsyg.2020.02200.

106. Ulrich RS. View through a window may influence recovery from surgery. Science. 1984;224(4647):420-1. doi: 10.1126/science.6143402.

107. Park SH, Mattson RH. Effects of flowering and foliage plants in hospital rooms on patients recovering from abdominal surgery. Horttechnology. 2008;18:563-8. doi: 10.21273/HORTTECH.18.4.563.

108. Park SH, Mattson RH. Ornamental indoor plants in hospital rooms enhanced health outcomes of patients recovering from surgery. J Altern Complement Med. 2009;15:975-80. doi: 10.1089/acm.2009.0075.

109. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on Community-Based Solutions to Promote Health Equity in the United States. Communities in action: pathways to health equity. Baciu A, Negussie Y, Geller A, Weinstein JN, editors. Washington (DC): US National Academies Press; 2017.

110. Ranganathan P, Pramesh CS, Buyse M. Common pitfalls in statistical analysis: the perils of multiple testing. Perspect Clin Res. 2016;7:106-7. doi: 10.4103/2229-3485.179436.

111. Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science. 1981;213:220-2. doi: 10.1126/science.6166045.

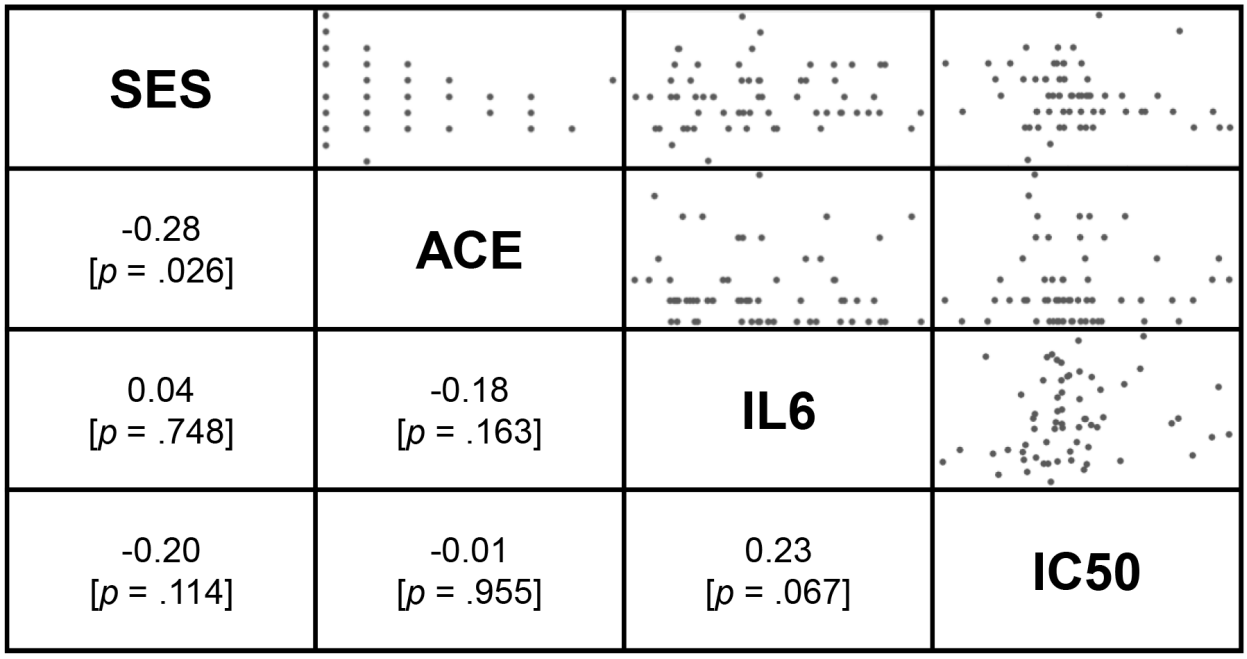
112. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Circulation. 1996;93:1043-65.

113. Wolf KL, Measells MK, Grado SC, Robbins AST. Economic values of metro nature health benefits: a life course approach. Urban For Urban Green. 2015;14:694-701. doi: 10.1016/j.ufug.2015.06.009.

114. Brochu P, Jimenez MP, James P, Kinney PL, Lane K. Benefits of increasing greenness on all-cause mortality in the largest metropolitan areas of the United States within the past two decades. Front Public Health. 2022;10:841936. doi: 10.3389/fpubh.2022.841936.

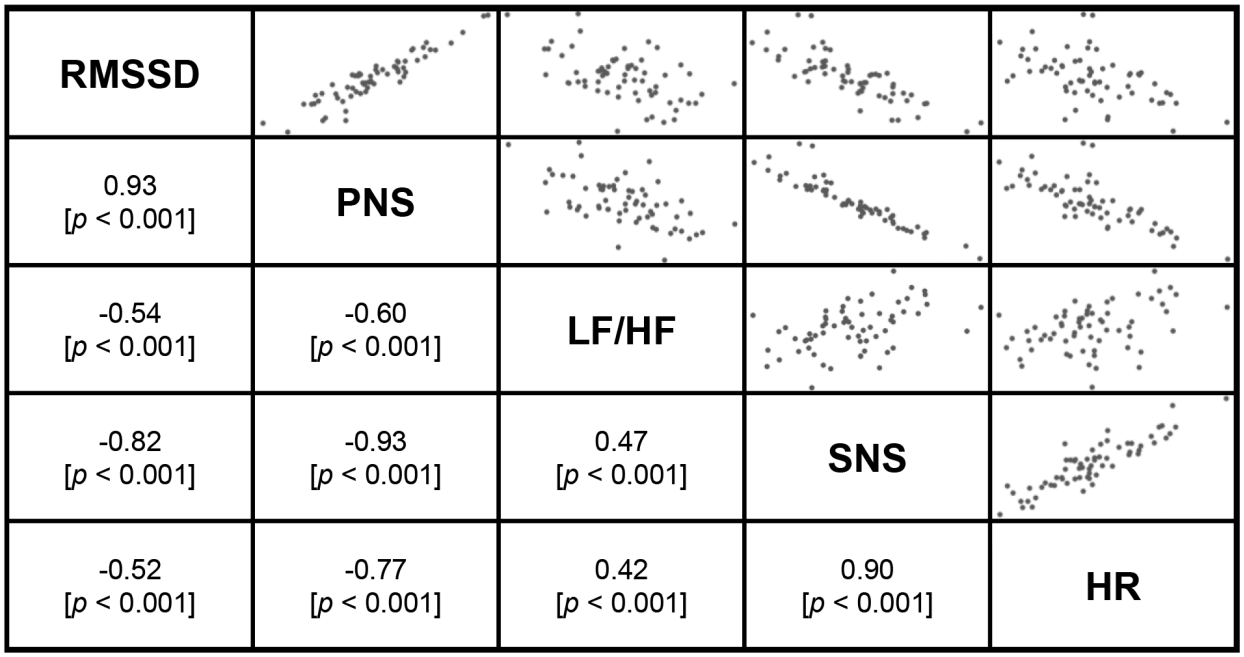
Supporting Information

S1 Table. Bivariate Correlations (Susceptibility Indicators)



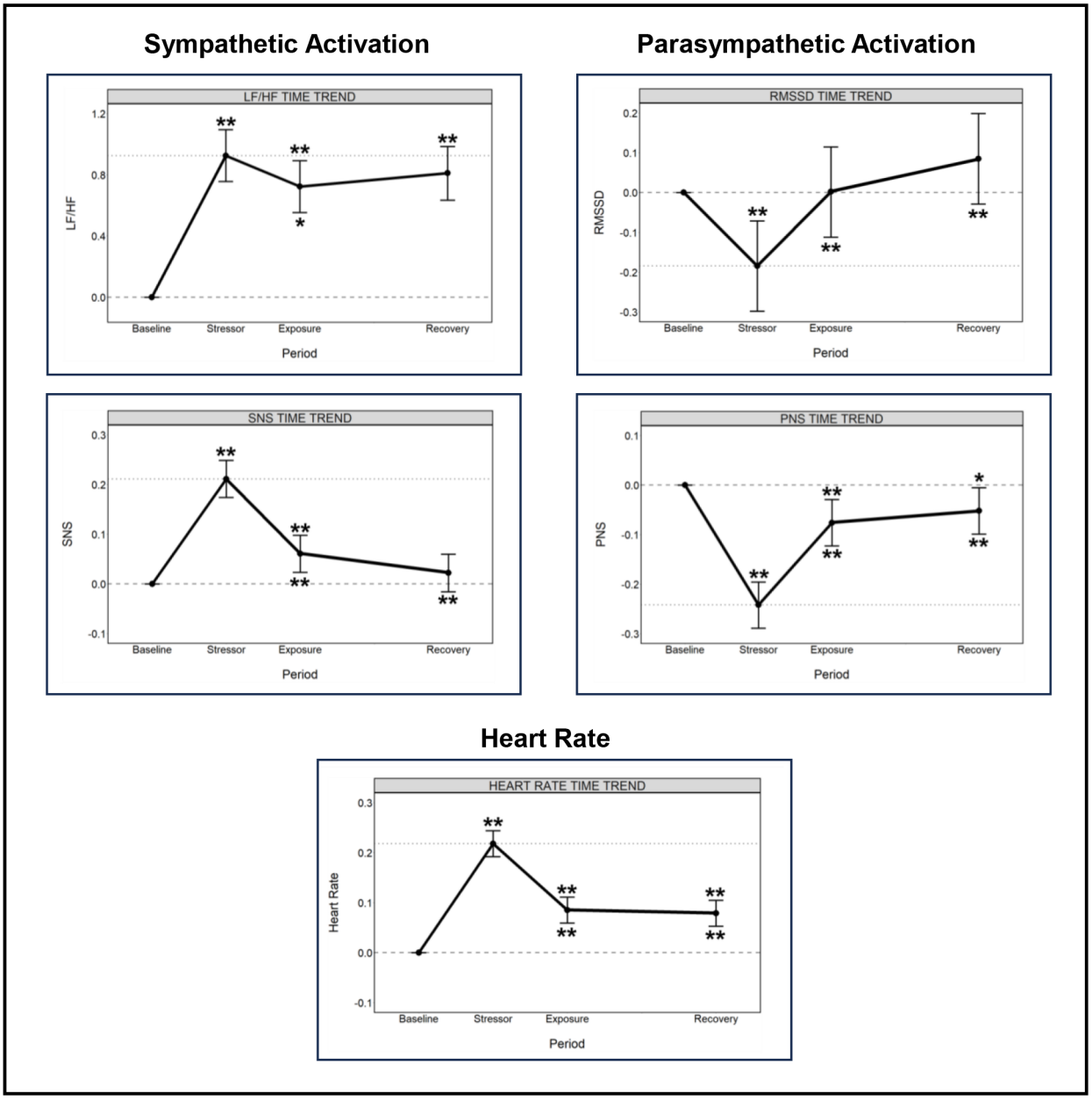
Distal indicators of susceptibility included socioeconomic status (SES) and adverse childhood experiences (ACE) while proximal indicators included inflammatory reactivity (IL6) and glucocorticoid resistance (IC50).

S2 Table. Bivariate Correlations (Baseline Autonomic Metrics)



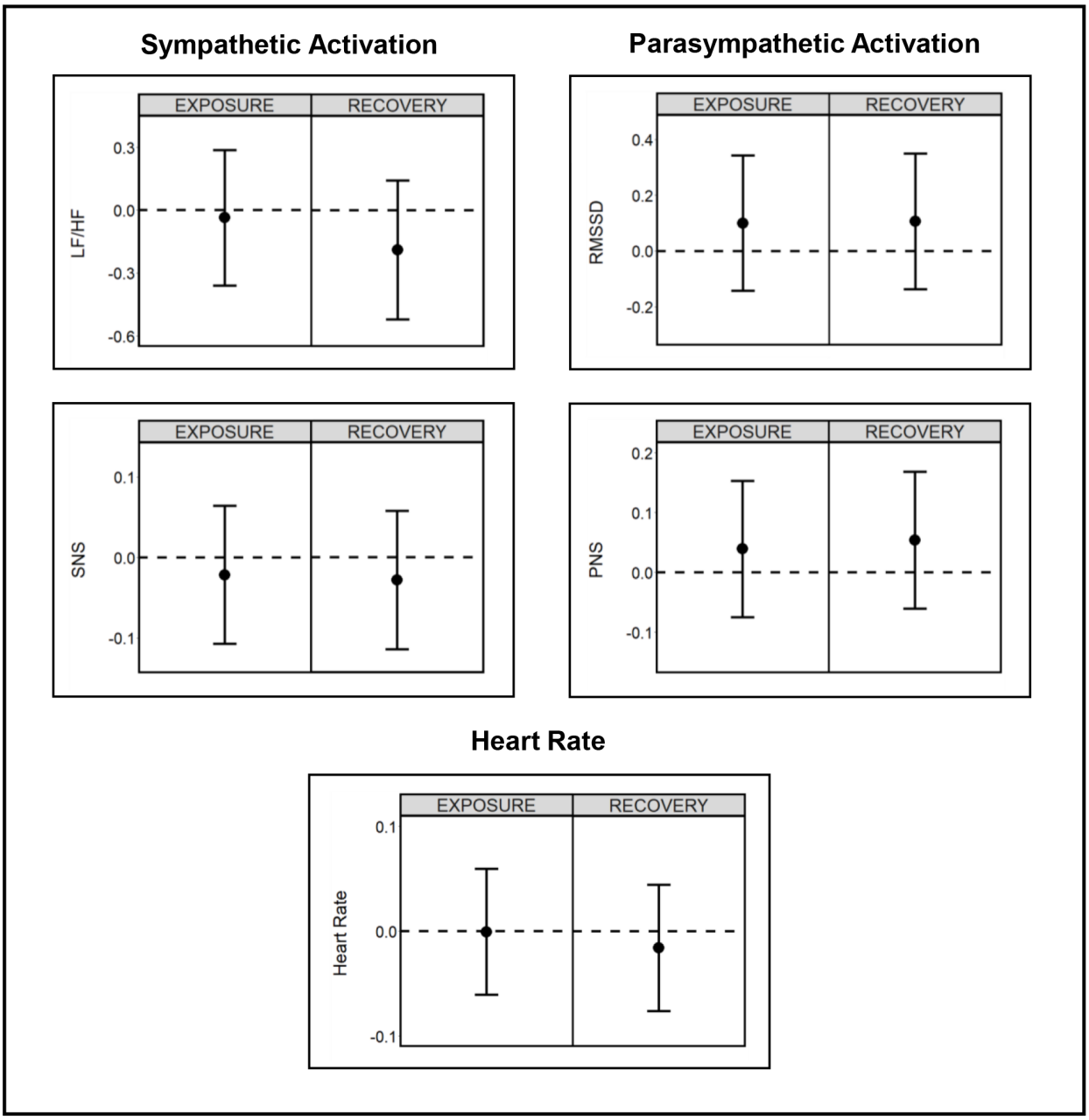
Autonomic metrics were separated into two profiles to index higher parasympathetic (RMSSD, PNS, HR↓) or sympathetic activation (LF/HF, SNS, HR↑).

S1 Figure. Cardiovascular Arousal and Recovery (Autonomic Activation)



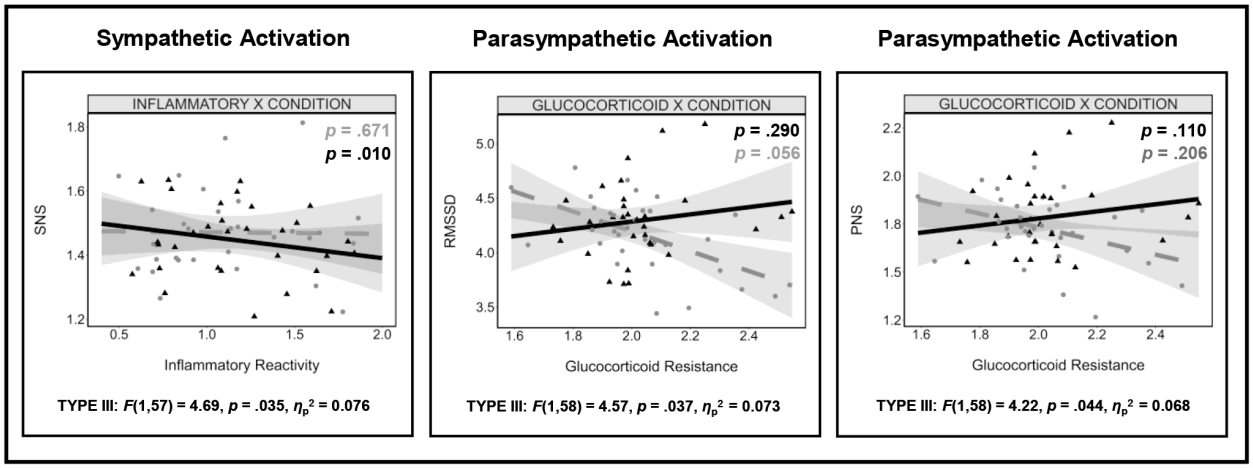
Time plots visualizing changes in sympathetic (LF/HF, SNS, HR↑) or parasympathetic (RMSSD, PNS, HR↓) activation throughout the experimental protocol, relative to the baseline period. X-axes present the study periods (baseline [10 min], stressor [20 min], exposure [10 min], recovery [40 min]). Y-axes present mean differences from the baseline period (Δ; points) and corresponding confidence intervals (95%; error bars) obtained from the pairwise contrasts, using corrections for multiple comparisons (mixed effect models without interaction terms). Asterisks above the error bars represent significant differences from the baseline period; asterisks below these error bars represent significant differences from the stressor period. Gray dashed lines highlight the mean value for the baseline period. Gray dotted lines highlight the mean value for the stressor period. *$p < .05$; **$p < .001$

S2 Figure. Nature Exposure and Stress Recovery (Autonomic Activation)



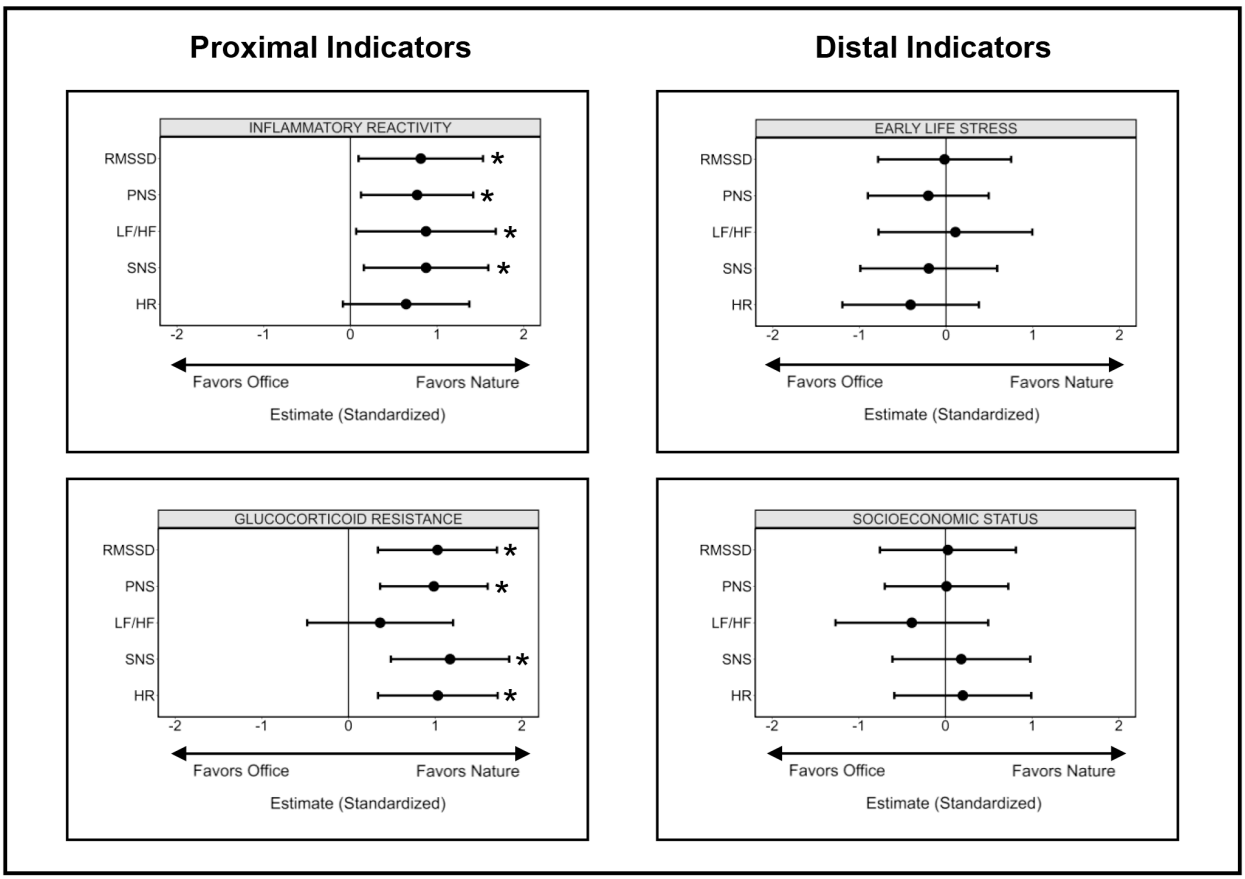
Mean and error plots visualizing group differences in sympathetic (LF/HF, SNS, HR↑) or parasympathetic (RMSSD, PNS, HR↓) activation during the exposure (left) or recovery (right) periods. Y-axes present mean differences between the nature versus office group obtained from the pairwise contrasts (mixed effect models with interaction terms). Points and confidence intervals (95% error bars) represent the nature condition compared to the office condition (dashed black line; y-intercept at zero).

S3 Figure. Interaction Plots: Maximum Information



Interaction plots visualizing significant associations (slopes) between susceptibility and stress recovery (autonomic activation) by condition group (nature [solid black line] versus office [dashed gray line]). Y-axes present sympathetic or parasympathetic activation using fitted values (unstandardized) from the corresponding regression model (baseline adjusted metric of autonomic activity [log] during the recovery period [40 min]). X-axes present susceptibility indicators using log-values. P-values denote the simple slope for the nature (black) or office (gray) condition; error bands represent the standard error for each slope. Points denote participants in the nature (black triangle) or office (gray circle) condition. Type III effects represent the interaction term.

S4 Figure. Forest Plots of Standardized Effects (Binary Interaction Terms)



Forest plots visualizing interaction terms (standardized coefficients and confidence intervals [95%]) across all linear regression models. Within these plots, all models were specified so that among participants with high versus low susceptibility (binary; median-value), positive interaction terms indicate better stress recovery (increased parasympathetic and reduced sympathetic activation) in the nature condition while negative terms indicate better stress recovery in the office condition. Interaction terms at zero indicate no differences in the association between susceptibility and stress recovery by condition group. *$p < .05$

Chapter Three

Title & Authorship

Susceptibility to stress and nature exposure: Evidence on the positive effects of early life stress

Aaron M. Eisen[1], Jose Guillermo Cedeño Laurent[2], John D. Spengler[3], George M. Slavich[4], Hector A. Olvera-Alvarez[1]

[1]School of Nursing, Oregon Health & Science University, Portland, OR

[2]School of Public Health, Rutgers University, Piscataway, NJ

[3]Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA

[4]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA

Funding Acknowledgments

This research was financially supported by the JPB Environmental Health Fellowship from the JPB Foundation, administered by the Harvard T.H. Chan School of Public Health [to Hector A. Olvera-Alvarez and Jose Guillermo Cedeño Laurent]; the Hoffman Program for Chemicals and Health at the Harvard T.H. Chan School of Public Health [to Hector A. Olvera-Alvarez and Jose Guillermo Cedeño Laurent]; Grant 5U54MD007592 from the National Institute on Minority Health and Health Disparities (NIMHD), a component of the National Institutes of Health (NIH) [to Hector A. Olvera-Alvarez]; Aaron M. Eisen was an ARCS Foundation Scholar. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Citation: PLOS ONE

Eisen AM, Cedeño Laurent JG, Spengler JD, Slavich GM, Olvera-Alvarez HA. Susceptibility to stress and nature exposure: Evidence on the positive effects of early life stress. PLoS One. 2025. Manuscript submitted for publication.

Directory of Tables & Figures

List of Tables

Table	Name	Page
1	Participant Demographics	**100**
2	Simple Slopes for Early Life Stress on the Nature–Glucose Association	**103**
S1	Estimates Across All Models	**127**

List of Figures

Figure	Title	Page
1	The Integrative Model of Environmental Sensitivity	**93**
2	Moderation Effect of Early Life Stress on the Nature–Glucose Association	**102**
S1	Bivariate Correlation Plot	**126**

Abstract

Background

Emerging epidemiological evidence indicates that groups in low socioeconomic positions exhibit more pronounced health benefits from nature exposure compared to more privileged groups. We have previously posited one possible mechanism underlying this phenomenon through our framework: (susceptibility to stress) groups in low socioeconomic positions are often exposed to more early-life stressors, which can induce a lifelong susceptibility to stress through various neurobiological pathways; (environmental sensitivity) susceptibility to stress, traditionally understood as heightened reactivity to stressors, could also encompass enhanced responsivity to health-protective exposures, inducing greater risks in adverse environments, but also greater benefits in protective environments.

Objective

Examine the moderation effect of early life stress on the association between residential nature exposure and fasting glucose.

Methods

We assessed the impact of residential nature exposure (quantified using the normalized difference vegetation index across different radial buffers, centered on the home address of each participant) on glucose dysregulation (elevated fasting blood glucose levels) with a specific focus on the moderation effect of early life stress (before age 18) using baseline data from a cohort of 340 nursing students.

Results

We found a significant curvilinear trend wherein participants with higher and lower levels of early life stress both exhibited more pronounced beneficial reductions in fasting glucose when living in greener neighborhoods. By contrast, participants with average levels of early life stress exhibited the smallest beneficial reductions when living in greener neighborhoods.

Discussion

Our findings contribute to growing evidence and further support the idea that increasing access to nature within disadvantaged neighborhoods could be an effective strategy to mitigate metabolic risks and attenuate health disparities among vulnerable populations. As the evidence for this theoretical framework expands, it could inform more targeted interventions that leverage individual differences in environmental sensitivity to promote health equity, ultimately providing more nuanced and socioeconomically attuned approaches to public health.

[1] Introduction

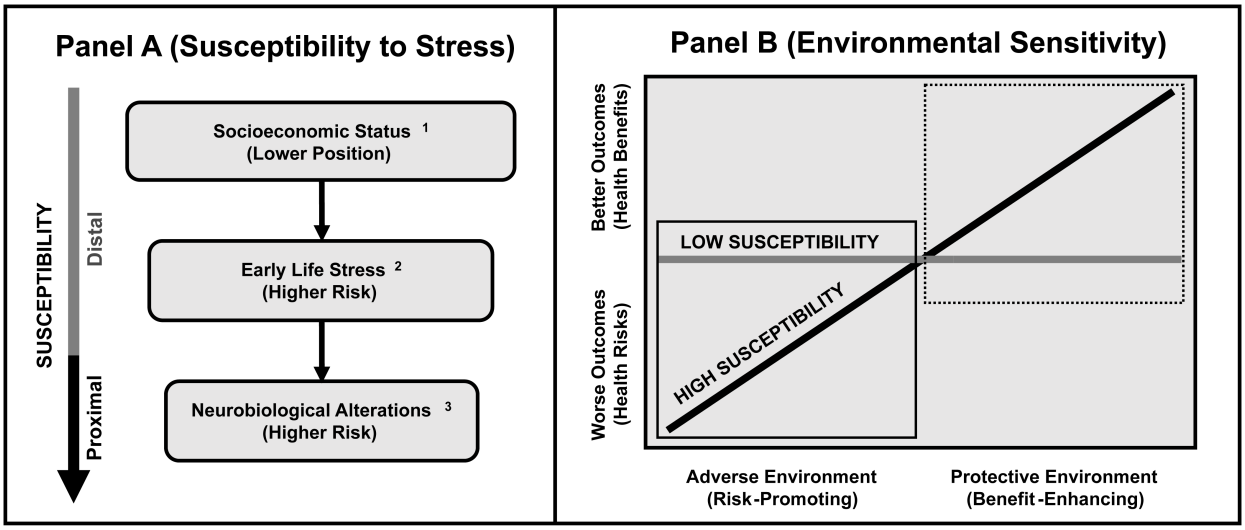
Emerging epidemiological evidence indicates that groups in low socioeconomic positions exhibit more pronounced health benefits from nature exposure (e.g., contact with natural green spaces) compared to more privileged groups [1–7]. This implies that increasing access to nature for disadvantaged communities could be a strategic approach to attenuate health disparities by alleviating the risks of chronic stressors among groups who are the most susceptible to stress [8–10]. However, the evidence supporting this possibility is mixed [11,12], including reports of null associations [13,14], and further research is thus needed to better understand the mechanisms underpinning this phenomenon [15]. Clarifying these mechanisms could reveal more effective pathways for reducing health disparities, as nature-based interventions offer a promising approach: they are passive, promoting health without requiring behavioral change; they are sustainable, often with low maintenance costs; and they can be implemented through public health policy to create lasting impacts.

[1.1] Theoretical Framework

One possible mechanism underpinning this phenomenon is described in the Integrative Model of Environmental Sensitivity (see Fig 1 [15]). Central to the premise of this framework is the idea that groups in lower socioeconomic positions often face higher exposure to persistent psychosocial stressors in early life [16–23], which in turn could induce a lifelong susceptibility to stress through various neurobiological pathways (i.e., Biological Embedding Model [24–31]). However, mounting evidence indicates that susceptibility to stress, traditionally understood as heightened reactivity to stressors, could also encompass enhanced responsivity to health-protective exposures, inducing greater risks in adverse environments, but also greater benefits in protective environments (i.e., Differential Susceptibility Hypothesis [32–39]). Put together, this evidence implies that early life stress might be better understood as not merely increasing susceptibility to stress, but as cultivating a broader form of environmental sensitivity, enhancing responsivity to both stressors and protective environmental factors. This reframing provides a plausible mechanistic

explanation as to why groups in lower versus higher socioeconomic positions could derive greater benefits from the health-protective effects of nature exposure.

Figure 1. The Integrative Model of Environmental Sensitivity



Emerging epidemiological evidence indicates that groups in low socioeconomic positions exhibit more pronounced health benefits from nature exposure compared to more privileged groups. One possible mechanism underpinning this evidence is described in the Integrative Model of Environmental Sensitivity. **Susceptibility to Stress:** groups in lower socioeconomic positions often face higher exposure to early-life stressors, which can induce a lifelong susceptibility to stress through various neurobiological pathways. **Environmental Sensitivity:** individuals who are susceptible to stress are more responsive to stressors and health-protective exposures, inducing greater risks in adverse environments but also greater benefits in protective environments, relative to less susceptible individuals.

(1) *Socioeconomic Status* is defined as the position of an individual in their society which is determined by both social and economic factors that impact exposure to and experiences with psychosocial stressors. (2) *Early Life Stress* is defined as persistent exposure to psychosocial stressors during childhood, with ranging degrees of perceived severity, that induce neurobiological responses and could promote developmental alterations over time. (3) *Developmental Alterations* are defined as enduring changes induced by early life stress across numerous neurobiological systems, which engage in multidirectional transactions throughout the lifespan, persistently amplifying crosstalk that increases reactivity to stressors. This figure was adapted from "Susceptibility to Stress and Nature Exposure: Unveiling Differential Susceptibility to Physical Environments; a Randomized Controlled Trial" by Aaron M. Eisen, Gregory N. Bratman, and Hector A. Olvera-Alvarez, 2024, PLOS ONE, 19(4): e0301473. Copyright 2024 Eisen et al.

In short, it is well-established that early life stress can induce developmental alterations that exert enduring effects, even decades later, across numerous neurobiological systems (e.g., central nervous system, autonomic nervous system, immune system, cardiovascular

system, endocrine system [40–47]). Together, these neurobiological systems engage in multidirectional transactions throughout the lifespan, persistently amplifying crosstalk that increases reactivity to stressors (e.g., Neuroimmune Network Hypothesis [48–50], Social Signal Transduction Theory of Depression [51–53]). Given that groups in lower versus higher socioeconomic positions often face higher lifetime stressor exposure (i.e., vulnerability) and are more sensitive to the health risks of chronic stress (i.e., susceptibility), early life stress could be a key pathway through which socioeconomic status becomes biologically embedded, altering how individuals experience and respond to environmental exposures across the lifespan and contributing to health disparities [54–61].

However, mounting evidence indicates that individuals who are susceptible to stress are also more responsive to protective environmental factors (e.g., Biological Sensitivity to Context Theory [62–64], Adaptive Calibration Model [65–67], Differential Susceptibility Theory [68–70]). For instance, a seminal review of 56 studies encompassing thousands of participants (n = 22,686) demonstrated that groups who were susceptible to stress (using an extensive range of behavioral, physiological, and genetic indicators) also exhibited greater benefits in response to protective social factors (e.g., social support, positive feedback), relative to less susceptible groups [71]. Put together, this evidence implies that groups with higher exposure to early-life stressors are more sensitive to both the health risks and benefits of their environmental conditions in a context-dependent manner. Therefore, it is plausible that groups in lower versus higher socioeconomic positions could derive greater benefits from the health-protective effects of nature exposure (e.g., Stress Reduction Theory [72,73], Attention Restoration Theory [74,75], Biophilia Hypothesis [76,77]) due to increased environmental sensitivity as a function of early life stress [15].

Notably, the evidence supporting this framework has centered on social environments and further research is needed to determine whether increased environmental sensitivity induced by early life stress could also promote greater health benefits in protective physical environments such as nature. Eisen et al. used an experimental paradigm to evaluate this hypothesis and found that participants who were susceptible to stress (indicated by a pro-inflammatory immune state) exhibited greater autonomic recovery from an acute

stressor in a virtual nature versus an office setting, relative to less susceptible participants [15]. However, even though a pro-inflammatory state is a well-established developmental alteration induced by early life stress [48–53,78–81], no differences in recovery were found for participants with higher versus lower exposure to early-life stressors.

The null findings for early life stress were unexpected and might have been attributed in part to the measure used (i.e., Adverse Childhood Experience Questionnaire [82]) and limited variability in this sample of college-aged males (n = 64 [15]). For instance, this measure might not have been comprehensive enough to detect differences in autonomic recovery, as it does not account for the subjective severity, frequency, timing, or duration of childhood stressors [83–85]. However, it is also possible that a pro-inflammatory state could be a more sensitive indicator of environmental sensitivity (proximal: direct pathway between the indicator and outcome; see Fig 1) relative to self-reported assessments of early life stress (distal: indirect pathway between the indicator and outcome that in turn, increases the risk of unmeasured confounders; see Fig 1). For instance, not all adults with high early-life stressor exposure develop susceptibility to stress due to protective factors and counteracting exposures (e.g., parental attachment, social support [86,87]).

[1.2] Present Study

Beyond the aforementioned investigation, to our knowledge, no other studies have examined whether early life stress may be associated with greater health benefits from nature exposure. Therefore, the purpose of the present study was to evaluate this association in a larger and more diverse sample (i.e., Nurse Engagement and Wellness Study [88]), and using a more comprehensive measure of early life stress (i.e., Stress and Adversity Inventory for Adults [89]).

In this context, we centered our investigation on glucose dysregulation, a risk factor for type 2 diabetes, which significantly contributes to the global burden of disease [90,91] and is more prevalent among groups in lower socioeconomic positions [92,93]. Evidence also indicates that residential nature exposure has protective effects on diabetes prevalence [94,95], incidence [96,97], insulin and glucose tolerance [98,99], and fasting blood glucose

[100,101], with some studies showing stronger protective effects among groups in lower versus higher socioeconomic positions [102–104].

Building on this foundation, we used an observational paradigm to evaluate the effect of residential nature exposure (quantified using the normalized difference vegetation index across different radial buffers [250 m, 500 m, and 1000 m], centered on the home address of each participant) on glucose dysregulation (elevated levels of fasting blood glucose), with a specific focus on the moderation effect of early life stress (before 18 years old). Based on the research summarized above, we hypothesized that the protective effect of residential nature exposure on fasting glucose levels (beneficial reductions) would be stronger (more pronounced beneficial reductions) among adult participants with higher versus lower exposure to early-life stressors.

Inherent to our hypothesis is the expectation that the association between early life stress and environmental sensitivity would be linear, increasing the protective effects of residential nature exposure in a dose-response pattern. However, we also tested for potential curvatures in the moderation effect of early life stress, as growing perspectives in the literature supporting our framework posit a curvilinear u-shaped association between early life stress and environmental sensitivity (i.e., Biological Sensitivity to Context Theory [62–64], Adaptive Calibration Model [65–67]).

[2] Materials & Methods

[2.1] Participants

Data were obtained from baseline measurements of a prospective cohort of men and women (n = 517; 18–55 years of age) enrolled during their first semester of the Bachelor of Science in Nursing program at the University of Texas at El Paso (i.e., Nurse Engagement and Wellness Study; described in detail elsewhere [88]). Measurements included early life stress, residential nature exposure, fasting glucose levels, and relevant demographics. Participants were recruited using emails, posters, flyers, media outlets, and information sessions between May 17, 2016 and November 29, 2018. All participants provided written

informed consent and measurements occurred during an in-person visit to the Biobehavioral Research Laboratory. This study was approved by the institutional review board at the University of Texas at El Paso (857149–1).

[2.2] Study Measures

[2.2.1] Early Life Stress

Early life stress was assessed using the well-validated Stress and Adversity Inventory for Adults (STRAIN [89]). This dynamic and interview-based assessment tool quantifies exposure to different types of chronic (n = 29) and episodic (n = 26) stressors across various life domains (e.g., housing, education, employment, finances, relationships) and core social-psychological characteristics (e.g., interpersonal loss, physical danger, entrapment, humiliation) with known implications for health and wellness [105,106]. For each stressor endorsed, follow-up questions are used to ascertain the subjective severity, frequency, exposure timing, and duration of the stressor. This information is then used to calculate cumulative stress scores by summing the counts and perceived severity ratings of all stressors endorsed, including in early life (before 18 years old) and adulthood (18+ years old). As research using this assessment tool has demonstrated that subjective stress severity is a more sensitive predictor of health outcomes (accounting for the "weight" of the stressors and capturing individual differences in susceptibility to stress [107]), early life stress was specified using the corresponding (time-specific) subjective severity index in our regression models.

[2.2.2] Residential Nature Exposure

Chronic exposure to residential nature (neighborhood-level green vegetation) was proxied using a cumulative opportunity approach across radial buffers centered on the home address of each participant. Levels of green vegetation were quantified using the normalized difference vegetation index (30 m^2 pixels [108]) from cloudless satellite images (Landsat 7 [109]) taken on a single summer day in 2016. Negative pixel values were present in a small portion of the region ($< 5\%$) and were reclassified as missing data to avoid potential

confounding effects of water bodies (e.g., rivers, irrigation canals). Pixel values were averaged across buffer sizes that corresponded to the amount of green vegetation within a 3–min (250 m), 6–min (500 m), and 12–min (1000 m) walk for a healthy adult in their mid-thirties [110]. This range of buffers was selected to focus on the local neighborhood and based on systematic evidence that larger buffer sizes are less robust in predicting health [111]. Pixel values could range from zero (no green vegetation) to one (maximum green vegetation) and were specified as percentages in our regression models to reflect changes in fasting glucose levels relative to a 1% increase in residential nature exposure.

[2.2.3] Fasting Blood Glucose

Glucose measurements were obtained following an overnight fast from 35 µL of whole blood (Lipid Panel + Glucose Panel Cassettes; range 2.8–27.8 mmol/L) using a Cholestech LDX Analyzer (Cholestech Corporation, Hayward, CA, USA). This instrument was calibrated before each measurement and used an enzymatic method (which has been shown to align with plasma concentrations using a hexokinase method; 95% CI: 92%–100% [112]). Glucose concentrations were expressed in mg/dL units, with higher values indicative of glucose dysregulation [113].

[2.2.4] Demographic Covariates

Demographic covariates included years of age, biological sex, and self-reported income ratios (household income divided by the federal poverty threshold for specific household size). In addition, we included other relevant demographic covariates to eliminate the most plausible alternative explanations and confounders. First, as higher socioeconomic status during adulthood is unable to reverse or undo the lifelong effects of early life stress [114], we included the highest level of maternal education as an indicator of socioeconomic status during childhood (“less than high school”, “some high school”, “high school graduate”, “some college”, “college graduate”). Second, as residential nature exposure could influence fasting glucose levels through promoting exercise and weight loss [115], we included the average duration of three common exercises (walking, running, and biking) per week,

during the past year (“0 min”, “1–5 min”, “6–20 min”, “21–59 min”, “1–2 hours”, “3–6 hours”, “7–10 hours”, “11+ hours”) along with body mass index. Third, as our proxy for residential nature exposure was based on the current address of each participant, we also included the duration of time that participants lived at their address.

[2.3] Analytical Approach

We restricted the sample to participants under the age of 40, as with older age comes the development of aging-related health states and different behavioral patterns that could confound our analysis [116]. In this sample, the number of participants who were 40 years of age or older was relatively small (n = 19; 4%). We also excluded participants who were missing nature exposure data (n = 16; 3%) and fasting glucose data (n = 28; 5%), in addition to a number of participants who did not complete the comprehensive early life stress assessment due to time constraints during the laboratory visit (n = 114; 22%). Therefore, the final analytical sample included 340 participants.

Our hypothesis was evaluated using linear regression models with continuous two-way interaction terms (Early Life Stress x Nature Exposure) to assess the moderation effect of early life stress on the association between residential nature exposure and fasting glucose. Interaction terms were tested across different buffer sizes for nature exposure (250 m, 500 m, and 1000 m) and were probed using Johnson-Neyman (J-N) intervals to determine the specific regions along the continuum of early life stress that significantly moderate the nature-glucose association. Potential curvatures in the moderation effect were tested by including a quadratic term for early life stress. Likelihood ratio tests were used to determine whether including the quadratic term significantly improved model fit, otherwise the model without the quadratic term was reported.

Main effects were centered and variance inflation factor values provided no evidence of multicollinearity (cutoff value > 2.0). Assumptions for linear regression were affirmed and model fit was assessed prior to interpreting our results. We also tested the sensitivity of our results using models unadjusted for relevant covariates and models with prominent outliers as determined by studentized residual values (cutoff value $> |2.5|$). Although we used alphas (0.05 level) to report significant results, our interpretations focused on effect

sizes and confidence intervals across all models. Data were analyzed using R (4.4.1) with the *interactions* package and the *ggplot2* package.

[3] Results

The sample consisted of 340 participants under the age of 40 (M = 24.0 ± 4.3 years of age; 77% female; see Table 1). On average, participants lived at their reported address for over a decade (M = 10.4 ± 7.9 years). At the 250 m buffer size, the proportion of residential nature exposure ranged from 6% – 28% (M = 11% ± 3%), which was consistent across buffer sizes. The results of correlation tests are provided in the supplemental materials (see the S1 Fig).

Table 1. Participant Demographics

Characteristic	M or (N)	SD or (%)	Observed Range
Demographics			
Years of Age	23.95	4.34	18.00 – 39.00
Female Bio-Sex	(262)	(77%)	- - - - - - - -
Income Ratio[1]	2.30	1.87	0.06 – 12.44
Maternal Education[2]	3.63	1.27	1.00 – 5.00
Exercise			
Walking[3]	4.23	1.59	0.00 – 7.00
Running[3]	2.74	1.96	0.00 – 7.00
Biking[3]	1.00	1.78	0.00 – 7.00
Health Indicators			
Body Mass Index	25.34	5.34	14.10 – 51.90
Glucose (mg/dL)	90.93	10.07	69.00 – 142.00
Early Life Stress			
Stress Severity[4]	11.63	10.80	0.00 – 69.00
Nature Exposure			
NDVI (250 m)	10.78	3.21	6.38 – 27.77
NDVI (500 m)	10.83	2.89	6.77 – 25.17
NDVI (1000 m)	10.90	2.61	6.78 – 25.85
Years of Residence[5]	10.39	7.87	0.00 – 28.00

(1) Self-reported household income divided by the federal poverty threshold for specific household size. (2) Maternal educational attainment from, 1 “less than high school” to 5 “college graduate”. (3) Average duration of exercise per week during the past year, from 0 “0 min” to 7 “11+ hours”. (4) Stress and Adversity Inventory for Adults (STRAIN [89]). (5) Duration of time that participants lived at their reported address. NDVI: Normalized Difference Vegetation Index.

[3.1] Moderation Effect of Early Life Stress

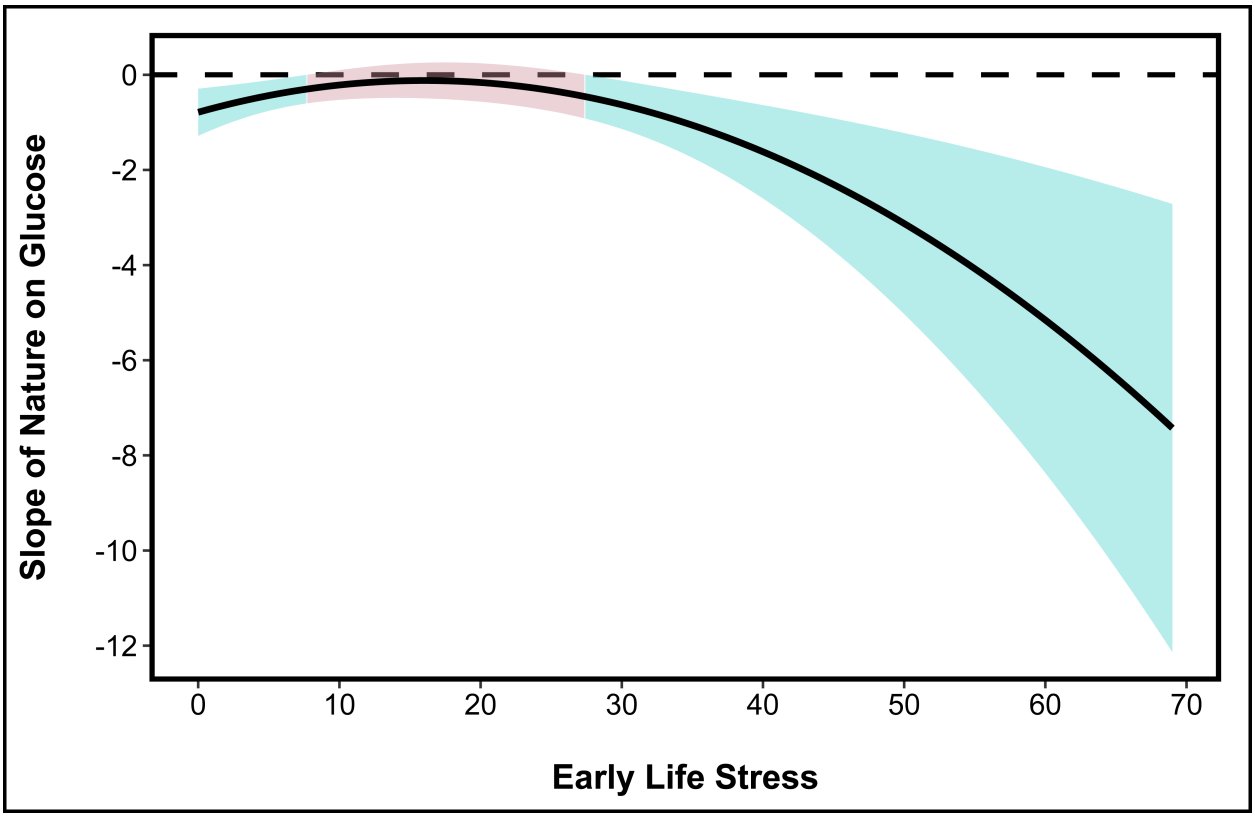
We first tested the two-way interaction term (Early Life Stress x Nature Exposure) at the 250 m buffer size. The likelihood ratio test provided evidence that including a quadratic term for early life stress significantly improved model fit ($X^2(2) = 11.66$, $p = .003$). In the resulting model, we observed that the linear interaction was non-significant ($B = 0.023$, 95% CI [-0.009, 0.055], $p = 0.162$) whereas the quadratic interaction was significant ($B =$ -0.003, 95% CI [-0.004, -0.001], $p = .005$), indicating a curvilinear trend in the moderation effect of early life stress on the nature-glucose association.

To better understand the characteristics of this interaction effect, we plotted the slope of nature exposure on fasting glucose along the continuum of early life stress (see Fig 2). In this plot, we observed that among participants with lower levels of early life stress, the protective effect of nature exposure on fasting glucose levels (negative regression slope) decreased (became less negative) as early life stress increased, an effect that was only significant ($p < .05$) when early life stress was within the interval of 0.0 – 7.7 points. We then identified a turning point (the vertex of the parabola) at 16.0 points (4.4 points above the sample mean), where the moderation effect changed direction. Specifically, we observed that among participants with higher levels of early life stress, the protective effect of nature exposure on fasting glucose levels (negative regression slope) increased (became more negative) as early life stress increased, an effect that was only significant ($p < .05$) when early life stress was within the interval of 27.5 – 69.0 points.

To understand the magnitude of these interaction effects, we then evaluated simple slopes for early life stress using the min and max values of the lower and higher intervals. In the lower interval (0.0 – 7.7 points), simple slopes provided evidence that for each percentage increase in nature exposure, fasting glucose levels would decrease by 0.79 mg/dL (95% CI

[-1.28, -0.29], p = .002) at the min value, to 0.30 mg/dL (95% CI [-0.60, -0.01], p = .049) at the max value. In the higher interval (27.5 – 69.0 points), simple slopes provided evidence that for each percentage increase in nature exposure, fasting glucose levels would decrease by 0.46 mg/dL (95% CI [-0.92, -0.01], p = .049) at the min value, to 7.43 mg/dL (95% CI [-12.16, -2.70], p = .002) at the max value. In addition to this, we also sequenced simple slopes for early life stress across the observed range of the total sample (0.0 – 69.0 points) using units of standard deviation (see Table 2). However, given the width of the confidence intervals at higher levels of early life stress, point estimates for simple slopes above two standard deviations should be interpreted with caution.

Figure 2. Moderation Effect of Early Life Stress on the Nature-Glucose Association



Johnson-Neyman plot visualizing changes in the slope of nature exposure on fasting glucose levels (y-axis) along the continuum of early life stress (x-axis). Blue regions denote intervals where the moderation effect of early life stress is significant ($p < .05$). Estimates were obtained from a regression model with a continuous two-way interaction term (Early Life Stress x Nature Exposure).

Table 2. Simple Slopes for Early Life Stress on the Nature-Glucose Association

Level	Score	Slope	SE	95% CI	P
-1 SD	0.78	-0.724	0.233	-1.183, -0.266	.002
M ($\bar{x}$)	11.64	-0.170	0.167	-0.499, 0.158	.308
+1 SD	22.49	-0.230	0.212	-0.649, 0.188	.279
+2 SD	33.35	-0.903	0.312	-1.517, -0.288	.004
+3 SD	44.20	-2.189	0.672	-3.513, -0.866	.001
+4 SD	55.06	-4.088	1.285	-6.617, -1.558	.002
+5 SD	65.92	-6.601	2.124	-10.783, -2.419	.002

Simple slopes for early life stress sequenced across the observed range of the total sample in standard deviation units. Estimates reflect changes in fasting glucose levels (mg/dL) relative to a percentage 1%) increase in residential nature exposure.

[3.2] Buffer Sizes & Sensitivity Analyses

We then tested the two-way interaction term across different buffer sizes for residential nature exposure and observed effects consistent with the 250 m buffer at the 500 m and 1000 m buffers. However, the significance of the moderation intervals was attenuated at larger buffer sizes (see the S1 Table). We then tested the sensitivity of our results using models with outliers and models unadjusted for relevant covariates. In the models with outliers, we observed consistent effects at the 250 m, 500 m, and 1000 m buffers. However, the higher moderation interval was no longer significant at the 1000 m buffer (S1 Table). In the unadjusted models, we observed consistent effects at the 250 m, 500 m, and 1000 m buffers. However, the higher moderation interval was attenuated, and both moderation intervals were no longer significant at the 1000 m buffer (S1 Table). We then included adult-life stressor exposure as another covariate in the main models and observed consistent effects at the 250 m, 500 m, and 1000 m buffers (S1 Table).

[4] Discussion

In this cross-sectional investigation, we observed partial support for our hypothesis that adult participants with higher exposure to early-life stressors would exhibit stronger protective effects from residential nature exposure, as evidenced by greater reductions in

fasting glucose. Specifically, relative to the sample average, we found that participants with higher levels of early life stress exhibited more pronounced beneficial reductions in fasting glucose when living in greener neighborhoods. However, we also found that relative to the sample average, participants with lower levels of early life stress also exhibited more pronounced beneficial reductions in fasting glucose when living in greener neighborhoods. By contrast, participants with average levels of early life stress exhibited the smallest beneficial reductions in fasting glucose when living in greener neighborhoods. Although the direction of our findings remained consistent across different buffer sizes for residential nature exposure (250 m, 500 m, and 1000 m), there was a decay of these effects with increasing buffer sizes (at a greater distance from the home address), a trend that was more evident among participants with higher levels of early life stress.

These findings reveal a complex interplay between social and physical environmental factors in relation to metabolic outcomes. Curiously, our hypothesis that participants with higher exposure to early-life stressors would exhibit stronger protective effects from nature exposure was supported only for participants above the sample average. This unexpected pattern raises key questions about the mechanisms underlying these associations and warrants further investigation.

[4.1] Theoretical Implications

In the context of our framework, we expected that environmental sensitivity induced by early life stress could promote greater health benefits from nature exposure. This was based on mounting evidence indicating that early life stress can induce a lifelong susceptibility to stress (i.e., Biological Embedding Model [24–31]), and that susceptibility to stress could reflect increased responsivity to both stressors and health-protective exposures (i.e., Differential Susceptibility Hypothesis [32–39]). Therefore, we expected that the association between early life stress and environmental sensitivity would be linear, increasing the protective effects of residential nature exposure in a dose-response pattern. However, we found that participants with higher and lower levels of early life stress both exhibited stronger protective effects of nature exposure, relative to participants near the sample aver-

age. This implies that the association between early life stress and environmental sensitivity might not be linear, but a more complex u-shaped association that might induce different adaptive phenotypes of environmental sensitivity along the continuum of early life stress, a concept that is well-grounded within evolutionary-developmental perspectives [62–67].

In short, these perspectives posit that: (1) early-life environments with high stressor exposure and low support upregulate a phenotype of environmental sensitivity that is adaptive in adverse environments (vigilant profile), increasing the capacity of an individual to identify and respond to external challenges and threats; (2) early-life environments with low stressor exposure and especially high support upregulate a phenotype of environmental sensitivity that is adaptive in supportive environments (sensitive profile), increasing susceptibility to social resources and ambient support; (3) and by contrast, early-life environments with moderate exposures in either direction downregulate environmental sensitivity (buffered profile), maximizing adaptive fitness in environments that are not particularly adverse or supportive, as experienced by the vast majority of individuals (for an excellent review on the u-shaped association, see the Biological Sensitivity to Context Theory [62–64], for the adaptive phenotypes, see the Adaptive Calibration Model [65–67]).

Integrating these evolutionary-developmental perspectives into our framework could provide some insight into our findings, where participants with higher levels of early life stress (vigilant profile) and lower levels of early life stress (sensitive profile) both exhibited stronger protective effects from nature exposure, relative to participants near the sample average (buffered profile). Although this implies that groups with higher and lower early-life stressor exposure are both particularly sensitive to the protective effects of nature exposure, these protective effects could be even more pronounced among groups with higher exposure to early-life stressors, given the heightened risk of disease in this population [117,118]. This also implies that a pro-inflammatory immune state could be a measure of environmental sensitivity specific to groups with higher exposure to early-life stressors. This interpretation aligns with our recent experimental findings, where participants with a pro-inflammatory state exhibited stronger protective effects from nature exposure in a dose-response pattern (greater autonomic recovery from an acute psychosocial stressor in a virtual nature versus office setting [15]).

We also found that the protective effects of residential nature exposure decayed with increasing buffer sizes (at a greater distance from the home address), a trend that was more evident among participants with higher versus lower levels of early life stress. This might suggest that groups with higher exposure to early-life stressors (vigilant profile) are more attuned to immediate threats, but are also more attuned to protective factors in the ambient environment. This interpretation aligns with psycho-evolutionary theories (e.g., Stress Reduction Theory [72,73], Attention Restoration Theory [74,75], Biophilia Hypothesis [76,77]), which posit that visual elements are an important mechanism underpinning the health-protective effects of nature exposure. By contrast, the more consistent effect found with increasing distance among participants with lower levels of early life stress (sensitive profile) might suggest that these groups are more attuned to broader (e.g., non-visual) pathways. Although our interpretations throughout this section are theoretical and speculative, they underscore the complexity of the moderation effect of early life stress and emphasize the need for further research to disentangle the intricate interplay between early life stress, nature exposure, and metabolic outcomes.

[4.2] Research Implications

Overall, our findings contribute to growing evidence indicating that the health-protective effects of nature exposure are not the same for everyone, but can vary significantly across individuals, groups, and populations [1–7]. Specifically, we found that early life stress moderated the protective effects of nature exposure in a way that either promoted or diminished beneficial reductions in fasting glucose levels. Hence, we urge future researchers to account for individual differences in life stress when investigating the protective effects of nature exposure. Failure to account for these differences could not only lead to replication challenges but also hinders our capacity to disentangle the complex role of life stress in nature and health relationships. By incorporating measures that quantify exposure to stressors across the lifespan, researchers can gain deeper insights into the mechanisms through which nature exposure influences health and well-being across diverse populations and socioeconomic gradients.

If future research corroborates these findings, this could necessitate a significant shift in how we conceptualize "susceptibility" in public health research. Traditionally, susceptibility has been primarily understood as heightened neurobiological sensitivity to the health risks of adverse environments, which could be a function of early-life exposures. However, our findings suggest a more nuanced understanding: that the same early-life exposures that increase sensitivity to adverse environments might also increase sensitivity to protective and supportive environments. Therefore, this bidirectional responsiveness might be more accurately conceptualized as a form of total "environmental sensitivity" rather than the unidirectional distinction of "susceptibility".

This reconceptualization ultimately proposes that individuals identified in various investigations as being more reactive to adverse conditions might also be more responsive to protective and supportive conditions. In other words, susceptible individuals may have a wider range of reaction norms, covering the full gamut of environmental exposures, whereas non-susceptible individuals may have a narrower range of reaction norms, responding less to adverse and protective environmental exposures. Therefore, certain aspects of what is currently recognized as susceptibility from an environmental health perspective might in some cases be better framed as increased sensitivity to both adverse and protective environments. This understanding, which is grounded within the concept of differential susceptibility in developmental psychology, could have widespread and far-reaching implications for public health and environmental health research, particularly in elucidating the differential impacts of physical and social environmental factors across diverse populations and socioeconomic gradients to inform targeted interventions.

[4.3] Public Health Implications

Our findings also support the value of further investigation into the idea that early life stress could be one mechanism underpinning epidemiological observations that nature exposure is associated with better health among groups in lower versus higher socioeconomic positions [1–7]. If future research corroborates these findings, this might further indicate that incorporating nature exposure into disadvantaged neighborhoods could be a strategic intervention target to curb disparities in health across socioeconomic gradi-

ents. For instance, incorporating nature exposure into residential settings is often a safe, feasible, sustainable, and cost-effective intervention target [119–122] with potential as a complementary health approach that: (1) could be installed as a passive intervention, (2) is a long-term intervention, promoting generational health, (3) could provide multiple co-benefits, and (4) could be implemented through public health policy [122].

In this regard, our findings suggest that urban planning initiatives should prioritize close-to-home nature-based interventions in these disadvantaged neighborhoods (e.g., public parks, green corridors, community gardens), especially considering that groups in low socioeconomic positions often experience environmental injustices, including neighborhood-level inequalities in their access to nature exposure [123]. Our findings also suggest that even small-scale increases in nature exposure might provide a protective effect in these neighborhoods, even in desert regions where the proportion of green vegetative cover is minimal relative to other regions. Therefore, it might be that the most relevant predictor of health is a change or difference in relative levels of nearby nature exposure, compared to absolute values without taking the local norm into account.

[4.4] Strengths & Limitations

To our knowledge, this is the first investigation to provide evidence suggesting that early life stress is associated with greater health benefits from nature exposure. While modest, these findings are supported by several study strengths, including our use of a comprehensive measure to quantify early life stress [89], the integration of various well-established theories to support our claims [49,51,62,65,68,73,75,77], and our focus on biomarkers of glucose dysregulation, a diabetes risk factor that significantly contributes to the global burden of disease [90,91]. Identifying a significant moderation effect of early life stress on the nature-glucose association at particularly low levels of nature exposure also increases our confidence in a robust association across these variables.

At the same time, several limitations should be considered. The use of a cross-sectional observational design limited causal inference, and additional research is needed to investigate the generalizability of the present findings to other populations. Although the normalized difference vegetation index is a reliable measure of nature exposure [108], this

measure does not distinguish between different types or account for the quality of the exposure, which could be important moderating factors. The interpretation of our findings was also based on long-term exposure to residential nature; however, without complete information on residential histories or time spent away from home, we were constrained to cumulative exposure estimates based on the current home address of each participant. Yet, considering that participants lived at their reported address for more than a decade, on average, and that spatial variation of green nature is limited in desert regions, these limitations are likely non-differential with respect to our findings.

There was also a large amount of missing data for the early life stress assessment (22%), resulting from time constraints during the laboratory visit due to the length of the comprehensive assessment ($\geq$ 20 min). Therefore, these data are considered to be missing completely at random, and no differences were observed between participants with missing data and the rest of the sample. Even though we adjusted for a range of relevant covariates to eliminate the most plausible alternative explanations and confounders (e.g., exercise, weight loss), it is possible that other unassessed factors might have contributed to our findings. Looking forward, future studies with more representative samples, more rigorous assessment of nature exposure and other potential confounding factors, and longitudinal designs to support causal modeling will be helpful.

[4.5] Conclusion

Ultimately, future research in line with this theoretical framework could lead to a greater understanding of the ways in which nature-based interventions could be leveraged to reduce disparities in health among vulnerable populations. Specifically, this could further underscore the value of integrating protective physical environments into public health strategies, especially for groups with higher exposure to early-life stressors, who are particularly susceptible to health risks but also might stand to experience the greatest health benefits from nature exposure. As the evidence for this framework expands, we could more effectively identify and target mechanisms of health risks and benefits among susceptible groups and tailor public health interventions, taking into account individual differences in environmental sensitivity to reduce disparities in health across socioeconomic gradients.

Acknowledgments

The authors thank Marcela Murga, Alan Medina, and Diana P. Flores from the Biobehavioral Research Lab at the School of Nursing, University of Texas at El Paso, for leading the NEWS data collection efforts. Special acknowledgment to John D. Spengler for his support throughout the entire project, including his mentorship and support of both Hector A. Olvera-Alvarez and Jose Guillermo Cedeño Laurent. The authors thank the Hoffman Program on Chemicals and Health for their support of both the NEWS and the development of this manuscript. The authors also thank Nicco C. Martin from the Biobehavioral Research Core at the School of Nursing, Oregon Health & Science University, for his support in developing the tables and figures used in this manuscript.

References

1. Mitchell R, Popham F. Effect of exposure to natural environment on health inequalities: an observational population study. Lancet. 2008;372: 1655–60. doi:10.1016/S0140-6736(08)61689-X

2. Mitchell RJ, Richardson EA, Shortt NK, Pearce JR. Neighborhood environments and socioeconomic inequalities in mental well-being. Am J Prev Med. 2015;49: 80–4. doi:10.1016/j.amepre.2015.01.017

3. Brown SC, Lombard J, Wang K, Byrne MM, Toro M, Plater-Zyberk E, et al. Neighborhood greenness and chronic health conditions in Medicare beneficiaries. Am J Prev Med. 2016;51: 78–89. doi:10.1016/j.amepre.2016.02.008

4. Brown SC, Perrino T, Lombard J, Wang K, Toro M, Rundek T, et al. Health disparities in the relationship of neighborhood greenness to mental health outcomes in 249,405 U.S. Medicare beneficiaries. Int J Environ Res Public Health. 2018;15: 430. doi:10.3390/ijerph15030430

5. Rigolon A, Browning MHEM, McAnirlin O, Yoon HV. Green space and health equity: a systematic review on the potential of green space to reduce health disparities. Int J Environ Res Public Health. 2021;18: 2563. doi:10.3390/ijerph18052563

6. Nicholls N, Caryl F, Olsen JR, Mitchell R. Neighbourhood natural space and the narrowing of socioeconomic inequality in years of life lost: a cross-sectional ecological analysis of the Scottish Burden of Disease. J Epidemiol Community Health. 2022;76: 976–83. doi:10.1136/jech-2022-219111

7. Wang R, Dong G, Cao M, Zhou Y, Dong G-H. Exploring “equigenesis” in the associations between green space and kidney health among middle-aged and older adults using street view data. Innov Aging. 2024;8: igad130. doi:10.1093/geroni/igad130

8. Craig JM, Prescott SL. Planning ahead: the mental health value of natural environments. Lancet Planet Health. 2017;1: e128–e129. doi:10.1016/S2542-5196(17)30068-2

9. Badland H, Pearce J. Liveable for whom? Prospects of urban liveability to address health inequities. Soc Sci Med. 2019;232: 94–105. doi:10.1016/j.socscimed.2019.05.001

10. Tost H, Reichert M, Braun U, Reinhard I, Peters R, Lautenbach S, et al. Neural correlates of individual differences in affective benefit of real-life urban green space exposure. Nat Neurosci. 2019;22: 1389–93. doi:10.1038/s41593-019-0451-y

11. Tomita A, Vandormael AM, Cuadros D, Di Minin E, Heikinheimo V, Tanser F, et al. Green environment and incident depression in South Africa: a geospatial analysis and mental health implications in a resource-limited setting. Lancet Planet Health. 2017;1: e152–e162. doi:10.1016/S2542-5196(17)30063-3

12. Moran MR, Bilal U, Dronova I, Ju Y, Gouveia N, Caiaffa WT, et al. The equigenic effect of greenness on the association between education with life expectancy and mortality in 28 large Latin American cities. Health Place. 2021;72: 102703. doi:10.1016/j.healthplace.2021.102703

13. Astell-Burt T, Feng X. Does the potential benefit of neighbourhood green space for body mass index depend upon socioeconomic circumstances and local built and transport environments? A test of the 'equigenesis' hypothesis in Australia. J Transp Health. 2017;5: S40. doi:10.1016/j.jth.2017.05.327

14. Feng X, Astell-Burt T. Do greener areas promote more equitable child health? Health Place. 2017;46: 267–73. doi:10.1016/j.healthplace.2017.05.006

15. Eisen AM, Bratman GN, Olvera-Alvarez HA. Susceptibility to stress and nature exposure: unveiling differential susceptibility to physical environments; a randomized controlled trial. PLoS One. 2024;19: e0301473. doi:10.1371/journal.pone.0301473

16. Evans GW, Kantrowitz E. Socioeconomic status and health: the potential role of environmental risk exposure. Annu Rev Public Health. 2002;23: 303–31. doi:10.1146/annurev.publhealth.23.112001.112349

17. Evans GW, English K. The environment of poverty: multiple stressor exposure, psychophysiological stress, and socioemotional adjustment. Child Dev. 2002;73: 1238–48. doi:10.1111/1467-8624.00469

18. Evans GW. The environment of childhood poverty. Am Psychol. 2004;59: 77–92. doi:10.1037/0003-066X.59.2.77

19. Evans GW, Gonnella C, Marcynyszyn LA, Gentile L, Salpekar N. The role of chaos in poverty and children's socioemotional adjustment. Psychol Sci. 2005;16: 560–5. doi:10.1111/j.0956-7976.2005.01575.x

20. Evans GW, Kim P. Childhood poverty and health: cumulative risk exposure and stress dysregulation. Psychol Sci. 2007;18: 953–7. doi:10.1111/j.1467-9280.2007.02008.x

21. Evans GW, Kim P. Childhood poverty and young adults' allostatic load: the mediating role of childhood cumulative risk exposure. Psychol Sci. 2012;23: 979–83. doi:10.1177/0956797612441218

22. Evans GW, Kim P. Childhood poverty, chronic stress, self-regulation, and coping. Child Dev Perspect. 2013;7: 43–8. doi:10.1111/cdep.12013

23. Giano Z, Wheeler DL, Hubach RD. The frequencies and disparities of adverse childhood experiences in the U.S. BMC Public Health. 2020;20: 1327. doi:10.1186/s12889-020-09411-z

24. Hertzman C, Boyce T. How experience gets under the skin to create gradients in developmental health. Annu Rev Public Health. 2010;31: 329–47. doi:10.1146/annurev.publhealth.012809.103538

25. Hertzman C. Putting the concept of biological embedding in historical perspective. Proc Natl Acad Sci U S A. 2012;109 Suppl 2: 17160–7. doi:10.1073/pnas.1202203109

26. McEwen BS. Brain on stress: how the social environment gets under the skin. Proc Natl Acad Sci U S A. 2012;109 Suppl 2: 17180–5. doi:10.1073/pnas.1121254109

27. Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol Behav. 2012;106: 29–39. doi:10.1016/j.physbeh.2011.08.019

28. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. JAMA. 2009;301: 2252–9. doi:10.1001/jama.2009.754

29. Kumsta R. The role of stress in the biological embedding of experience. Psychoneuroendocrinology. 2023;156: 106364. doi:10.1016/j.psyneuen.2023.106364

30. Heim CM, Entringer S, Buss C. Translating basic research knowledge on the biological embedding of early-life stress into novel approaches for the developmental programming of lifelong health. Psychoneuroendocrinology. 2019;105: 123–37. doi:10.1016/j.psyneuen.2018.12.011

31. Vaiserman AM, Koliada AK. Early-life adversity and long-term neurobehavioral outcomes: epigenome as a bridge? Hum Genomics. 2017;11: 34. doi:10.1186/s40246-017-0129-z

32. Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, van Ijzendoorn MH. Differential susceptibility to the environment: an evolutionary–neurodevelopmental theory. Dev Psychopathol. 2011;23: 7–28. doi:10.1017/S0954579410000611

33. Boyce WT. Differential susceptibility of the developing brain to contextual adversity and stress. Neuropsychopharmacology. 2016;41: 142–62. doi:10.1038/npp.2015.294

34. Ellis BJ, Del Giudice M. Developmental adaptation to stress: an evolutionary perspective. Annu Rev Psychol. 2019;70: 111–39. doi:10.1146/annurev-psych-122216-011732

35. Ellis BJ, Del Giudice M. Beyond allostatic load: rethinking the role of stress in regulating human development. Dev Psychopathol. 2014;26: 1–20. doi:10.1017/S0954579413000849

36. Belsky J, Pluess M. Beyond risk, resilience, and dysregulation: phenotypic plasticity and human development. Dev Psychopathol. 2013;25: 1243–61. doi:10.1017/S095457941300059X

37. Ellis BJ, Bianchi J, Griskevicius V, Frankenhuis WE. Beyond risk and protective factors: an adaptation-based approach to resilience. Perspect Psychol Sci. 2017;12: 561–87. doi:10.1177/1745691617693054

38. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? Mol Psychiatry. 2009;14: 746–54. doi:10.1038/mp.2009.44

39. Hartman S, Belsky J, Pluess M. Prenatal programming of environmental sensitivity. Transl Psychiatry. 2023;13: 1–10. doi:10.1038/s41398-023-02461-y

40. Taylor SE. Mechanisms linking early life stress to adult health outcomes. Proc Natl Acad Sci U S A. 2010;107: 8507–12. doi:10.1073/pnas.1003890107

41. Tyrka AR, Burgers DE, Philip NS, Price LH, Carpenter LL. The neurobiological correlates of childhood adversity and implications for treatment. Acta Psychiatr Scand. 2013;128: 434–47. doi:10.1111/acps.12143

42. Berens AE, Jensen SKG, Nelson CA. Biological embedding of childhood adversity: from physiological mechanisms to clinical implications. BMC Med. 2017;15: 135. doi:10.1186/s12916-017-0895-4

43. Danese A, J Lewis S. Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma? Neuropsychopharmacology. 2017;42: 99–114. doi:10.1038/npp.2016.198

44. Agorastos A, Pervanidou P, Chrousos GP, Kolaitis G. Early life stress and trauma: developmental neuroendocrine aspects of prolonged stress system dysregulation. Hormones (Athens). 2018;17: 507–20. doi:10.1007/s42000-018-0065-x

45. Agorastos A, Pervanidou P, Chrousos GP, Baker DG. Developmental trajectories of early life stress and trauma: a narrative review on neurobiological aspects beyond stress system dysregulation. Front Psychiatry. 2019;10: 118. doi:10.3389/fpsyt.2019.00118

46. Chen MA, LeRoy AS, Majd M, Chen JY, Brown RL, Christian LM, et al. Immune and epigenetic pathways linking childhood adversity and health across the lifespan. Front Psychol. 2021;12: 788351. doi:10.3389/fpsyg.2021.788351

47. Malave L, van Dijk MT, Anacker C. Early life adversity shapes neural circuit function during sensitive postnatal developmental periods. Transl Psychiatry. 2022;12: 306. doi:10.1038/s41398-022-02092-9

48. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol Bull. 2011;137: 959–97. doi:10.1037/a0024768

49. Nusslock R, Miller GE. Early-life adversity and physical and emotional health across the lifespan: a neuroimmune network hypothesis. Biol Psychiatry. 2016;80: 23–32. doi:10.1016/j.biopsych.2015.05.017

50. Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, et al. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc Natl Acad Sci U S A. 2009;106: 14716–21. doi:10.1073/pnas.0902971106

51. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull. 2014;140: 774–815. doi:10.1037/a0035302

52. Slavich GM, Sacher J. Stress, sex hormones, inflammation, and major depressive disorder: extending Social Signal Transduction Theory of Depression to account for sex differences in mood disorders. Psychopharmacology (Berl). 2019;236: 3063–79. doi:10.1007/s00213-019-05326-9

53. Slavich GM, Giletta M, Helms SW, Hastings PD, Rudolph KD, Nock MK, et al. Interpersonal life stress, inflammation, and depression in adolescence: testing Social Signal Transduction Theory of Depression. Depress Anxiety. 2020;37: 179–93. doi:10.1002/da.22987

54. Kim P, Evans GW, Chen E, Miller G, Seeman T. How socioeconomic disadvantages get under the skin and into the brain to influence health development across the lifespan. In: Halfon N, Forrest CB, Lerner RM, Faustman EM, editors. Handbook of life course health development [Internet]. Cham (CH): Springer; 2018. doi:10.1007/978-3-319-47143-3_19

55. Evans GW, Chen E, Miller G, Seeman T. How poverty gets under the skin: a life course perspective. In: King RB, Maholmes V, editors. The Oxford handbook of poverty and child development. New York: Oxford University Press; 2012. pp. 13–36.

56. Evans GW, Kim P. Multiple risk exposure as a potential explanatory mechanism for the socioeconomic status-health gradient. Ann N Y Acad Sci. 2010;1186: 174–89. doi:10.1111/j.1749-6632.2009.05336.x

57. Kim P, Evans GW, Angstadt M, Ho SS, Sripada CS, Swain JE, et al. Effects of childhood poverty and chronic stress on emotion regulatory brain function in adulthood. Proc Natl Acad Sci U S A. 2013;110: 18442–7. doi:10.1073/pnas.1308240110

58. Sripada RK, Swain JE, Evans GW, Welsh RC, Liberzon I. Childhood poverty and stress reactivity are associated with aberrant functional connectivity in default mode network. Neuropsychopharmacology. 2014;39: 2244–51. doi:10.1038/npp.2014.75

59. Evans GW, Schamberg MA. Childhood poverty, chronic stress, and adult working memory. Proc Natl Acad Sci U S A. 2009;106: 6545–9. doi:10.1073/pnas.0811910106

60. Evans GW, Cassells RC. Childhood poverty, cumulative risk exposure, and mental health in emerging adults. Clin Psychol Sci. 2014;2: 287–96. doi:10.1177/2167702613501496

61. Wells NM, Evans GW, Beavis A, Ong AD. Early childhood poverty, cumulative risk exposure, and body mass index trajectories through young adulthood. Am J Public Health. 2010;100: 2507–12. doi:10.2105/AJPH.2009.184291

62. Boyce WT, Ellis BJ. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. Dev Psychopathol. 2005;17: 271–301. doi:10.1017/s0954579405050145

63. Ellis BJ, Essex MJ, Boyce WT. Biological sensitivity to context: II. Empirical explorations of an evolutionary-developmental theory. Dev Psychopathol. 2005;17: 303–28. doi:10.1017/s0954579405050157

64. Ellis BJ, Jackson JJ, Boyce WT. The stress response systems: universality and adaptive individual differences. Dev Rev. 2006;26: 175–212. doi:10.1016/j.dr.2006.02.004

65. Del Giudice M, Ellis BJ, Shirtcliff EA. The Adaptive Calibration Model of stress responsivity. Neurosci Biobehav Rev. 2011;35: 1562–92. doi:10.1016/j.neubiorev.2010.11.007

66. Del Giudice M, Hinnant JB, Ellis BJ, El-Sheikh M. Adaptive patterns of stress responsivity: a preliminary investigation. Dev Psychol. 2012;48: 775–90. doi:10.1037/a0026519

67. Ellis BJ, Oldehinkel AJ, Nederhof E. The Adaptive Calibration Model of stress responsivity: an empirical test in the Tracking Adolescents' Individual Lives Survey study. Dev Psychopathol. 2017;29: 1001–21. doi:10.1017/S0954579416000985

68. Belsky J, Bakermans-Kranenburg MJ, van IJzendoorn MH. For better and for worse: differential susceptibility to environmental influences. Curr Dir Psychol Sci. 2007;16: 300–4. doi:10.1111/j.1467-8721.2007.00525.x

69. Belsky J. Differential susceptibility to environmental influences. Int J Child Care Educ Policy. 2013;7: 15–31. doi:10.1007/2288-6729-7-2-15

70. Pluess M, Belsky J. Prenatal programming of postnatal plasticity? Dev Psychopathol. 2011;23: 29–38. doi:10.1017/S0954579410000623

71. Belsky J, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. Psychol Bull. 2009;135: 885–908. doi:10.1037/a0017376

72. Ulrich RS. Aesthetic and affective response to natural environment. In: Altman I, Wohlwill JF, editors. Behavior and the natural environment. New York: Plenum Press; 1983. pp. 85–125.

73. Ulrich RS, Simons RF, Losito BD, Fiorito E, Miles MA, Zelson M. Stress recovery during exposure to natural and urban environments. J Environ Psychol. 1991;11: 201–30. doi:10.1016/S0272-4944(05)80184-7

74. Kaplan R, Kaplan S. The experience of nature: a psychological perspective. New York: Cambridge University Press; 1989.

75. Kaplan S. The restorative benefits of nature: toward an integrative framework. J Environ Psychol. 1995;15: 169–82. doi:10.1016/0272-4944(95)90001-2

76. Wilson EO. Biophilia: the human bond with other species. Cambridge (MA): Harvard University Press; 1984.

77. Kellert SR, Wilson EO. The biophilia hypothesis. Washington DC: Island Press; 1993.

78. Miller GE, Chen E. Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. Psychol Sci. 2010;21: 848–56. doi:10.1177/0956797610370161

79. Carpenter LL, Gawuga CE, Tyrka AR, Lee JK, Anderson GM, Price LH. Association between plasma IL-6 response to acute stress and early-life adversity in healthy adults. Neuropsychopharmacology. 2010;35: 2617–23. doi:10.1038/npp.2010.159

80. Ehrlich KB, Ross KM, Chen E, Miller GE. Testing the biological embedding hypothesis: is early life adversity associated with a later proinflammatory phenotype? Dev Psychopathol. 2016;28: 1273–83. doi:10.1017/S0954579416000845

81. Schreier HMC, Kuras YI, McInnis CM, Thoma MV, St Pierre DG, Hanlin L, et al. Childhood physical neglect is associated with exaggerated systemic and intracellular inflammatory responses to repeated psychosocial stress in adulthood. Front Psychiatry. 2020;11: 504. doi:10.3389/fpsyt.2020.00504

82. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998;14: 245–58. doi:10.1016/s0749-3797(98)00017-8

83. McEwen CA, Gregerson SF. A critical assessment of the Adverse Childhood Experiences Study at 20 years. Am J Prev Med. 2019;56: 790–4. doi:10.1016/j.amepre.2018.10.016

84. Anda RF, Porter LE, Brown DW. Inside the adverse childhood experience score: strengths, limitations, and misapplications. Am J Prev Med. 2020;59: 293–5. doi:10.1016/j.amepre.2020.01.009

85. Slavich GM. Stressnology: the primitive (and problematic) study of life stress exposure and pressing need for better measurement. Brain Behav Immun. 2019;75: 3–5. doi:10.1016/j.bbi.2018.08.011

86. Crouch E, Radcliff E, Strompolis M, Srivastav A. Safe, stable, and nurtured: protective factors against poor physical and mental health outcomes following exposure to adverse childhood experiences (ACEs). J Child Adolesc Trauma. 2019;12: 165–73. doi:10.1007/s40653-018-0217-9

87. Brinker J, Cheruvu VK. Social and emotional support as a protective factor against current depression among individuals with adverse childhood experiences. Prev Med Rep. 2017;5: 127–33. doi:10.1016/j.pmedr.2016.11.018

88. Olvera Alvarez HA, Provencio-Vasquez E, Slavich GM, Laurent JGC, Browning M, McKee-Lopez G, et al. Stress and health in nursing students: the Nurse Engagement and Wellness Study. Nurs Res. 2019;68: 453–63. doi:10.1097/NNR.0000000000000383

89. Slavich GM, Shields GS. Assessing lifetime stress exposure using the Stress and Adversity Inventory for Adults (Adult STRAIN): an overview and initial validation. Psychosom Med. 2018;80: 17–27. doi:10.1097/PSY.0000000000000534

90. Lin X, Xu Y, Pan X, Xu J, Ding Y, Sun X, et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep. 2020;10: 14790. doi:10.1038/s41598-020-71908-9

91. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023;402: 203–34. doi:10.1016/S0140-6736(23)01301-6

92. Hill-Briggs F, Adler NE, Berkowitz SA, Chin MH, Gary-Webb TL, Navas-Acien A, et al. Social determinants of health and diabetes: a scientific review. Diabetes Care. 2020;44: 258–79. doi:10.2337/dci20-0053

93. Volaco A, Cavalcanti AM, Filho RP, Précoma DB. Socioeconomic status: the missing link between obesity and diabetes mellitus? Curr Diabetes Rev. 2018;14: 321–6. doi:10.2174/1573399813666170621123227

94. Bodicoat DH, O'Donovan G, Dalton AM, Gray LJ, Yates T, Edwardson C, et al. The association between neighbourhood greenspace and type 2 diabetes in a large cross-sectional study. BMJ Open. 2014;4: e006076. doi:10.1136/bmjopen-2014-006076

95. Astell-Burt T, Feng X, Kolt GS. Is neighborhood green space associated with a lower risk of type 2 diabetes? Evidence from 267,072 Australians. Diabetes Care. 2014;37: 197–201. doi:10.2337/dc13-1325

96. Ccami-Bernal F, Soriano-Moreno DR, Fernandez-Guzman D, Tuco KG, Castro-Díaz SD, Esparza-Varas AL, et al. Green space exposure and type 2 diabetes mellitus incidence: a systematic review. Health Place. 2023;82: 103045. doi:10.1016/j.healthplace.2023.103045

97. Doubleday A, Knott CJ, Hazlehurst MF, Bertoni AG, Kaufman JD, Hajat A. Neighborhood greenspace and risk of type 2 diabetes in a prospective cohort: the Multi-Ethncity Study of Atherosclerosis. Environ Health. 2022;21: 18. doi:10.1186/s12940-021-00824-w

98. Yang B-Y, Markevych I, Heinrich J, Bowatte G, Bloom MS, Guo Y, et al. Associations of greenness with diabetes mellitus and glucose-homeostasis markers: The 33 Communities Chinese Health Study. Int J Hyg Environ Health. 2019;222: 283–90. doi:10.1016/j.ijheh.2018.12.001

99. Liao J, Chen X, Xu S, Li Y, Zhang B, Cao Z, et al. Effect of residential exposure to green space on maternal blood glucose levels, impaired glucose tolerance, and gestational diabetes mellitus. Environ Res. 2019;176: 108526. doi:10.1016/j.envres.2019.108526

100. Lin B-C, Yen Y-T, Lao XQ, Chen Y-H, Chan T-C. Association between neighborhood greenspace and fasting plasma glucose from a large cohort study in Taiwan. Urban For Urban Green. 2019;44: 126439. doi:10.1016/j.ufug.2019.126439

101. Olvera-Alvarez HA, Browning MHEM, Neophytou AM, Bratman GN. Associations of residential brownness and greenness with fasting glucose in young healthy adults living in the desert. Int J Environ Res Public Health. 2021;18: 520. doi:10.3390/ijerph18020520

102. Thiering E, Markevych I, Brüske I, Fuertes E, Kratzsch J, Sugiri D, et al. Associations of residential long-term air pollution exposures and satellite-derived greenness with insulin resistance in German adolescents. Environ Health Perspect. 2016;124: 1291–8. doi:10.1289/ehp.1509967

103. Qu Y, Yang B, Lin S, Bloom MS, Nie Z, Ou Y, et al. Associations of greenness with gestational diabetes mellitus: The Guangdong Registry of Congenital Heart Disease (GRCHD) study. Environ Pollut. 2020;266: 115127. doi:10.1016/j.envpol.2020.115127

104. Dadvand P, Poursafa P, Heshmat R, Motlagh ME, Qorbani M, Basagaña X, et al. Use of green spaces and blood glucose in children; a population-based CASPIAN-V study. Environ Pollut. 2018;243: 1134–40. doi:10.1016/j.envpol.2018.09.094

105. Cazassa MJ, Oliveira M da S, Spahr CM, Shields GS, Slavich GM. The Stress and Adversity Inventory for Adults (Adult STRAIN) in Brazilian Portuguese: initial validation and links with executive function, sleep, and mental and physical health. Front Psychol. 2019;10: 3083. doi:10.3389/fpsyg.2019.03083

106. Sturmbauer SC, Shields GS, Hetzel E-L, Rohleder N, Slavich GM. The Stress and Adversity Inventory for Adults (Adult STRAIN) in German: an overview and initial validation. PLoS One. 2019;14: e0216419. doi:10.1371/journal.pone.0216419

107. Shields GS, Fassett-Carman A, Gray ZJ, Gonzales JE, Snyder HR, Slavich GM. Why is subjective stress severity a stronger predictor of health than stressor exposure? A preregistered two-study test of two hypotheses. Stress Health. 2023;39: 87–102. doi:10.1002/smi.3165

108. Rhew IC, Vander Stoep A, Kearney A, Smith NL, Dunbar MD. Validation of the normalized difference vegetation index as a measure of neighborhood greenness. Ann Epidemiol. 2011;21: 946–52. doi:10.1016/j.annepidem.2011.09.001

109. Vermote E, Justice C, Claverie M, Franch B. Preliminary analysis of the performance of the Landsat 8/OLI land surface reflectance product. Remote Sens Environ. 2016;185: 46–56. doi:10.1016/j.rse.2016.04.008

110. Bohannon RW. Comfortable and maximum walking speed of adults aged 20—79 years: reference values and determinants. Age Ageing. 1997;26: 15–9. doi:10.1093/ageing/26.1.15

111. Browning M, Lee K. Within what distance does "greenness" best predict physical health? A systematic review of articles with GIS buffer analyses across the lifespan. Int J Environ Res Public Health. 2017;14: 675. doi:10.3390/ijerph14070675

112. Shemesh T, Rowley KG, Shephard M, Piers LS, O'Dea K. Agreement between laboratory results and on-site pathology testing using Bayer DCA2000+ and Cholestech LDX point-of-care methods in remote Australian Aboriginal communities. Clin Chim Acta. 2006;367: 69–76. doi:10.1016/j.cca.2005.11.014

113. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of care in diabetes-2024. Diabetes Care. 2024;47: S20–S42. doi:10.2337/dc24-S002

114. Miller G, Chen E. Unfavorable socioeconomic conditions in early life presage expression of proinflammatory phenotype in adolescence. Psychosom Med. 2007;69: 402–9. doi:10.1097/PSY.0b013e318068fcf9

115. Villeneuve PJ, Jerrett M, Su JG, Weichenthal S, Sandler DP. Association of residential greenness with obesity and physical activity in a US cohort of women. Environ Res. 2018;160: 372–84. doi:10.1016/j.envres.2017.10.005

116. Davis JW, Chung R, Juarez DT. Prevalence of comorbid conditions with aging among patients with diabetes and cardiovascular disease. Hawaii Med J. 2011;70: 209–13.

117. Merrick MT, Ford DC, Ports KA, Guinn AS, Chen J, Klevens J, et al. Vital signs: estimated proportion of adult health problems attributable to adverse childhood experiences and implications for prevention – 25 states, 2015-2017. MMWR Morb Mortal Wkly Rep. 2019;68: 999–1005. doi:10.15585/mmwr.mm6844e1

118. Jones CM, Merrick MT, Houry DE. Identifying and preventing adverse childhood experiences: implications for clinical practice. JAMA. 2020;323: 25–6. doi:10.1001/jama.2019.18499

119. Wolf KL, Measells MK, Grado SC, Robbins AST. Economic values of metro nature health benefits: a life course approach. Urban For Urban Green. 2015;14: 694–701. doi:10.1016/j.ufug.2015.06.009

120. Brochu P, Jimenez MP, James P, Kinney PL, Lane K. Benefits of increasing greenness on all-cause mortality in the largest metropolitan areas of the United States within the past two decades. Front Public Health. 2022;10: 841936. doi:10.3389/fpubh.2022.841936

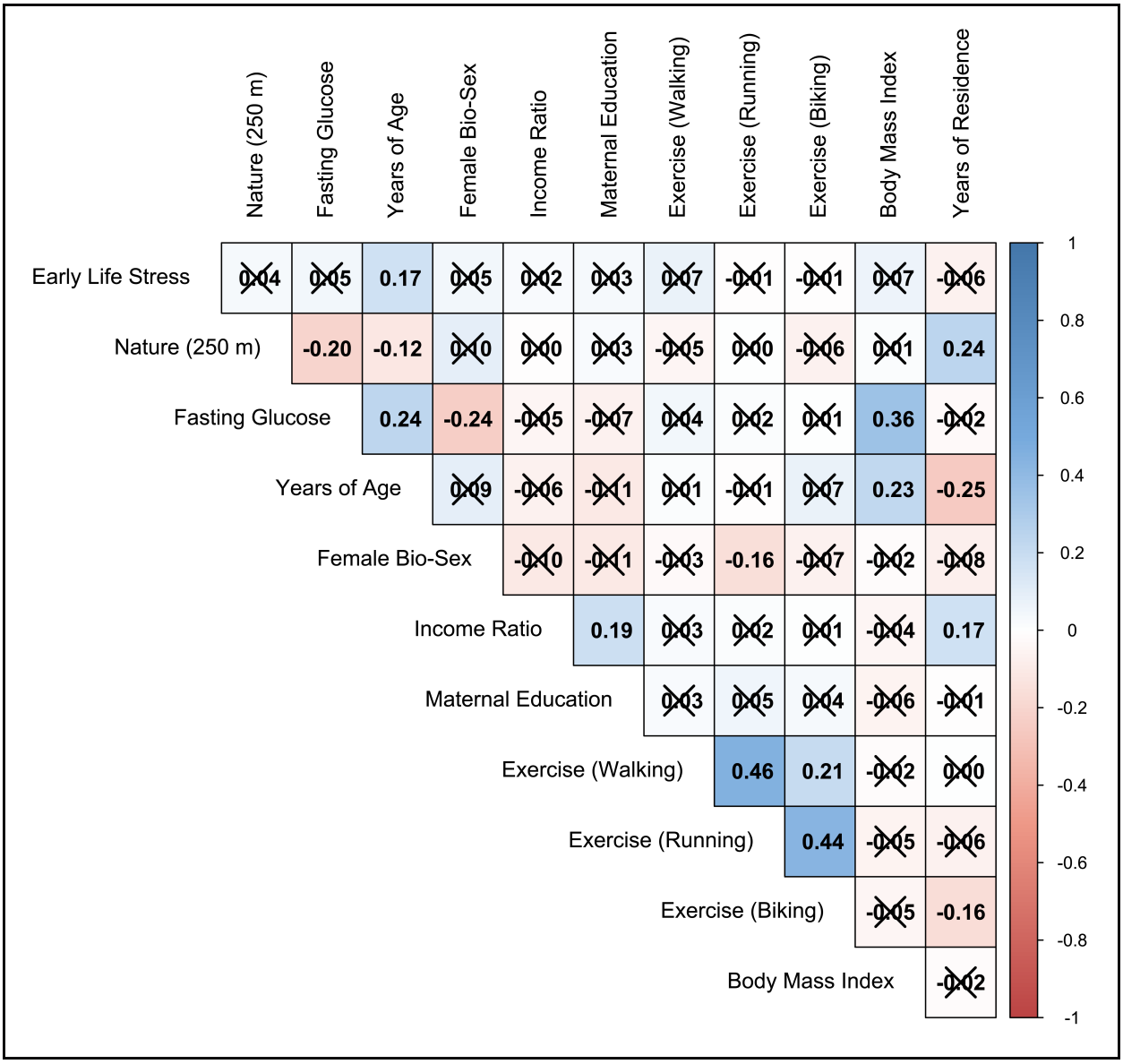
121. Wilson J, Xiao X. The economic value of health benefits associated with urban park investment. Int J Environ Res Public Health. 2023;20: 4815. doi:10.3390/ijerph20064815

122. Frumkin H, Bratman GN, Breslow SJ, Cochran B, Kahn PH, Lawler JJ, et al. Nature contact and human health: a research agenda. Environ Health Perspect. 2017;125: 075001. doi:10.1289/EHP1663

123. Rigolon A, Browning M, Jennings V. Inequities in the quality of urban park systems: an environmental justice investigation of cities in the United States. Landsc Urban Plan. 2018;178: 156–69. doi:10.1016/j.landurbplan.2018.05.026

Supporting Information

S1 Figure. Bivariate Correlation Plot



Parametric correlations across our included measures. Diagonal lines are superimposed over non-significant correlations. Correlations for nature exposure were consistent across buffer sizes (250 m, 500 m, and 1000 m).

S1 Table. Estimates Across All Models

	Buffer Size	Interaction Term	Lower Interval ($p < .05$)		Vertex	Higher Interval ($p < .05$)	
(1) Main Models	250 Meters	-0.0026** (-0.0044, -0.0008)	0.00 points (-0.79 mg/dL)	7.68 points (-0.30 mg/dL)	16.01 points	27.46 points (-0.46 mg/dL)	69.00 points (-7.43 mg/dL)
	500 Meters	-0.0030** (-0.0051, -0.0009)	0.00 points (-0.81 mg/dL)	5.73 points (-0.35 mg/dL)	16.37 points	30.34 points (-0.59 mg/dL)	69.00 points (-8.25 mg/dL)
	1000 Meters	-0.0024* (-0.0044, -0.0003)	0.00 points (-0.64 mg/dL)	0.97 points (-0.57 mg/dL)	15.97 points	33.59 points (-0.77 mg/dL)	69.00 points (-6.66 mg/dL)
(2) With Outliers	250 Meters	-0.0025* (-0.0048, -0.0002)	0.00 points (-0.94 mg/dL)	8.44 points (-0.39 mg/dL)	17.26 points	31.87 points (-0.73 mg/dL)	69.00 points (-6.89 mg/dL)
	500 Meters	-0.0028* (-0.0055, -0.0001)	0.00 points (-0.93 mg/dL)	6.27 points (-0.44 mg/dL)	17.34 points	37.60 points (-1.24 mg/dL)	69.00 points (-7.52 mg/dL)
	1000 Meters	-0.0025 (-0.0052, 0.0002)	0.00 points (-1.01 mg/dL)	6.51 points (-0.47 mg/dL)	19.71 points	---	---
(3) No Covariates	250 Meters	-0.0016 (-0.0035, 0.0004)	0.00 points (-0.65 mg/dL)	10.45 points (-0.34 mg/dL)	14.68 points	25.06 points (-0.48 mg/dL)	54.17 points (-2.73 mg/dL)
	500 Meters	-0.0019 (-0.0042, 0.0004)	0.00 points (-0.72 mg/dL)	7.87 points (-0.35 mg/dL)	16.18 points	33.78 points (-0.82 mg/dL)	43.98 points (-1.71 mg/dL)
	1000 Meters	-0.0015 (-0.0038, 0.0009)	---	---	15.84 points	---	---
(4) Adult Stressors	250 Meters	-0.0026** (-0.0044, -0.0008)	0.00 points (-0.77 mg/dL)	7.23 points (-0.31 mg/dL)	15.94 points	27.64 points (-0.47 mg/dL)	69.00 points (-7.51 mg/dL)
	500 Meters	-0.0031** (-0.0051, -0.0010)	0.00 points (-0.79 mg/dL)	5.32 points (-0.35 mg/dL)	16.22 points	30.16 points (-0.59 mg/dL)	69.00 points (-8.50 mg/dL)
	1000 Meters	-0.0025* (-0.0046, -0.0004)	0.00 points (-0.64 mg/dL)	0.79 points (-0.58 mg/dL)	15.85 points	33.00 points (-0.75 mg/dL)	69.00 points (-7.05 mg/dL)

Estimates were obtained from continuous two-way interaction terms used to assess the moderation effect of early life stress on the association between residential nature exposure and fasting glucose levels across different buffer sizes. Interaction terms were probed using Johnson-Neyman intervals to determine the specific regions along the continuum of early life stress that significantly moderate the nature-glucose association. Interaction terms were tested across models: (1) adjusted for covariates and excluding outliers, (2) adjusted for covariates and including outliers, (3) unadjusted for covariates and excluding outliers, and (4) adjusted for covariates, excluding outliers, and adjusted for adult-life stressor exposure. Outliers included nine participants identified through studentized residual values. Simple slopes are shown at the min and max values (points) of the significant region for the lower and higher moderation intervals and reflect changes in fasting glucose levels (mg/dL) relative to a 1% increase in nature exposure. The vertex refers to the turning point (the score at the top of the curve) where the moderation effect changed direction. $^{**}p < .01$, $^{*}p < .05$

Chapter Four

Title & Authorship

Susceptibility to stress and nature exposure: Demonstrating the Integrative Model of Environmental Sensitivity

Aaron M. Eisen[1], Jose Guillermo Cedeño Laurent[2], John D. Spengler[3], George M. Slavich[4], Hector A. Olvera-Alvarez[1]

[1]School of Nursing, Oregon Health & Science University, Portland, OR

[2]School of Public Health, Rutgers University, Piscataway, NJ

[3]Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA

[4]Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA

Funding Acknowledgments

This research was financially supported by the JPB Environmental Health Fellowship from the JPB Foundation, administered by the Harvard T.H. Chan School of Public Health [to Hector A. Olvera-Alvarez and Jose Guillermo Cedeño Laurent]; the Hoffman Program for Chemicals and Health at the Harvard T.H. Chan School of Public Health [to Hector A. Olvera-Alvarez and Jose Guillermo Cedeño Laurent]; Grant 5U54MD007592 from the National Institute on Minority Health and Health Disparities (NIMHD), a component of the National Institutes of Health (NIH) [to Hector A. Olvera-Alvarez]; Aaron M. Eisen was an ARCS Foundation Scholar. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Citation: PLOS ONE

Eisen AM, Cedeño Laurent JG, Spengler JD, Slavich GM, Olvera-Alvarez HA. Susceptibility to stress and nature exposure: demonstrating the Integrative Model of Environmental Sensitivity. PLoS One. 2025. Manuscript ready for submission.

Directory of Tables & Figures

List of Tables

Table	Name	Page
1	Descriptive Statistics by Cluster Membership	**146**
S1	Cumulative Exposure to Socioeconomic Stressors	**169**
S2	Cumulative Exposure to Life Stressors	**169**
S3	General Health Symptoms & Complaints	**169**
S4	Parental Attachment & Relationship Qualities	**170**
S5	Objective Socioeconomic Status Across the Lifespan	**170**

List of Figures

Figure	Title	Page
1	The Integrative Model of Environmental Sensitivity	**134**
2	Cumulative Exposure to Socioeconomic Stressors	**143**
3	Cumulative Exposure to Life Stressors	**143**
4	General Health Symptoms & Complaints	**144**
5	Parental Attachment & Relationship Qualities	**145**
6	Objective Socioeconomic Status Across the Lifespan	**145**
7	Adjusted Slope of Nature Exposure (250 m) on Fasting Glucose Levels	**147**
8	Adjusted Slope of Nature Exposure (500 m) on Fasting Glucose Levels	**148**
9	Adjusted Slope of Nature Exposure (1000 m) on Fasting Glucose Levels	**149**

Abstract

Background

Emerging epidemiological evidence indicates that groups in low socioeconomic positions exhibit more pronounced health benefits from nature exposure compared to more privileged groups. We have previously posited one possible mechanism underlying this phenomenon through the Integrative Model of Environmental Sensitivity: (susceptibility to stress) groups in low socioeconomic positions are often exposed to more early-life stressors, which can induce a lifelong susceptibility to stress through various neurobiological pathways; (environmental sensitivity) susceptibility to stress, traditionally understood as heightened reactivity to stressors, could also encompass enhanced responsivity to health-protective exposures, inducing greater risks in adverse environments, but also greater benefits in protective environments.

Objective

Examine whether residential nature exposure could be associated with better health among groups in lower socioeconomic positions with higher exposure to early-life stressors.

Methods

We conducted a latent cluster analysis based on five lifetime stressor counts of life domains associated with the social determinants of health (exposures related to finances, education, healthcare, housing, and social contexts) using baseline data from a cohort of 362 nursing students. We then examined differences in targeted life patterns between the resulting clusters (general health symptoms and complaints, parental attachment and relationship qualities, and objective socioeconomic status across the lifespan) using pairwise contrasts, and the effect of residential nature exposure (quantified using the normalized difference vegetation index across different buffer sizes, centered on the home address of each participant) on glucose dysregulation (elevated levels of fasting blood glucose) within each cluster, using structural equation modeling.

Results

As expected, participants with high exposure to socioeconomic stressors (26% of the sample) reported the highest levels of early life stress, the lowest levels of parental attachment, and the worst general health outcomes, while participants with low exposure to socioeconomic stressors (12% of the sample) reported the lowest levels of early life stress, the highest levels of parental attachment, and the best general health outcomes. By contrast, participants with average exposure to socioeconomic stressors (62% of the sample) reported relatively moderate levels of early life stress and parental attachment, and intermediate health outcomes. Trend-level findings suggested that participants with high exposure to socioeconomic stressors had the lowest objective socioeconomic status across the lifespan. Further, participants with high and low exposure to socioeconomic stressors both exhibited stronger protective effects from nature exposure, as evidenced by more pronounced beneficial reductions in fasting glucose levels when living in greener neighborhoods, while participants with average exposure to socioeconomic stressors exhibited weaker and non-significant associations.

Discussion

Our findings align with past research and provide crucial insights as to why epidemiological evidence indicates that groups in lower versus higher socioeconomic positions exhibit more pronounced health benefits from nature exposure. First, they highlight that even if groups in lower and higher socioeconomic positions are both particularly sensitive to the health-protective effects of nature exposure, these protective effects could be even more pronounced among groups in lower socioeconomic positions with higher early-life stressor exposure, given the heightened risk of disease in this population. Second, they outline that the proportion of individuals who are environmentally sensitive in higher socioeconomic positions could be significantly less than the proportion of individuals who are environmentally sensitive in lower socioeconomic positions. Put together, these interpretations further support the idea that increasing access to nature within disadvantaged neighborhoods could be an effective strategy to reduce disparities in health among vulnerable populations. As the evidence for this framework continues to expand, it could

inform more targeted interventions that leverage individual differences in environmental sensitivity to promote health equity, ultimately providing more nuanced, strategic, and socioeconomically attuned approaches to public health.

[1] Introduction

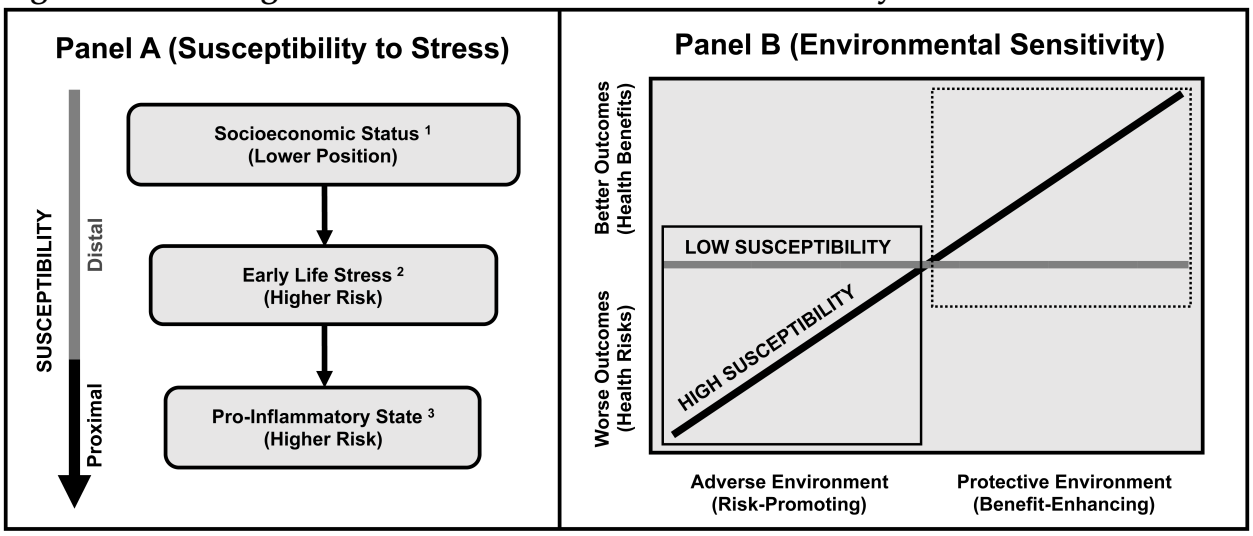
Emerging epidemiological evidence indicates that groups in low socioeconomic positions exhibit more pronounced health benefits from nature exposure (e.g., contact with natural green spaces) compared to more privileged groups [1–7]. This implies that increasing access to nature for disadvantaged communities could be a strategic approach to attenuate health disparities by alleviating the risks of chronic stressors among groups who are the most susceptible to stress [8–10]. However, the evidence supporting this possibility is mixed [11,12], including reports of null associations [13,14], and further research is thus needed to better understand the mechanisms underpinning this phenomenon [15,16]. Clarifying these mechanisms could reveal more effective pathways for reducing health disparities, as nature-based interventions offer a promising approach: they are passive, promoting health without requiring behavioral change; they are sustainable, often with low maintenance costs; and they can be implemented through public health policy to create lasting impacts.

[1.1] Theoretical Framework

One possible mechanism underpinning this phenomenon is described in the Integrative Model of Environmental Sensitivity (see Fig 1 [15,16]). In short, mounting evidence demonstrates that groups in lower socioeconomic positions often face higher exposure to persistent psychosocial stressors in early life [17–24]. Mounting evidence also demonstrates that early-life stressor exposure can induce a lifelong susceptibility to stress through various neurobiological pathways (i.e., Biological Embedding Model [25–32]). One of the most well-established pathways consists of early life stress inducing a pro-inflammatory immune state, observed as heightened neuroimmune reactivity to stressors (e.g., Neuroimmune Network Hypothesis [33–35], Social Signal Transduction Theory of Depression [36–38]). However, mounting evidence also demonstrates that individuals who are susceptible to stress are also more susceptible to health-protective exposures (i.e., Differential Susceptibility Hypothesis [39–46]). This implies that early life stress might be better understood as not merely increasing susceptibility to stress, but as cultivating a broader form

of environmental sensitivity, enhancing responsiveness to both stressors and protective factors (e.g., Biological Sensitivity to Context Theory [47–49], Adaptive Calibration Model [50–52]). This reframing provides a plausible mechanistic explanation as to why groups in lower versus higher socioeconomic positions could derive greater benefits from the health-protective effects of nature exposure.

Figure 1. The Integrative Model of Environmental Sensitivity



Emerging epidemiological evidence indicates that groups in low socioeconomic positions exhibit more pronounced health benefits from nature exposure compared to more privileged groups. One possible mechanism underpinning this evidence is described in the Integrative Model of Environmental Sensitivity. **Susceptibility to Stress:** groups in lower socioeconomic positions often face higher exposure to early-life stressors, which can induce a lifelong susceptibility to stress through various neurobiological pathways, including a pro-inflammatory immune state. **Environmental Sensitivity:** individuals who are susceptible to stress are more responsive to stressors and health-protective exposures, inducing greater risks in adverse environments but also greater benefits in protective environments, relative to less susceptible individuals.

(1) *Socioeconomic Status* is defined as the position of an individual in their society which is determined by both social and economic factors that impact exposure to and experiences with psychosocial stressors. (2) *Early Life Stress* is defined as persistent exposure to psychosocial stressors during childhood, with ranging degrees of perceived severity, that induce neurobiological responses and could promote developmental alterations over time. (3) A *Pro-Inflammatory Immune State* is defined as heightened neuroimmune reactivity to psychological and biological stressors combined with resistance to anti-inflammatory signals. This figure was adapted from "Susceptibility to Stress and Nature Exposure: Unveiling Differential Susceptibility to Physical Environments; a Randomized Controlled Trial" by Aaron M. Eisen, Gregory N. Bratman, and Hector A. Olvera-Alvarez, 2024, PLOS ONE, 19(4): e0301473. Copyright 2024 Eisen et al.

Notably, the evidence supporting this framework has centered on social environments and further investigation is needed to determine whether increased environmental sensi-

tivity induced by early life stress could also promote greater health benefits in protective physical environments such as nature. Eisen et al. used an experimental paradigm to evaluate this hypothesis and found that participants with a pro-inflammatory immune state exhibited greater autonomic recovery from an acute stressor in a virtual nature versus an office setting, relative to less susceptible participants [15]. Eisen et al. also used an observational paradigm to evaluate this hypothesis and found that participants with higher exposure to early-life stressors exhibited more pronounced beneficial reductions in fasting glucose levels when living in greener neighborhoods [16]. However, this finding was only relative to the sample average, and participants with lower exposure to early-life stressors also exhibited more pronounced beneficial reductions in fasting glucose levels when living in greener neighborhoods. By contrast, participants with relatively average exposure to early-life stressors exhibited the smallest changes in fasting glucose levels when living in greener neighborhoods.

Overall, this evidence supports the idea that the association between early life stress and environmental sensitivity might not be linear, but a more complex u-shaped association that could induce different adaptive phenotypes of environmental sensitivity along the continuum of early life stress, a concept that is well-grounded within evolutionary-developmental perspectives [47–52]. In short, these perspectives propose a conditional adaptation model of developmental variation in the stress response system based on two propositions. The first proposition is that the stress response system is a complex and integrated consort of neurobiological responses (e.g., autonomic, neuroendocrine, neuroimmune, cardiometabolic) designed to prepare humans for challenges or threats, but also functions to increase susceptibility to social resources and supportive factors in the ambient environment. This dual function signifies the need to conceptualize stress reactivity more broadly as heightened neurobiological sensitivity to context. The second proposition is that the stress response system operates as a mechanism of conditional adaptation, encoding information about levels of support versus adversity in the early-life environment; this information is then used to regulate the activation thresholds and response magnitudes of the stress response system to match those specific environmental conditions.

Based on this conditional adaptation model of the stress response system, these evolutionary-developmental perspectives posit that: (1) early-life environments with high stressor exposure and low support upregulate a phenotype of environmental sensitivity that is adaptive in adverse environments (vigilant profile), increasing the capacity of an individual to identify and respond to external challenges and threats; (2) early-life environments with low stressor exposure and especially high support upregulate a phenotype of environmental sensitivity that is adaptive in supportive environments (sensitive profile), increasing susceptibility to social resources and ambient support; (3) and by contrast, early-life environments with moderate exposures in either direction downregulate environmental sensitivity (buffered profile), maximizing adaptive fitness in environments that are not particularly adverse or supportive, as experienced by the vast majority of individuals (for an excellent review on the u-shaped association, see the Biological Sensitivity to Context Theory [47–49], for the adaptive phenotypes, see the Adaptive Calibration Model [50–52]).

In further detail, one of the core distinctions between the vigilant and sensitive profiles is the development of different life history strategies. Life History Theory [53–57] is a central branch of evolutionary biology used to explain coordinated patterns of human development, encompassing growth, reproduction, and survival over the life course. Maximizing adaptive fitness in specific environmental contexts necessitates inherent trade-offs in these developmental investments, characterized as slower versus faster life history strategies [58]. Assuming that basic bioenergetic resources are met, slower life history strategies are the product of supportive early-life environments and are oriented towards future outcomes, including long-term health and well-being. By contrast, faster life history strategies are the product of adverse early-life environments and are oriented towards immediate outcomes, including survival under threatening conditions experienced throughout our evolutionary history (e.g., predatory threats, hostile conspecifics), prompting developmental trade-offs that are often detrimental for long-term health and well-being. For instance, one mechanism through which early life stress could promote a faster life history strategy is by calibrating the immune system to induce a pro-inflammatory immune state, protecting the individual against infection from frequent engagement in flight or fight behaviors while also increasing their allostatic load over time [33–38].

Integrating these perspectives into our framework implies that groups with higher and lower exposure to early-life stressors are both particularly sensitive to the health-protective effects of nature exposure, yet with important differences in core life patterns. Specifically, we expect that groups with higher early-life stressor exposure (vigilant profile) would exhibit the worst health outcomes, the lowest levels of parental support, and the lowest socioeconomic positions, while groups with lower early-life stressor exposure (sensitive profile) would exhibit the best health outcomes, the highest levels of parental support, and the highest socioeconomic positions. By contrast, groups with relatively moderate exposures (buffered profile) would be less sensitive to the health-protective effects of nature exposure and exhibit moderate levels across these core life patterns. Even though this implies that groups in lower and higher socioeconomic positions are both particularly sensitive to the health-protective effects of nature exposure, it is plausible these effects would be even more pronounced among groups in lower socioeconomic positions with higher early-life stressor exposure, given the heightened risk of disease in this population [59,60].

[1.2] Present Study

The overarching objective of the present study was to bridge the evidence gaps between socioeconomic status, early life stress, and environmental sensitivity to nature exposure within our framework, through the lens of these evolutionary-developmental perspectives (Biological Sensitivity to Context Theory [47–49]; Adaptive Calibration Model [50–52]). Based on mounting evidence that groups in lower socioeconomic positions face often higher exposure to stressors across the lifespan as a result of social inequities [61–64], we conducted a latent cluster analysis using lifetime stressor counts of life domains associated with the social determinants of health (exposures related to finances, education, healthcare, housing, and social contexts). We then evaluated the alignment between the resulting clusters and the expected vigilant, sensitive, and buffered profiles of environmental sensitivity by examining: (1) differences in core life patterns between the clusters, with a focus on general health symptoms and complaints, parental attachment and relationship qualities, and objective indicators of socioeconomic status from early to adult life; and

(2) environmental sensitivity to nature exposure within each cluster, with a focus on the association between residential nature exposure and fasting glucose levels.

Notably, this study expands the findings of our prior investigations in several important ways. First, even though it is well-established that early-life stressor exposure increases the risk of negative outcomes across the lifespan [25–32], we were unable to demonstrate this without measures of general health. Second, the evolutionary-developmental perspectives emphasize that it is not just early life stress, but the ratio of early life stress to support that signals the development of different adaptive phenotypes [47–52]; while it is reasonable to assume that high exposure to early-life stressors corresponds to low levels of support, we were unable to demonstrate this without measures of parental attachment and relationship qualities. Third, although it is well-established that groups in lower socioeconomic positions face higher exposure to early-life stressors [17–24], we were unable to demonstrate this without the latent cluster analysis. Demonstrating these associations, while also replicating the moderation effect of early life stress observed in our prior studies would provide a comprehensive demonstration of our framework.

[2] Materials & Methods

[2.1] Participants

Data were obtained from baseline measurements of a prospective cohort of men and women (n = 517; 18–55 years of age) enrolled during their first semester of the Bachelor of Science in Nursing program at the University of Texas at El Paso (i.e., Nurse Engagement and Wellness Study; described in detail elsewhere [65]). Measurements included lifetime stressor exposure, socioenvironmental factors, health indicators, and relevant demographics. Participants were recruited using emails, posters, flyers, media outlets, and information sessions between May 17, 2016 and November 29, 2018. All participants provided written informed consent and measurements occurred during an in-person visit to the Biobehavioral Research Laboratory. This study was approved by the institutional review board at the University of Texas at El Paso (857149–1).

[2.2] Measures

This study included measures used to (1) determine cluster membership (lifetime stressor counts); (2) explore targeted life patterns between clusters (general health, parental attachment, and objective socioeconomic status); (3) examine environmental sensitivity to the health-protective effects of residential nature exposure within each cluster (with a specific focus on fasting glucose levels).

[2.2.1] Cluster Membership

Lifetime Stressor Exposure was assessed using the well-validated Stress and Adversity Inventory for Adults (STRAIN [66]). This dynamic and interview-based assessment tool quantifies exposure to different types of episodic (n = 26) and chronic (n = 29) stressors across various life domains (e.g., life-threatening situations, legal challenges, possessions, reproduction) and core social-psychological characteristics (e.g., humiliation, entrapment, physical danger, interpersonal loss) with known implications for health and wellness [67,68]. For each stressor endorsed, follow-up questions are used to ascertain the subjective severity, frequency, exposure timing, and duration of the stressor. This information is then used to calculate cumulative stress scores by summing the counts and perceived severity ratings of each stressor endorsed. As the focus of the present study was on stressors related to the social determinants of health, the variables used to determine cluster membership in our analysis included five lifetime stressor counts of associated life domains (exposure related to finances, education, healthcare, housing, and social contexts).

[2.2.2] Targeted Life Patterns

General Health symptoms and complaints during the preceding month were assessed using the well-validated Physical Health Questionnaire-14 (PHQ-14 [69]), the Patient Health Questionnaire-9 (PHQ-9 [70]), the Kessler 6-Item Psychological Distress Inventory (K-6 [71]), and the Mood and Feelings Questionnaire (MFQ-33 [72]); higher scores indicate more somatic symptoms, depressive symptoms, psychological distress, and unpleasant emotions, respectively.

Parental Attachment and relationship qualities were assessed using the Maternal Attachment Index and Paternal Attachment Index of the well-validated Inventory of Parent and Peer Attachment (IPPA [73]). Each index provides a global assessment of maternal or paternal attachment and relationship qualities, with three sub-scores reflecting trust, communication, and alienation (reverse scored). Higher index scores indicate greater parental attachment and better relationship qualities.

Objective Socioeconomic Status during childhood was quantified as the highest level of maternal education ("less than high school", "some high school", "high school graduate", "some college", "college graduate"), while objective socioeconomic status during adulthood was quantified as per capita household income (self-reported household income divided by household size).

[2.2.3] Environmental Sensitivity to Nature Exposure

Chronic Residential Nature Exposure (neighborhood-level green vegetation) was proxied using a cumulative opportunity approach across radial buffers centered on the home address of each participant. Levels of green vegetation were quantified using the normalized difference vegetation index (30 m^2 pixels [74]) from cloudless satellite images (Landsat 7 [75]) taken on a single summer day in 2016. Negative pixel values were present in a small portion of the region ($< 5\%$) and were reclassified as missing data to avoid potential confounding effects of water bodies (e.g., rivers, irrigation canals). Pixel values were averaged across buffer sizes that corresponded to the amount of green vegetation within a 3–min (250 m), 6–min (500 m), and 12–min (1000 m) walk for a healthy adult in their mid-thirties [76]. Pixel values could range from zero (no green vegetation) to one (maximum green vegetation) and were specified as percentages in our models to reflect changes in fasting glucose levels relative to a 1% increase in residential nature exposure.

Fasting Blood Glucose levels were obtained following an overnight fast from 35 µL of whole blood (Lipid Panel + Glucose Panel Cassettes; 2.8–27.8 mmol/L) using a Cholestech LDX Analyzer (Cholestech Corporation, Hayward, CA, USA). This instrument was calibrated before each measurement and used an enzymatic method (which has been shown

to align with plasma concentrations using a hexokinase method; 95% CI: 92%–100% [77]). Glucose concentrations were expressed in mg/dL units, with higher values indicative of glucose dysregulation [78].

[2.3] Analytical Approach

We restricted the sample to participants under the age of 40, as with older age comes the development of aging-related health states and different behavioral patterns that could confound our analysis [79]. In this sample, the number of participants who were 40 years of age or older was relatively small (n = 19; 4%). We also excluded participants who were unable to complete the comprehensive lifetime stressor assessment due to time constraints during the study visit (n = 136; 26%). Hence, the final analytical sample included 362 participants.

[2.3.1] Analysis 1: Cluster Membership and Targeted Life Patterns

We conducted a latent cluster analysis using lifetime stressor counts for each of the five domains of the social determinants of health (exposure related to finances, education, healthcare, housing, and social contexts). Gaussian finite mixture modeling (GMM) using an Expectation-Maximization (EM) algorithm was used to fit one through nine clusters to the lifetime stressor count data with either equal or unequal variance modeled between clusters. Data were standardized and the best-fitting model was selected based on the Bayesian Information Criterion (BIC) and the Integrated Completed Likelihood (ICL). Descriptive statistics and pairwise contrasts with corrections for multiple comparisons (Bonferroni procedure) were used to explore targeted life patterns between the clusters (general health, parental attachment, and objective socioeconomic status). To reduce the number of comparisons and streamline interpretations, normalized scores for each measure were averaged to create a general health index, a parental attachment index, and an objective socioeconomic status index. Data were analyzed using R (4.4.1) with the *mlcust* package for the mixture modeling, the *emmeans* package for the pairwise contrasts, and the *ggplot2* package to generate z-plots.

[2.3.2] Analysis 2: Environmental Sensitivity to Nature Exposure

To examine environmental sensitivity to the health-protective effect of residential nature exposure within each cluster, we used structural equation modeling (SEM) to perform a multiple-group analysis (MGA). We first fitted a linear regression model where the slope of nature exposure on fasting glucose and covariate effects were constrained to be equal across the clusters. We then used a likelihood ratio test (LRT) to determine whether removing these equality constraints significantly improved model fit. A significant likelihood ratio test indicates that the estimated slopes are not the same within each cluster, providing a statistical justification to allow the slopes to be freely estimated. Models were tested across different buffer sizes for residential nature exposure (250 m, 500 m, and 1000 m) and adjusted for seminal demographic covariates (years of age, biological sex, body mass index, and per capita household income). Parameters were estimated using full information maximum likelihood estimation (FIML) and data were analyzed using Mplus (8.4). Although we used alphas (0.05 level) to report significant findings, our interpretations focused on effect sizes and confidence intervals across all models, regardless of statistical significance.

[3] Results

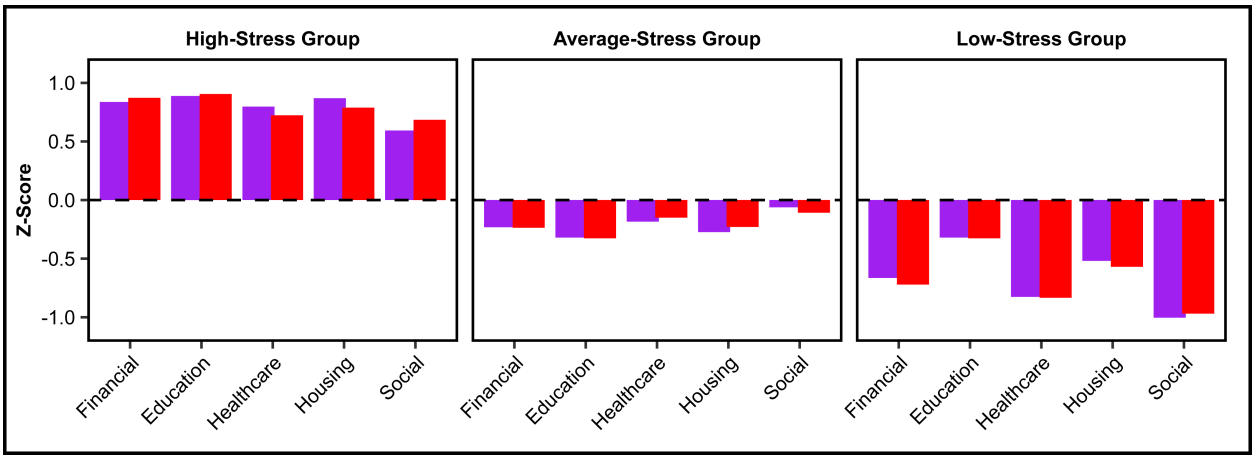
The sample consisted of 362 participants who were under the age of 40 (M = 24.1 ± 4.4 years; 77% female). Participants were exposed to an average of 14.4 (± 10.7) stressors over their lifespan with an average severity score of 34.0 points (± 25.9), corresponding to a "low to moderate" severity rating for each stressor endorsed. With respect to life domains, approximately half of these stressors (43.4%) encompassed the primary domains of the social determinants of health, including finances (4.7%), education (1.0%), healthcare (10.0%), housing (6.9%), and social contexts (20.8%).

[3.1] Analysis 1: Cluster Membership and Targeted Life Patterns

The latent cluster analysis provided evidence that a three-cluster model with unequal variance best fit the underlying distribution of the five lifetime stressor counts related to the social determinants of health. Relative to the sample mean (M = 6.3 ± 5.3), the first

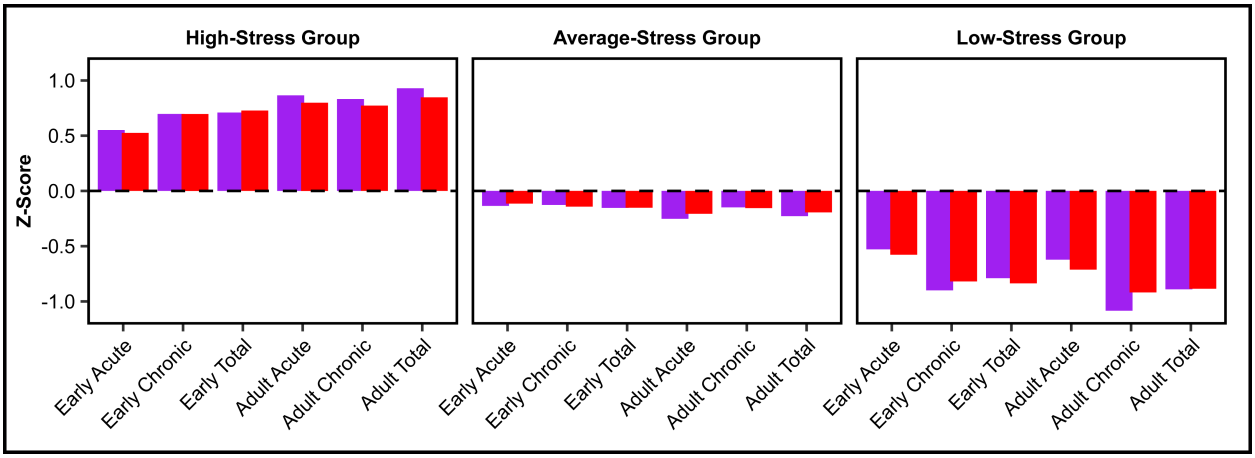
cluster was identified as a high-stress group (M = 12.2 ± 5.3; *n* = 96), the second as an average-stress group (M = 4.9 ± 3.0; *n* = 223), and the third as a low-stress group (M = 0.3 ± 0.5; *n* = 43; see Fig 2; S1 Table). As expected from clusters based on lifetime stressor counts, participants in the high-stress group reported the highest exposure to stressors across their lifespan (Early = 7.2 ± 5.3; Adult = 17.7 ± 9.5) while participants in the low-stress group reported the lowest exposure (Early = 1.1 ± 1.4; Adult = 2.8 ± 2.9). By comparison, participants in the average-stress group reported relatively moderate exposures (Early = 3.7 ± 3.0; Adult = 8.2 ± 5.5; see Fig 3; S2 Table).

Figure 2. Cumulative Exposure to Socioeconomic Stressors



Bar chart of standardized (z) scores visualizing cumulative exposure to socioeconomic stressors by group membership. Purple bars represent exposure counts while the red bars represent subjective severity.

Figure 3. Cumulative Exposure to Life Stressors

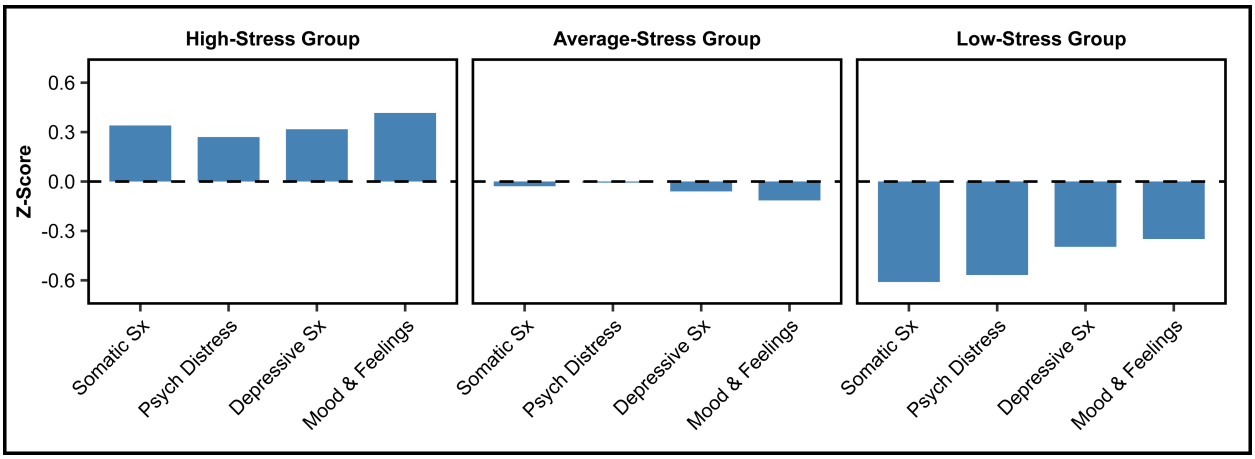


Bar chart of standardized (z) scores visualizing cumulative exposure to life stressors by group membership. Purple bars represent exposure counts while the red bars represent subjective severity.

[3.1.1] General Health

In terms of general health, participants in the high-stress group reported the highest rates of symptoms and complaints while participants in the low-stress group reported the lowest rates (see Fig 4; S3 Table). By comparison, participants in the average-stress group reported relatively moderate rates. Pairwise contrasts provided evidence of significant differences in general health between the high versus average-stress groups (MΔ = 7.3, 95% CI [2.6, 12.0], Hedges' g = 0.45, $p < .001$) and the low versus average-stress groups (MΔ = 8.6, 95% CI [2.1, 15.0], Hedges' g = 0.57, p = .005).

Figure 4. General Health Symptoms & Complaints

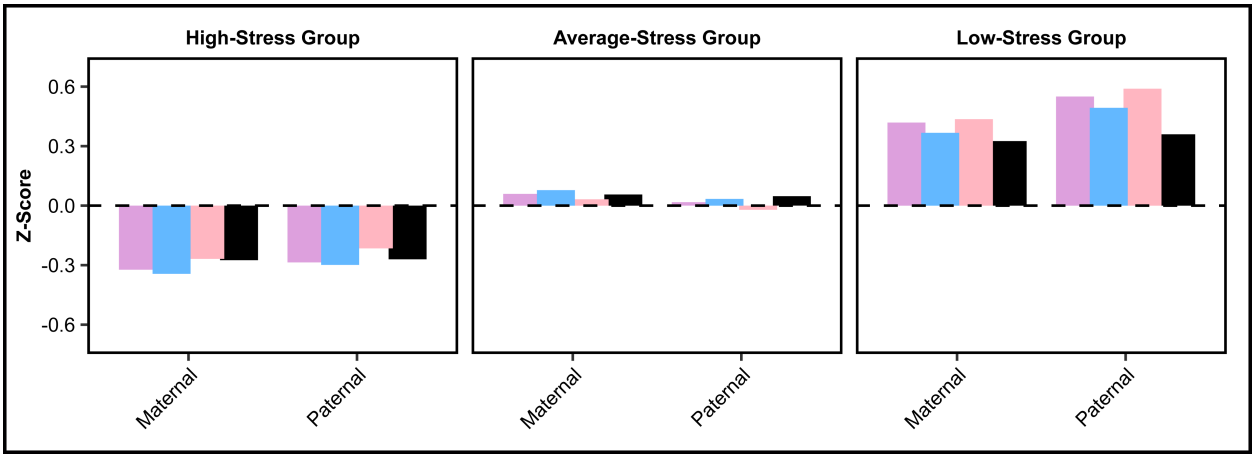


Bar chart of standardized (z) scores visualizing general health symptoms and complaints (past month) by group membership: somatic symptoms; psychological distress; depressive symptoms; unpleasant emotions.

[3.1.2] Parental Attachment

In terms of parental attachment, participants in the high-stress group reported the lowest levels of parental attachment and relationship qualities while participants in the low-stress group reported the highest levels (see Fig 5; S4 Table). By comparison, participants in the average-stress group reported relatively moderate levels. Pairwise contrasts provided evidence of significant differences in parental attachment between the high versus average-stress groups (MΔ = 6.0, 95% CI [1.9, 10.0], Hedges' g = 0.43, p = .001) and the low versus average-stress groups (MΔ = 8.0, 95% CI [2.5, 13.5], Hedges' g = 0.60, p = .002).

Figure 5. Parental Attachment & Relationship Qualities

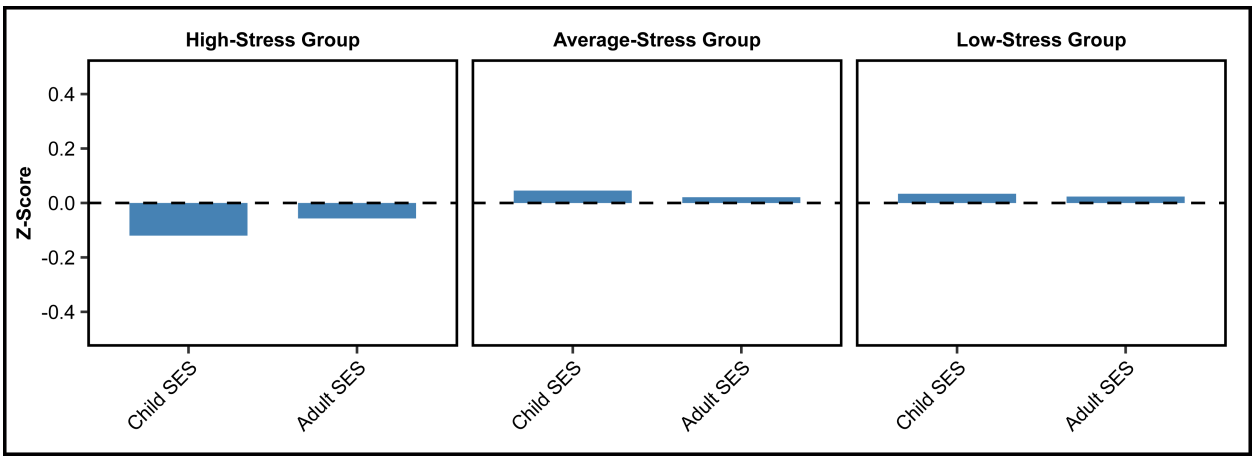


Bar chart of standardized (z) scores visualizing maternal or paternal attachment (purple bar) and relationship qualities: trust (blue bar); communication (pink bar); alienation (black bar; reversed); by group membership.

[3.1.3] Objective Socioeconomic Status

In terms of objective socioeconomic status, participants in the high-stress group reported the lowest levels of maternal education and per capita household income while participants in the low and average-stress groups reported relatively moderate levels (see Fig 6; S5 Table). Pairwise contrasts did not provide evidence of significant differences in objective socioeconomic status between the high versus average-stress groups (MΔ = 2.1, 95% CI [-2.4, 6.5], Hedges' g = 0.15, p = .813) or the low versus average-stress groups (MΔ = 0.1, 95% CI [-6.6, 6.5], Hedges' g = 0.00, p = .999).

Figure 6. Objective Socioeconomic Status Across the Lifespan



Bar chart of standardized (z) scores of objective socioeconomic status indicators by group membership: childhood socioeconomic status (maternal education); adult socioeconomic status (per capita household income).

[3.2] Analysis 2: Environmental Sensitivity to Nature Exposure

Differences in the distribution of demographic covariates followed trends that could be expected based on prior research (see Table 1). Specifically, relative to the low and average-stress groups, participants in the high-stress group were older on average (pairwise contrasts: $p < .001$), and non-significant trends suggested that these participants were more often females with higher body mass indices, higher fasting glucose levels, and lower per capita household income levels.

Table 1. Descriptive Statistics by Cluster Membership

Variable	M ± (SD) or N (%)				*p*-value[1]
	Total Sample *(n = 362)*	**High Stress** *(n = 96)*	**Average Stress** *(n = 223)*	**Low Stress** *(n = 43)*	
Demographics					
Age (Years)	24.06 ± 4.37	26.50 ± 4.95	23.28 ± 3.96	22.63 ± 2.65	<.001
Sex (Female)	280 (77%)	79 (82%)	169 (76%)	32 (74%)	.394
Income ($K)	15.14 ± 14.50	14.32 ± 11.28	15.44 ± 15.39	15.48 ± 16.70	.782
Health Indicators					
BMI (kg/m^2)	25.39 ± 5.34	25.53 ± 5.02	25.35 ± 5.42	25.30 ± 5.67	.952
Glucose (mg/dL)	90.87 ± 9.95	91.63 ± 11.16	90.76 ± 9.20	89.71 ± 10.93	.632
Nature Exposure					
G250 (%)	10.72 ± 3.19	10.84 ± 2.90	10.64 ± 3.25	10.83 ± 3.53	.849
G500 (%)	10.79 ± 2.87	10.95 ± 2.49	10.62 ± 2.90	11.30 ± 3.39	.358
G1000 (%)	10.85 ± 2.59	11.06 ± 2.27	10.68 ± 2.63	11.34 ± 2.94	.254

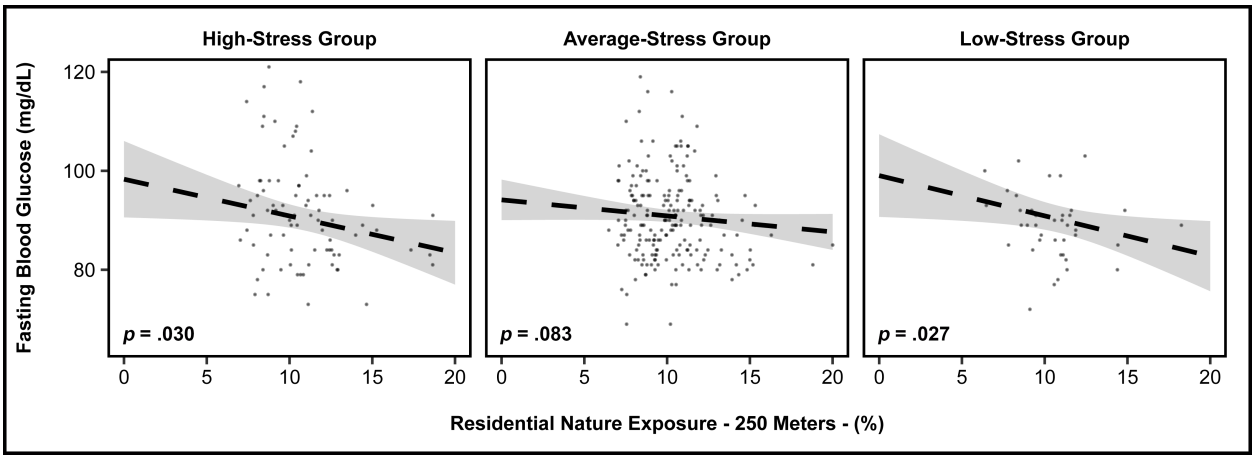
[1] one-way test assuming unequal variance; chi-square test

[3.2.1] 250 M Buffer Size

In the total sample, for each percentage increase in nature exposure, the model estimated that fasting glucose levels would decrease by 0.50 mg/dL (95% CI [0.20, 0.81], $p < .001$). When we stratified the model and constrained the effects to be equal across the groups, the likelihood ratio test was significant ($X^2(10) = 25.40$, $p = .005$), indicating that the estimated effects were not the same within each group and therefore, the unconstrained model was

interpreted. Relative to the average-stress group, participants in the high and low-stress groups both demonstrated more pronounced beneficial reductions in fasting glucose levels when living in greener neighborhoods. Specifically, for each percentage increase in nature exposure, the model estimated that fasting glucose levels would decrease by 0.74 mg/dL (95% CI [0.07, 1.41], p = .030) in the high-stress group and 0.81 mg/dL (95% CI [0.09, 1.54], p = .027) in the low-stress group (see Fig 7). By comparison, the estimated effect of nature exposure in the average-stress group was less pronounced and not statistically different than zero (B = -0.32, 95% CI [-0.69, 0.04], p = .083).

Figure 7. Adjusted Slope of Nature Exposure (250 m) on Fasting Glucose Levels



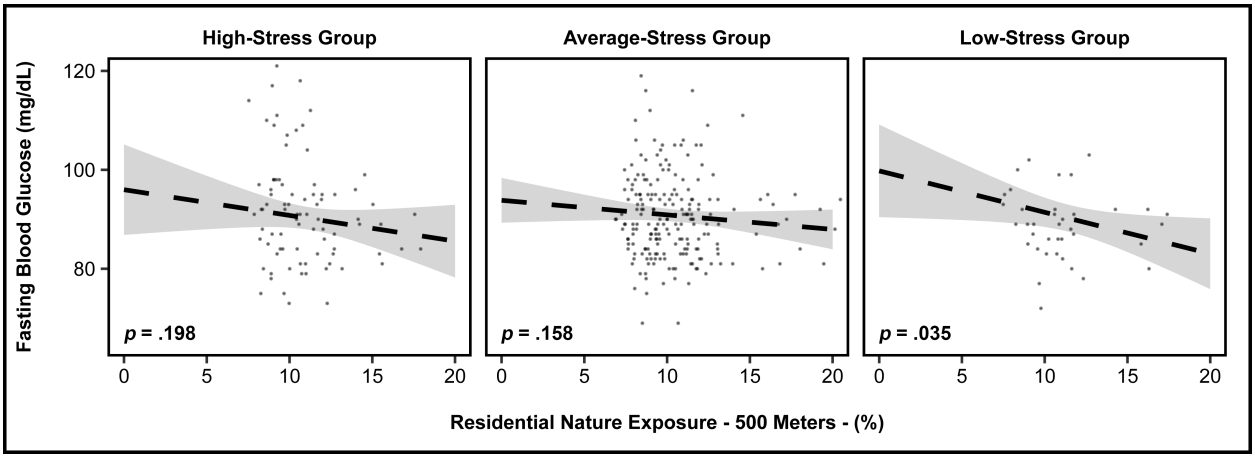
Partial effects plot visualizing the slope of nature exposure on glucose by group membership, adjusted for years of age, biological sex, body mass index, and household income. Bands denote 95% confidence intervals.

[3.2.2] 500 M Buffer Size

In the total sample, for each percentage increase in nature exposure, the model estimated that fasting glucose levels would decrease by 0.45 mg/dL (95% CI [0.11, 0.79], p = .010). The likelihood ratio test was significant ($X^2(10) = 24.62$, p = .006) and therefore, the unconstrained model was interpreted. Relative to the high and average-stress groups, participants in the low-stress group demonstrated more pronounced beneficial reductions in fasting glucose levels when living in greener neighborhoods. Specifically, for each percentage increase in nature exposure, the model estimated that fasting glucose levels would decrease by 0.84 mg/dL (95% CI [0.06, 1.64], p = .035) in the low-stress group (see

Fig 8). By comparison, the effect of nature exposure in the high-stress group (B = -0.52, 95% CI [-1.31, 0.27], p = .198) and the average-stress group (B = -0.29, 95% CI [-0.70, 0.12], p = .158) was less pronounced and not statistically different than zero.

Figure 8. Adjusted Slope of Nature Exposure (500 m) on Fasting Glucose Levels

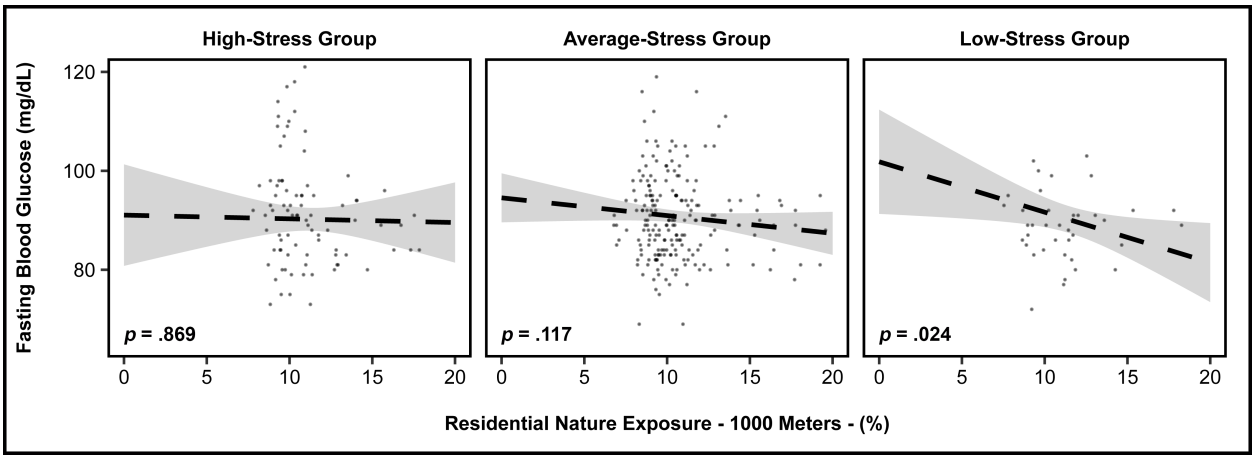


Partial effects plot visualizing the slope of nature exposure on glucose by group membership, adjusted for years of age, biological sex, body mass index, and household income. Bands denote 95% confidence intervals.

[3.2.3] 1000 M Buffer Size

In the total sample, for each percentage increase in nature exposure, the model estimated that fasting glucose levels would decrease by 0.41 mg/dL (95% CI [0.03, 0.79], p = .033). The likelihood ratio test was significant ($X^2(10) = 25.83$, p = .004) and therefore, the unconstrained model was interpreted. Relative to the high and average-stress groups, participants in the low-stress group demonstrated more pronounced beneficial reductions in fasting glucose levels when living in greener neighborhoods. Specifically, for each percentage increase in nature exposure, the model estimated that fasting glucose levels would decrease by 1.02 mg/dL (95% CI [0.14, 1.90], p = .024) in the low-stress group (see Fig 9). By comparison, the effect of nature exposure in the high-stress group (B = -0.08, 95% CI [-0.96, 0.81], p = .869) and the average-stress group (B = -0.36, 95% CI [-0.81, 0.09], p = .117) was less pronounced and not statistically different than zero, with the confidence interval for the high-stress group indicating a high degree of uncertainty whether an effect was present.

Figure 9. Adjusted Slope of Nature Exposure (1000 m) on Fasting Glucose Levels



Partial effects plot visualizing the slope of nature exposure on glucose by group membership, adjusted for years of age, biological sex, body mass index, and household income. Bands denote 95% confidence intervals.

[4] Discussion

In this cross-sectional study, we observed patterns that aligned with the expectations of our framework based on lifetime stressor counts associated with the social determinants of health (exposures related to finances, education, healthcare, housing, and social contexts). Specifically, the latent cluster analysis identified three groups with high exposure (26% of the sample), average exposure (62% of the sample), and low exposure (12% of the sample) to socioeconomic stressors. We found that participants with high exposure to socioeconomic stressors reported the highest levels of early life stress, the lowest levels of parental attachment, and the worst general health outcomes, while participants with low exposure to socioeconomic stressors reported the lowest levels of early life stress, the highest levels of parental attachment, and the best general health outcomes. By contrast, participants with average exposure to socioeconomic stressors reported relatively moderate levels of early life stress and parental attachment, and intermediate health outcomes.

We also found that participants with high and low exposure to socioeconomic stressors both exhibited stronger health-protective effects from residential nature exposure, as evidenced by more pronounced beneficial reductions in fasting glucose when living in greener neighborhoods, while participants with average exposure to socioeconomic

stressors exhibited weaker and non-significant associations. Notably, we observed a decay of these effects with increasing buffer sizes among participants with high exposure to socioeconomic stressors, but a consistent effect magnitude across buffer sizes among participants with low and average exposure to socioeconomic stressors.

While significant between-group differences were not found in terms of objective socioeconomic status indicators, participants with high exposure to socioeconomic stressors tended to have the lowest per capita household income and maternal education levels, whereas participants with low and average exposure to socioeconomic stressors tended to have similar levels that were relatively moderate.

[4.1] Theoretical Implications

Based on our framework, we expected that participants in lower and higher socioeconomic positions would both be more sensitive to the health-protective effects of nature exposure, relative to participants in moderate positions, but with important differences in core life patterns. Specifically, we expected that the life patterns of participants in lower socioeconomic positions would align with the high-stress "vigilant phenotype" of environmental sensitivity (the highest levels of early life stress, the lowest levels of parental support, and the worst health outcomes) while the life patterns of participants in higher socioeconomic positions would align with the low-stress "sensitive phenotype" of environ¬mental sensitivity (the lowest levels of early life stress, the highest levels of parental support, and the best health outcomes) [47–52]. In turn, this could provide some insight as to why epidemiological evidence indicates that groups in lower socioeconomic positions exhibit greater health benefits from nature exposure, even if groups in lower and higher socioeconomic positions are both particularly sensitive to these health-protective effects. In other words, the protective effects of nature exposure could be even more pronounced among groups in lower socioeconomic positions with higher early-life stressor exposure due to the heightened risk of disease in this population [59,60]. This heightened risk is attributed in part to susceptibility to stress induced by early life stress (e.g., a pro-inflammatory immune state), which is further exacerbated by high exposure to stressors across the lifespan, often as a result of compromised access to the social determinants of health [61–64].

Overall, our findings supported these expectations, where participants with high and low exposure to socioeconomic stressors both exhibited heightened sensitivity to the protective effects of nature exposure and demonstrated distinct life patterns, aligning with the vigilant and sensitive phenotypes of environmental sensitivity, respectively. By contrast, participants with average exposure to socioeconomic stressors were less sensitive to nature exposure and demonstrated relatively moderate life patterns, aligning with the buffered phenotype of environmental sensitivity. Our findings were also consistent with the hypothesized population-level distribution of these adaptive phenotypes [39,40,47,50], where the buffered profile was the most common phenotype (62% of the sample) and the sensitive profile was a less common phenotype relative to the vigilant profile (12% versus 26% of the sample), aligning with distributions observed in other studies [48,51,52]. This might also provide some insight as to why epidemiological evidence indicates that groups in lower socioeconomic positions exhibit greater health benefits from nature exposure, considering that the proportion of individuals who are environmentally sensitive in higher socioeconomic positions could be significantly less than the proportion of individuals who are environmentally sensitive in lower socioeconomic positions. In other words, the early-life conditions that induce a sensitive phenotype (low levels of early life stress and especially high levels of support) might be less common, even among groups in higher socioeconomic positions, compared to the conditions that induce a vigilant phenotype (high levels of early life stress and low support) which unfortunately, are relatively common among groups in lower socioeconomic positions [17–24].

We also found that the protective effects of nature exposure decayed with increasing buffer sizes, but only among participants with high exposure to socioeconomic stressors. This further supports our argument that while groups in lower and higher socioeconomic positions might both be particularly sensitive to the health-protective effects of nature exposure, there could be different neurobiological mechanisms underpinning these effects [16]. For instance, our recent experimental findings suggest that a pro-inflammatory immune state could be a mechanism underpinning this effect for the high-stress group [15], which might explain the distance decay effect as the stress response system could be more attuned to protective factors in the immediate environment. By contrast, we would not expect

the low-stress group to have a pro-inflammatory state, which could implicate a different neurobiological mechanism, one that is more attuned to broader, non-visual pathways.

While we did find trends indicating that participants with high exposure to socioeconomic stressors had the lowest per capita household income and maternal education levels, the lack of significant between-group differences was unexpected, and the moderate levels observed among participants with low exposure to socioeconomic stressors were surprising. One explanation for these trend-level findings is that objective socioeconomic indicators are less sensitive predictors of health outcomes relative to subjective indicators [80–83]. For instance, household income and maternal education levels do not capture family-level coping strategies (e.g., social support) or other available resources (e.g., food assistance programs) that could buffer against the effects of socioeconomic stressors. However, this might also be attributed to limited variability in the distribution of household income and maternal education levels in this sample of college students. Therefore, further research is needed to better understand these findings in samples with more variability and broader socioeconomic indexes that capture other domains of the social determinants of health.

Although our interpretations throughout this section are theoretical and in some cases speculative, they underscore the complexity of the moderation effect of life stress on health and well-being across the lifespan and emphasize the need for further research to disentangle the intricate interplay between socioeconomic status, early life stress, and sensitivity to the health-protective effects of nature exposure.

[4.2] Research Implications

Overall, our findings support the idea that individuals who are susceptible to risks of adverse environments are also more susceptible to the benefits of protective environments [39–46]. If future research corroborates our findings, this could necessitate a significant shift in how we conceptualize "susceptibility" in public health research. Traditionally, susceptibility has been primarily understood as heightened neurobiological sensitivity to the health risks of adverse environments, which could be a function of early life exposures. However, our findings suggest a far more nuanced understanding: that the same early-life

exposures that increase sensitivity to adverse environments might also increase sensitivity to protective and supportive environments. Therefore, this bidirectional responsiveness might be more accurately conceptualized as a form of total "environmental sensitivity" rather than the unidirectional distinction of "susceptibility".

Although this idea is grounded within the concept of differential susceptibility in developmental psychology, the literature supporting this idea has centered on social environments. To our knowledge, the present line of research is the first to elucidate that differential susceptibility might also extend to protective physical environments. If future research corroborates our findings, this could have widespread and far-reaching implications for public health and environmental health research, particularly in disentangling the differential impacts of physical and social environmental factors across diverse populations and socioeconomic gradients.

Expanding the concept of differential susceptibility to physical environments also raises important nuances to the question of whether differential susceptibility is "domain general" or "domain specific" [84]. For instance, while a core argument of our framework is that sensitive individuals are more responsive to both social and physical environmental exposures, it is entirely possible that some individuals are more sensitive to one domain versus another, and even on one neurobiological system versus another. Domain specificity aligns with the widely embraced idea that different neurobiological systems respond to different environmental inputs and influence different developmental outputs [50]. At the same time, a certain degree of domain generality is required to regulate developmental outputs that ultimately form different adaptive phenotypes of environmental sensitivity [50]. Efforts to better understand the domain specificity versus generality of neurobiological responses to social and physical environmental exposures represent an important area for further research.

[4.3] Public Health Implications

Our findings further support the value of considering person x environment interactions when designing and implementing public health initiatives. To date, public health

initiatives have predominantly considered the effects of socioenvironmental factors on population-level health outcomes, without considering how individual differences in environmental sensitivity modify these effects. This distinction is critical, as the majority of individuals in a population are likely to be non-sensitive [39,40,47,50], masking the effects for the smaller proportion of individuals who are especially sensitive to the risks and benefits of their environment. This has resulted in missed opportunities for targeted interventions that leverage individual differences in environmental sensitivity to more effectively maintain and improve population-level health outcomes.

Our findings also support the value of further investigation into the idea that early life stress could be one mechanism underpinning epidemiological observations that nature exposure is associated with better health among groups in lower versus higher socioeconomic positions [1–7]. If future research corroborates our findings, this might further indicate that incorporating nature exposure into disadvantaged neighborhoods could be a strategic intervention target to curb disparities in health across socioeconomic gradients. For instance, incorporating nature exposure into residential settings is often a safe, feasible, sustainable, and cost-effective intervention target [85–88] with potential as a complementary health approach that: (1) could be installed as a passive intervention, (2) is a long-term intervention, promoting generational health (3) could provide multiple co-benefits, and (4) could be implemented through public health policy [88].

In this regard, our findings suggest that urban planning initiatives should prioritize close-to-home nature-based interventions in these disadvantaged neighborhoods (e.g., public parks, green corridors, community gardens), especially considering that groups in low socioeconomic positions often experience environmental injustices, including neighborhood-level inequalities in their access to nature exposure [89]. Our findings also suggest that even small-scale increases in nature exposure might provide a protective effect in these neighborhoods, even in desert regions where the proportion of green vegetative cover is minimal relative to other regions. Therefore, it might be that the most relevant predictor of health is a change or difference in relative levels of nearby nature exposure, compared to absolute values without taking the local norm into account.

[4.4] Strengths & Limitations

To our knowledge, this is the first study to provide evidence suggesting that groups in lower socioeconomic positions are more sensitive to the health-protective effects of nature expo-sure due to increased environmental sensitivity as a function of early-life stress. While modest, these findings are supported by several strengths, including our use of a comprehensive measure to quantify exposure to socioeconomic stressors [66], the integration of well-established theories to support our claims (e.g., [34,36,47,50]), and our focus on biomarkers of glucose dysregulation, a diabetes risk factor that significantly contributes to the global burden of disease [90]. Further, our focus on glucose dysregulation allowed us to expand upon our prior findings and better understand their implications across the array of studies used to examine our framework [15,16].

At the same time, several limitations should be considered. The use of a cross-sectional observational design limited causal inference, and additional research is needed to investigate the generalizability of the present findings to other populations and other health-related outcomes. There is always a risk of over-fitting the clusters to the observed data and it is possible that other factors beyond lifetime stressor counts might have contributed to cluster membership. However, given the tight alignment of the resulting clusters with the expectations of our framework, these clusters are considered to be practical approximations of the underlying homogeneous groups. There was also a lot of missing data for the lifetime stressor counts (26%) resulting from time constraints during the study visit due to the length of the comprehensive assessment ($\geq$ 20 min). Therefore, these data are considered to be missing completely at random, and no significant differences were observed between participants with missing data and the rest of the sample.

The indicators used in our general health assessment primarily included measures of mental and emotional distress and may have underrepresented physical symptoms in the composite index. However, given the strong interconnection between mental and physical health [91], we consider these indicators to be a useful approximation of general health status. Further, as the sample was comprised of college-aged participants, men-

tal and emotional distress might have been particularly relevant indicators of general health, considering that young adult populations often experience fewer chronic physical conditions relative to older populations [79].

While the normalized difference vegetation index is a reliable measure of nature exposure [74], this measure does not distinguish between different types or account for the quality of the exposure, which could be important moderating factors. The interpretation of our findings was also based on long-term exposure to residential nature; however, without complete information on residential histories or time spent away from home, we were constrained to cumulative exposure estimates based on the current home address of each participant. Yet, considering that participants lived at their reported address for more than a decade, on average, and that spatial variation of green nature is limited in desert regions, these limitations are likely non-differential with respect to our findings. Looking forward, future studies with more representative samples, longitudinal designs to support causal modeling, and more rigorous assessments of health status, nature exposure, objective socioeconomic status, and other potential confounders will be helpful.

[4.5] Conclusion

Ultimately, future research in line with the Integrative Model of Environmental Sensitivity could lead to a better understanding of how nature-based interventions could be harnessed to reduce disparities in health among vulnerable populations. Specifically, this could further underscore the value of integrating protective physical environments into public health strategies, especially for groups in low socioeconomic positions with a history of early-life stressor exposure, who are particularly susceptible to health risks but also might stand to experience the greatest health benefits from nature exposure. As the evidence for this continues to expand, it could inform more targeted interventions that leverage individual differences in environmental sensitivity to promote health equity, providing more nuanced and socioeconomically attuned approaches to public health.

Acknowledgments

The authors thank Marcela Murga, Alan Medina, and Diana P. Flores from the Biobehavioral Research Lab at the School of Nursing, University of Texas at El Paso, for leading the NEWS data collection efforts. Special acknowledgment to John D. Spengler for his support throughout the entire project, including his mentorship and support of both Hector A. Olvera-Alvarez and Jose Guillermo Cedeno Laurent. The authors thank the Hoffman Program on Chemicals and Health for their support of both the NEWS and the development of this manuscript. The authors also thank Nicco C. Martin from the Biobehavioral Research Core at the School of Nursing, Oregon Health & Science University, for his support in developing the tables and figures used in this manuscript.

References

1. Mitchell R, Popham F. Effect of exposure to natural environment on health inequalities: an observational population study. Lancet. 2008;372: 1655–60. doi:10.1016/S0140-6736(08)61689-X

2. Mitchell RJ, Richardson EA, Shortt NK, Pearce JR. Neighborhood environments and socioeconomic inequalities in mental well-being. Am J Prev Med. 2015;49: 80–4. doi:10.1016/j.amepre.2015.01.017

3. Brown SC, Lombard J, Wang K, Byrne MM, Toro M, Plater-Zyberk E, et al. Neighborhood greenness and chronic health conditions in Medicare beneficiaries. Am J Prev Med. 2016;51: 78–89. doi:10.1016/j.amepre.2016.02.008

4. Brown SC, Perrino T, Lombard J, Wang K, Toro M, Rundek T, et al. Health disparities in the relationship of neighborhood greenness to mental health outcomes in 249,405 U.S. Medicare beneficiaries. Int J Environ Res Public Health. 2018;15: 430. doi:10.3390/ijerph15030430

5. Rigolon A, Browning MHEM, McAnirlin O, Yoon HV. Green space and health equity: a systematic review on the potential of green space to reduce health disparities. Int J Environ Res Public Health. 2021;18: 2563. doi:10.3390/ijerph18052563

6. Nicholls N, Caryl F, Olsen JR, Mitchell R. Neighbourhood natural space and the narrowing of socioeconomic inequality in years of life lost: a cross-sectional ecological analysis of the Scottish Burden of Disease. J Epidemiol Community Health. 2022;76: 976–83. doi:10.1136/jech-2022-219111

7. Wang R, Dong G, Cao M, Zhou Y, Dong G-H. Exploring “equigenesis” in the associations between green space and kidney health among middle-aged and older adults using street view data. Innov Aging. 2024;8: igad130. doi:10.1093/geroni/igad130

8. Craig JM, Prescott SL. Planning ahead: the mental health value of natural environments. Lancet Planet Health. 2017;1: e128–e129. doi:10.1016/S2542-5196(17)30068-2

9. Badland H, Pearce J. Liveable for whom? Prospects of urban liveability to address health inequities. Soc Sci Med. 2019;232: 94–105. doi:10.1016/j.socscimed.2019.05.001

10. Tost H, Reichert M, Braun U, Reinhard I, Peters R, Lautenbach S, et al. Neural correlates of individual differences in affective benefit of real-life urban green space exposure. Nat Neurosci. 2019;22: 1389–93. doi:10.1038/s41593-019-0451-y

11. Tomita A, Vandormael AM, Cuadros D, Di Minin E, Heikinheimo V, Tanser F, et al. Green environment and incident depression in South Africa: a geospatial analysis and mental health implications in a resource-limited setting. Lancet Planet Health. 2017;1: e152–e162. doi:10.1016/S2542-5196(17)30063-3

12. Moran MR, Bilal U, Dronova I, Ju Y, Gouveia N, Caiaffa WT, et al. The equigenic effect of greenness on the association between education with life expectancy and mortality in 28 large Latin American cities. Health Place. 2021;72: 102703. doi:10.1016/j.healthplace.2021.102703

13. Astell-Burt T, Feng X. Does the potential benefit of neighbourhood green space for body mass index depend upon socioeconomic circumstances and local built and transport environments? A test of the 'equigenesis' hypothesis in Australia. J Transp Health. 2017;5: S40. doi:10.1016/j.jth.2017.05.327

14. Feng X, Astell-Burt T. Do greener areas promote more equitable child health? Health Place. 2017;46: 267–73. doi:10.1016/j.healthplace.2017.05.006

15. Eisen AM, Bratman GN, Olvera-Alvarez HA. Susceptibility to stress and nature exposure: unveiling differential susceptibility to physical environments; a randomized controlled trial. PLoS One. 2024;19: e0301473. doi:10.1371/journal.pone.0301473

16. Eisen AM, Cedeño Laurent JG, Spengler JD, Slavich GM, Olvera-Alvarez HA. Susceptibility to stress and nature exposure: evidence on the positive effects of early life stress. PLoS One. 2025. Manuscript submitted for publication.

17. Evans GW, Kantrowitz E. Socioeconomic status and health: the potential role of environmental risk exposure. Annu Rev Public Health. 2002;23: 303–31. doi:10.1146/annurev.publhealth.23.112001.112349

18. Evans GW. The environment of childhood poverty. Am Psychol. 2004;59: 77–92. doi:10.1037/0003-066X.59.2.77

19. Evans GW, Gonnella C, Marcynyszyn LA, Gentile L, Salpekar N. The role of chaos in poverty and children's socioemotional adjustment. Psychol Sci. 2005;16: 560–5. doi:10.1111/j.0956-7976.2005.01575.x

20. Evans GW, Schamberg MA. Childhood poverty, chronic stress, and adult working memory. Proc Natl Acad Sci U S A. 2009;106: 6545–9. doi:10.1073/pnas.0811910106

21. Evans GW, Kim P. Multiple risk exposure as a potential explanatory mechanism for the socioeconomic status-health gradient. Ann N Y Acad Sci. 2010;1186: 174–89. doi:10.1111/j.1749-6632.2009.05336.x

22. Wells NM, Evans GW, Beavis A, Ong AD. Early childhood poverty, cumulative risk exposure, and body mass index trajectories through young adulthood. Am J Public Health. 2010;100: 2507–12. doi:10.2105/AJPH.2009.184291

23. Kim P, Evans GW, Angstadt M, Ho SS, Sripada CS, Swain JE, et al. Effects of childhood poverty and chronic stress on emotion regulatory brain function in adulthood. Proc Natl Acad Sci U S A. 2013;110: 18442–7. doi:10.1073/pnas.1308240110

24. Sripada RK, Swain JE, Evans GW, Welsh RC, Liberzon I. Childhood poverty and stress reactivity are associated with aberrant functional connectivity in default mode network. Neuropsychopharmacology. 2014;39: 2244–51. doi:10.1038/npp.2014.75

25. Hertzman C, Boyce T. How experience gets under the skin to create gradients in developmental health. Annu Rev Public Health. 2010;31: 329–47. doi:10.1146/annurev.publhealth.012809.103538

26. Hertzman C. Putting the concept of biological embedding in historical perspective. Proc Natl Acad Sci U S A. 2012;109 Suppl 2: 17160–7. doi:10.1073/pnas.1202203109

27. McEwen BS. Brain on stress: how the social environment gets under the skin. Proc Natl Acad Sci U S A. 2012;109 Suppl 2: 17180–5. doi:10.1073/pnas.1121254109

28. Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol Behav. 2012;106: 29–39. doi:10.1016/j.physbeh.2011.08.019

29. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. JAMA. 2009;301: 2252–9. doi:10.1001/jama.2009.754

30. Danese A, J Lewis S. Psychoneuroimmunology of early-life stress: the hidden wounds of childhood trauma? Neuropsychopharmacology. 2017;42: 99–114. doi:10.1038/npp.2016.198

31. Taylor SE. Mechanisms linking early life stress to adult health outcomes. Proc Natl Acad Sci U S A. 2010;107: 8507–12. doi:10.1073/pnas.1003890107

32. Agorastos A, Pervanidou P, Chrousos GP, Baker DG. Developmental trajectories of early life stress and trauma: a narrative review on neurobiological aspects beyond stress system dysregulation. Front Psychiatry. 2019;10: 118. doi:10.3389/fpsyt.2019.00118

33. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol Bull. 2011;137: 959–97. doi:10.1037/a0024768

34. Nusslock R, Miller GE. Early-life adversity and physical and emotional health across the lifespan: a neuroimmune network hypothesis. Biol Psychiatry. 2016;80: 23–32. doi:10.1016/j.biopsych.2015.05.017

35. Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, et al. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc Natl Acad Sci U S A. 2009;106: 14716–21. doi:10.1073/pnas.0902971106

36. Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull. 2014;140: 774–815. doi:10.1037/a0035302

37. Slavich GM, Sacher J. Stress, sex hormones, inflammation, and major depressive disorder: extending Social Signal Transduction Theory of Depression to account for sex differences in mood disorders. Psychopharmacology (Berl). 2019;236: 3063–79. doi:10.1007/s00213-019-05326-9

38. Slavich GM, Giletta M, Helms SW, Hastings PD, Rudolph KD, Nock MK, et al. Interpersonal life stress, inflammation, and depression in adolescence: testing Social Signal Transduction Theory of Depression. Depress Anxiety. 2020;37: 179–93. doi:10.1002/da.22987

39. Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, van Ijzendoorn MH. Differential susceptibility to the environment: an evolutionary–neurodevelopmental theory. Dev Psychopathol. 2011;23: 7–28. doi:10.1017/S0954579410000611

40. Boyce WT. Differential susceptibility of the developing brain to contextual adversity and stress. Neuropsychopharmacology. 2016;41: 142–62. doi:10.1038/npp.2015.294

41. Ellis BJ, Del Giudice M. Developmental adaptation to stress: an evolutionary perspective. Annu Rev Psychol. 2019;70: 111–39. doi:10.1146/annurev-psych-122216-011732

42. Ellis BJ, Del Giudice M. Beyond allostatic load: rethinking the role of stress in regulating human development. Dev Psychopathol. 2014;26: 1–20. doi:10.1017/S0954579413000849

43. Belsky J, Pluess M. Beyond risk, resilience, and dysregulation: phenotypic plasticity and human development. Dev Psychopathol. 2013;25: 1243–61. doi:10.1017/S095457941300059X

44. Ellis BJ, Bianchi J, Griskevicius V, Frankenhuis WE. Beyond risk and protective factors: an adaptation-based approach to resilience. Perspect Psychol Sci. 2017;12: 561–87. doi:10.1177/1745691617693054

45. Belsky J, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. Psychol Bull. 2009;135: 885–908. doi:10.1037/a0017376

46. Hartman S, Belsky J, Pluess M. Prenatal programming of environmental sensitivity. Transl Psychiatry. 2023;13: 1–10. doi:10.1038/s41398-023-02461-y

47. Boyce WT, Ellis BJ. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. Dev Psychopathol. 2005;17: 271–301. doi:10.1017/s0954579405050145

48. Ellis BJ, Essex MJ, Boyce WT. Biological sensitivity to context: II. Empirical explorations of an evolutionary-developmental theory. Dev Psychopathol. 2005;17: 303–28. doi:10.1017/s0954579405050157

49. Ellis BJ, Jackson JJ, Boyce WT. The stress response systems: universality and adaptive individual differences. Dev Rev. 2006;26: 175–212. doi:10.1016/j.dr.2006.02.004

50. Del Giudice M, Ellis BJ, Shirtcliff EA. The Adaptive Calibration Model of stress responsivity. Neurosci Biobehav Rev. 2011;35: 1562–92. doi:10.1016/j.neubiorev.2010.11.007

51. Del Giudice M, Hinnant JB, Ellis BJ, El-Sheikh M. Adaptive patterns of stress responsivity: a preliminary investigation. Dev Psychol. 2012;48: 775–90. doi:10.1037/a0026519

52. Ellis BJ, Oldehinkel AJ, Nederhof E. The Adaptive Calibration Model of stress responsivity: an empirical test in the Tracking Adolescents' Individual Lives Survey study. Dev Psychopathol. 2017;29: 1001–21. doi:10.1017/S0954579416000985

53. Hill K. Life History Theory and evolutionary anthropology. Evol Anthropol. 1993;2: 78–88. doi:10.1002/evan.1360020303

54. McNamara JM, Houston AI. State-dependent life histories. Nature. 1996;380: 215–21. doi:10.1038/380215a0

55. Roff DA. Life history evolution. Sunderland: Sinauer; 2002.

56. Penke L. Bridging the gap between modern evolutionary psychology and the study of individual differences. In: Buss DM, Hawley PH, editors. The evolution of personality and individual differences. New York: Oxford University Press; 2010.

57. Del Giudice M, Kaplan HS, Gangestad SW. Life History Theory and evolutionary psychology. In: Buss DM, editor. The handbook of evolutionary psychology. 2nd ed. Hoboken: Wiley; 2015. pp. 88–114.

58. Ellis BJ, Figueredo AJ, Brumbach BH, Schlomer GL. The impact of harsh versus unpredictable environments on the evolution and development of life history strategies. Hum Nat. 2009;20: 204–68. doi:10.1007/s12110-009-9063-7

59. Merrick MT, Ford DC, Ports KA, Guinn AS, Chen J, Klevens J, et al. Vital signs: estimated proportion of adult health problems attributable to adverse childhood experiences and implications for prevention – 25 states, 2015-2017. MMWR Morb Mortal Wkly Rep. 2019;68: 999–1005. doi:10.15585/mmwr.mm6844e1

60. Jones CM, Merrick MT, Houry DE. Identifying and preventing adverse childhood experiences: implications for clinical practice. JAMA. 2020;323: 25–6. doi:10.1001/jama.2019.18499

61. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on Community-Based Solutions to Promote Health Equity in the United States. The root causes of health inequity. In: Baciu A, Negussie Y, Geller A, Weinstein JN, editors. Communities in action: pathways to health equity. Washington DC: National Academies Press; 2017. pp. 99–184.

62. National Academies of Sciences, Engineering, and Medicine, National Academy of Medicine, Committee on the Future of Nursing 2020–2030. Social determinants of health and health equity. In: Flaubert JL, Menestrel SL, Williams DR, Wakefield MK, editors. The future of nursing 2020-2030: charting a path to achieve health equity. Washington DC: National Academies Press; 2021. pp. 38–51.

63. Kim P, Evans GW, Chen E, Miller G, Seeman T. How socioeconomic disadvantages get under the skin and into the brain to influence health development across the lifespan. In: Halfon N, Forrest CB, Lerner RM, Faustman EM, editors. Handbook of life course health development [Internet]. Cham (CH): Springer; 2018. doi:10.1007/978-3-319-47143-3_19

64. Evans GW, Chen E, Miller G, Seeman T. How poverty gets under the skin: a life course perspective. In: King RB, Maholmes V, editors. The Oxford handbook of poverty and child development. New York: Oxford University Press; 2012. pp. 13–36.

65. Olvera Alvarez HA, Provencio-Vasquez E, Slavich GM, Laurent JGC, Browning M, McKee-Lopez G, et al. Stress and health in nursing students: the Nurse Engagement and Wellness Study. Nurs Res. 2019;68: 453–63. doi:10.1097/NNR.0000000000000383

66. Slavich GM, Shields GS. Assessing lifetime stress exposure using the Stress and Adversity Inventory for Adults (Adult STRAIN): an overview and initial validation. Psychosom Med. 2018;80: 17–27. doi:10.1097/PSY.0000000000000534

67. Cazassa MJ, Oliveira M da S, Spahr CM, Shields GS, Slavich GM. The Stress and Adversity Inventory for Adults (Adult STRAIN) in Brazilian Portuguese: initial validation and links with executive function, sleep, and mental and physical health. Front Psychol. 2019;10: 3083. doi:10.3389/fpsyg.2019.03083

68. Sturmbauer SC, Shields GS, Hetzel E-L, Rohleder N, Slavich GM. The Stress and Adversity Inventory for Adults (Adult STRAIN) in German: an overview and initial validation. PLoS One. 2019;14: e0216419. doi:10.1371/journal.pone.0216419

69. Schat ACH, Kelloway EK, Desmarais S. The Physical Health Questionnaire (PHQ): construct validation of a self-report scale of somatic symptoms. J Occup Health Psychol. 2005;10: 363–81. doi:10.1037/1076-8998.10.4.363

70. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16: 606–13. doi:10.1046/j.1525-1497.2001.016009606.x

71. Kessler RC, Andrews G, Colpe LJ, Hiripi E, Mroczek DK, Normand SLT, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychol Med. 2002;32: 959–76. doi:10.1017/s0033291702006074

72. Wood A, Kroll L, Moore A, Harrington R. Properties of the mood and feelings questionnaire in adolescent psychiatric outpatients: a research note. J Child Psychol Psychiatry. 1995;36: 327–34. doi:10.1111/j.1469-7610.1995.tb01828.x

73. Armsden GC, Greenberg MT. The Inventory of Parent and Peer Attachment: individual differences and their relationship to psychological well-being in adolescence. J Youth Adolesc. 1987;16: 427–54. doi:10.1007/BF02202939

74. Rhew IC, Vander Stoep A, Kearney A, Smith NL, Dunbar MD. Validation of the normalized difference vegetation index as a measure of neighborhood greenness. Ann Epidemiol. 2011;21: 946–52. doi:10.1016/j.annepidem.2011.09.001

75. Vermote E, Justice C, Claverie M, Franch B. Preliminary analysis of the performance of the Landsat 8/OLI land surface reflectance product. Remote Sens Environ. 2016;185: 46–56. doi:10.1016/j.rse.2016.04.008

76. Bohannon RW. Comfortable and maximum walking speed of adults aged 20—79 years: reference values and determinants. Age Ageing. 1997;26: 15–9. doi:10.1093/ageing/26.1.15

77. Shemesh T, Rowley KG, Shephard M, Piers LS, O'Dea K. Agreement between laboratory results and on-site pathology testing using Bayer DCA2000+ and Cholestech LDX point-of-care methods in remote Australian Aboriginal communities. Clin Chim Acta. 2006;367: 69–76. doi:10.1016/j.cca.2005.11.014

78. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of care in diabetes-2024. Diabetes Care. 2024;47: S20–S42. doi:10.2337/dc24-S002

79. Davis JW, Chung R, Juarez DT. Prevalence of comorbid conditions with aging among patients with diabetes and cardiovascular disease. Hawaii Med J. 2011;70: 209–13.

80. Singh-Manoux A, Marmot MG, Adler NE. Does subjective social status predict health and change in health status better than objective status? Psychosom Med. 2005;67: 855–61. doi:10.1097/01.psy.0000188434.52941.a0

81. Cundiff JM, Matthews KA. Is subjective social status a unique correlate of physical health?: a meta-analysis. Health Psychol. 2017;36: 1109–25. doi:10.1037/hea0000534

82. Navarro-Carrillo G, Alonso-Ferres M, Moya M, Valor-Segura I. Socioeconomic status and psychological well-being: revisiting the role of subjective socioeconomic status. Front Psychol. 2020;11: 1303. doi:10.3389/fpsyg.2020.01303

83. Präg P. Subjective socio-economic status predicts self-rated health irrespective of objective family socio-economic background. Scand J Public Health. 2020;48: 707–14. doi:10.1177/1403494820926053

84. Belsky J, Zhang X, Sayler K. Differential susceptibility 2.0: are the same children affected by different experiences and exposures? Dev Psychopathol. 2022;34: 1025–33. doi:10.1017/S0954579420002205

85. Wolf KL, Measells MK, Grado SC, Robbins AST. Economic values of metro nature health benefits: a life course approach. Urban For Urban Green. 2015;14: 694–701. doi:10.1016/j.ufug.2015.06.009

86. Brochu P, Jimenez MP, James P, Kinney PL, Lane K. Benefits of increasing greenness on all-cause mortality in the largest metropolitan areas of the United States within the past two decades. Front Public Health. 2022;10: 841936. doi:10.3389/fpubh.2022.841936

87. Wilson J, Xiao X. The economic value of health benefits associated with urban park investment. Int J Environ Res Public Health. 2023;20: 4815. doi:10.3390/ijerph20064815

88. Frumkin H, Bratman GN, Breslow SJ, Cochran B, Kahn PH, Lawler JJ, et al. Nature contact and human health: a research agenda. Environ Health Perspect. 2017;125: 075001. doi:10.1289/EHP1663

89. Rigolon A, Browning M, Jennings V. Inequities in the quality of urban park systems: an environmental justice investigation of cities in the United States. Landsc Urban Plan. 2018;178: 156–69. doi:10.1016/j.landurbplan.2018.05.026

90. GBD 2021 Diabetes Collaborators. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2023;402: 203–34. doi:10.1016/S0140-6736(23)01301-6

91. Doherty AM, Gaughran F. The interface of physical and mental health. Soc Psychiatry Psychiatr Epidemiol. 2014;49: 673–82. doi:10.1007/s00127-014-0847-7

Supporting Information

S1 Table. Cumulative Exposure to Socioeconomic Stressors

Domain	Total Sample	High-Stress	Average Stress	Low Stress
Financial	0.68 ± 1.03	1.54 ± 1.42	0.44 ± 0.62	0.00 ± 0.00
Education	0.14 ± 0.45	0.54 ± 0.74	0.00 ± 0.00	0.00 ± 0.00
Healthcare	1.44 ± 1.74	2.82 ± 2.42	1.12 ± 1.04	0.00 ± 0.00
Housing	1.00 ± 1.92	2.67 ± 2.94	0.47 ± 0.79	0.00 ± 0.00
Social Contexts	2.99 ± 2.67	4.57 ± 2.81	2.82 ± 2.39	0.30 ± 0.46
Total Count	**6.25 ± 5.25**	**12.15 ± 5.29**	**4.85 ± 3.00**	**0.30 ± 0.46**

M ± (SD); Total Sample (n = 362); High-Stress (n = 96); Average-Stress (n = 223); Low Stress (n = 43)

S2 Table. Cumulative Exposure to Life Stressors

Domain	Total Sample	High-Stress	Average Stress	Low Stress
Early Acute	2.11 ± 2.81	3.66 ± 3.85	1.73 ± 2.15	0.63 ± 1.09
Early Chronic	2.19 ± 1.92	3.53 ± 2.21	1.95 ± 1.54	0.47 ± 0.74
Early Total	**4.30 ± 4.07**	**7.19 ± 5.25**	**3.68 ± 2.95**	**1.09 ± 1.44**
Adult Acute	5.46 ± 5.16	9.93 ± 6.31	4.16 ± 3.55	2.26 ± 2.64
Adult Chronic	4.62 ± 3.77	7.76 ± 4.06	4.06 ± 2.86	0.53 ± 0.74
Adult Total	**10.08 ± 8.19**	**17.69 ± 9.45**	**8.22 ± 5.51**	**2.79 ± 2.94**

M ± (SD); Total Sample (n = 362); High-Stress (n = 96); Average-Stress (n = 223); Low Stress (n = 43)

S3 Table. General Health Symptoms & Complaints

Domain	Total Sample	High-Stress	Average Stress	Low Stress
Physical Symptoms	22.22 ± 11.11	26.00 ± 11.04	21.90 ± 10.52	15.44 ± 10.97
Depressive Symptoms	4.70 ± 4.65	6.17 ± 5.22	4.42 ± 4.38	2.86 ± 3.71
Psychological Distress	6.64 ± 5.15	8.03 ± 5.01	6.61 ± 5.11	3.72 ± 4.46
Unpleasant Emotions	10.78 ± 11.81	15.69 ± 14.31	9.43 ± 10.36	6.66 ± 9.19
General Health Index	**24.77 ± 16.40**	**31.10 ± 17.93**	**23.83 ± 15.33**	**15.26 ± 12.39**

M ± (SD); Total Sample (n = 362); High-Stress (n = 96); Average-Stress (n = 223); Low Stress (n = 43)

S4 Table. Parental Attachment & Relationship Qualities

Domain	Total Sample	High-Stress	Average Stress	Low Stress
Maternal Attachment	99.56 ± 19.61	93.23 ± 21.66	100.71 ± 18.60	107.77 ± 15.69
Maternal Trust	41.78 ± 7.76	39.11 ± 9.07	42.38 ± 7.17	44.63 ± 5.70
Maternal Communication	34.17 ± 8.63	31.85 ± 9.15	34.44 ± 8.44	37.93 ± 6.85
Maternal Alienation	12.39 ± 4.91	13.74 ± 5.17	12.11 ± 4.50	10.79 ± 5.70
Paternal Attachment	88.29 ± 24.38	81.31 ± 25.96	88.71 ± 23.26	101.70 ± 20.60
Paternal Trust	38.12 ± 10.18	35.07 ± 11.28	38.46 ± 9.77	43.14 ± 7.16
Paternal Communication	27.88 ± 10.42	25.64 ± 9.75	27.66 ± 10.47	34.02 ± 9.41
Paternal Alienation	13.71 ± 6.24	15.40 ± 6.48	13.41 ± 5.91	11.47 ± 6.54
Parental Attachment Index	**75.14 ± 14.30**	**69.82 ± 15.05**	**75.77 ± 13.32**	**83.79 ± 12.79**

M ± (SD); Total Sample (n = 362); High-Stress (n = 96); Average-Stress (n = 223); Low Stress (n = 43)

S5 Table. Objective Socioeconomic Status Across the Lifespan

Domain	Total Sample	High-Stress	Average Stress	Low Stress
Household Income[1]	15.14 ± 14.50	14.32 ± 11.28	15.44 ± 15.39	15.48 ± 16.70
Maternal Education	3.63 ± 1.27	3.48 ± 1.29	3.69 ± 1.26	3.67 ± 1.29
Objective SES Index	**41.22 ± 14.38**	**39.71 ± 13.74**	**41.78 ± 14.30**	**41.83 ± 16.47**

M ± (SD); Total Sample (n = 362); High-Stress (n = 96); Average-Stress (n = 223); Low Stress (n = 43); [1]$K

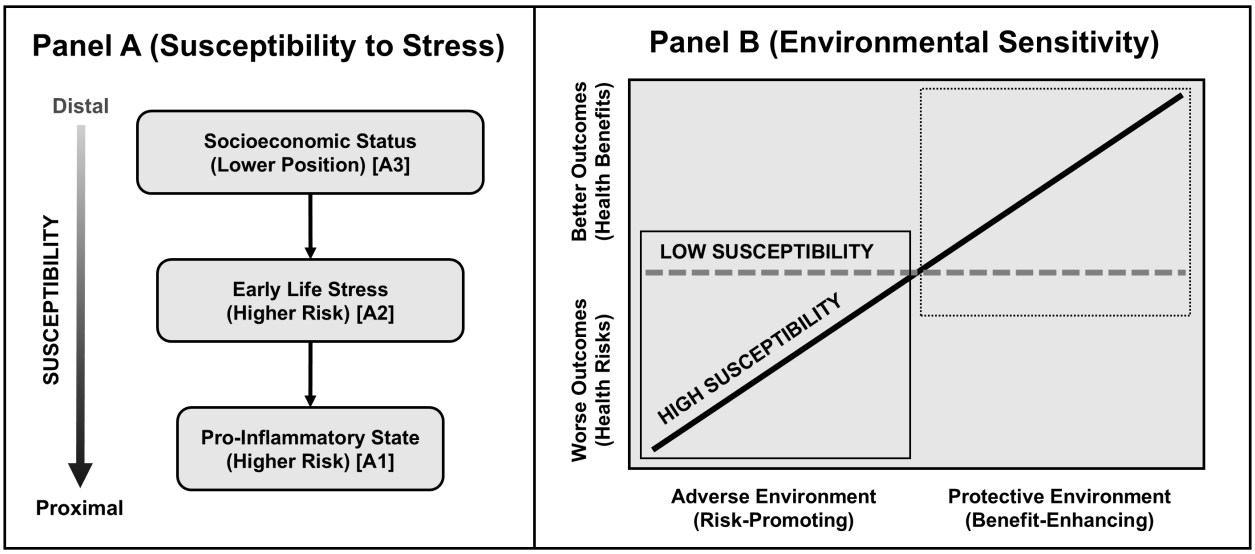
Chapter Five

The objective of this program of research was to uncover potential causal mechanisms underpinning emerging epidemiological evidence that groups in low socioeconomic positions exhibit more pronounced health benefits from nature exposure (contact with natural green spaces) compared to more privileged groups [1–7]. To guide this inquiry, we developed the Integrative Model of Environmental Sensitivity, a theoretical framework for synthesizing knowledge from disparate literatures to better understand how individual differences in environmental sensitivity could be leveraged to reduce disparities in health across socioeconomic gradients (Fig 1 [8–10]). Central to this framework are two overarching ideas: (susceptibility to stress) groups in lower socioeconomic positions often face higher exposure to persistent psychosocial stressors in early life, which in turn could induce a lifelong susceptibility to stress through various neurobiological pathways; (environmental sensitivity) susceptibility to stress, traditionally understood as heightened reactivity to stressors, could also encompass enhanced responsivity to health-protective exposures, inducing greater risks in adverse environments, but also greater benefits in protective environments. Put together, these ideas provide a plausible mechanistic explanation as to why groups in lower versus higher socioeconomic positions could derive greater health benefits from nature exposure.

[1] Integration of Evidence

Based on our framework, we operationalized environmental sensitivity across three levels of analysis: a pro-inflammatory immune state as a neurobiological correlate of susceptibility to stress; early life stress as a causal antecedent of susceptibility to stress; and socioeconomic status as the broader context through which social and health relationships are shaped, serving as an upstream facilitator of susceptibility to stress (Fig 1 [8–10]). Our specific aims were addressed in a three-study series with a focus on each level of analysis, using a bottom-up approach to provide a systematic examination of environmental sensitivity to the health-protective effects of nature exposure, progressively building from neurobiological mechanisms to broader societal contexts.

Figure 1. Theoretical Framework & Specific Aims



Susceptibility to Stress: groups in low socioeconomic positions, compared to more privileged groups, often face higher exposure to persistent psychosocial stressors in early life, which can induce a lifelong susceptibility to stress through various neurobiological pathways, including a pro-inflammatory immune state; **Environmental Sensitivity**: susceptibility to stress, traditionally understood as a heightened reactivity to stressors, could also encompass enhanced responsivity to health-protective exposures, inducing greater risks in adverse environments, but also greater benefits in protective environments.

[1.1] Level One: Pro-Inflammatory Phenotype (A1)

The aim of the first study was to establish experimental evidence that a pro-inflammatory immune state could be associated with greater autonomic recovery from an acute psychosocial stressor in a nature versus office environment. To achieve this, we used a randomized controlled trial to examine differences in autonomic recovery (increased parasympathetic activation and reduced sympathetic activation) caused by a virtual reality exposure to either a nature condition (a public park) or an office condition (the same room as the experiment, but in virtual reality) following exposure to a validated laboratory stressor (Trier Social Stress Test [11]) among 64 healthy college-aged males. Based on our framework, susceptibility to stress was indicated as a pro-inflammatory state (increased inflammatory reactivity and glucocorticoid resistance in response to an in vitro bacterial challenge) and secondarily as exposure to early-life stressors (Adverse Childhood Experience Questionnaire [12]) and subjective social status (MacArthur Scale of Subjective Social Status [13]). In this experiment, we observed that participants with a pro-inflammatory

state exhibited greater autonomic recovery from the acute stressor in the nature versus office condition, relative to less susceptible participants. However, even though a pro-inflammatory state is a well-established developmental alteration induced by early life stress [14–17], no differences in recovery were found among participants with higher versus lower exposure to early-life stressors or among participants in lower versus higher socioeconomic positions (see Chapter Two).

The null findings for early life stress and socioeconomic status were unexpected and might have been attributed in part to the measures used and limited variability in this sample of college-aged males. For instance, our measure of early-life stressor exposure might not have been comprehensive enough to detect differences in autonomic recovery, as it does not account for the subjective severity, frequency, timing, or duration of childhood stressors [18–20]. However, it is also possible that a pro-inflammatory state could be a more sensitive indicator of environmental sensitivity (proximal: direct pathway between the indicator and outcome) relative to self-report assessments of early life stress and socioeconomic status (distal: indirect pathway between the indicator and outcome that in turn, increases the risk of unmeasured confounders). For instance, not all adults with high exposure to early-life stressors develop susceptibility to stress due to protective factors and counteracting exposures (e.g., parental attachment, social support [21,22]).

[1.2] Level Two: Early Life Stress (A2)

The aim of the second study was to re-examine whether early life stress could be associated with greater health benefits from nature exposure, using a larger and more diverse sample (i.e., Nurse Engagement and Wellness Study [23]) and a more comprehensive measure of early-life stressor exposure (i.e., Stress and Adversity Inventory for Adults [24]). To achieve this, we used an observational paradigm to evaluate the effect of residential nature exposure (quantified using the normalized difference vegetation index across different radial buffers centered on the residential address of each participant) on glucose dysregulation (elevated levels of fasting blood glucose), with a specific focus on the moderation effect of early life stress. We observed that relative to the sample average,

participants with higher levels of early life stress exhibited more pronounced beneficial reductions in fasting glucose levels when living in greener neighborhoods. However, we also observed that relative to the sample average, participants with lower levels of early life stress also exhibited more pronounced beneficial reductions in fasting glucose levels when living in greener neighborhoods. By contrast, participants with relatively average levels of early life stress exhibited the smallest changes in fasting glucose levels when living in greener neighborhoods (see Chapter Three).

When interpreting the findings from both our experimental and observational studies, this evidence collectively supports the idea that the association between early life stress and environmental sensitivity might not be linear, but a more complex u-shaped association that might induce different adaptive phenotypes of environmental sensitivity along the continuum of early life stress, a concept that is well-grounded within evolutionary-developmental perspectives (Biological Sensitivity to Context Theory [25,26]; Adaptive Calibration Model [27,28]). While integrating these perspectives into our framework implies that groups with lower and higher exposure to early-life stressors are both particularly sensitive to the health-protective effects of nature exposure, these protective effects could be even more pronounced among groups in lower socioeconomic positions with higher early-life stressor exposure, given the heightened risk of disease in this population [29,30]. This heightened risk is attributed in part to susceptibility to stress induced by early life stress (e.g., a pro-inflammatory state), which is further exacerbated by high exposure to stressors across the lifespan, often as a result of compromised access to the social determinants of health [31–34].

[1.3] Level Three: Socioeconomic Status (A3)

The aim of the third study was to bridge the evidence gaps between socioeconomic status, early life stress, and environmental sensitivity to nature exposure within our framework, through the lens of these evolutionary-developmental perspectives (Biological Sensitivity to Context Theory [25,26]; Adaptive Calibration Model [27,28]). To achieve this, we re-analyzed the data from our second study using a latent cluster analysis based on five

lifetime stressor counts of life domains associated with the social determinants of health (exposures related to finances, education, healthcare, housing, and social contexts). We expected that participants in lower socioeconomic positions would exhibit the highest exposure to early-life stressors, the lowest levels of parental support, and the worst health outcomes, while participants in higher socioeconomic positions would exhibit the lowest exposure to early-life stressors, the highest levels of parental support, and the best health outcomes. By contrast, participants in moderate positions would exhibit relatively moderate levels across these variables. Based on our prior findings, we also expected that participants in lower and higher socioeconomic positions would both be more sensitive to the protective effects of nature exposure, as compared to participants in moderate positions (see Chapter Four).

Notably, this re-analysis expands the findings of our second study in several important ways. First, even though it is well-established that early-life stressor exposure increases the risk of negative outcomes across the lifespan [35–38], we were unable to demonstrate this without measures of general health. Second, the evolutionary-developmental perspectives emphasize that it is not just early life stress, but the ratio of early life stress to support that signals the development of different adaptive phenotypes [25–28]; while it is reasonable to assume that high exposure to early-life stressors corresponds to low levels of support, we were unable to demonstrate this without measures of parental support and relationship qualities. Third, although it is well-established that groups in lower socioeconomic positions face higher exposure to early-life stressors [39–42], we were unable to demonstrate this without the latent cluster analysis. Demonstrating these associations, while also replicating the moderation effect of early life stress on the nature-glucose association observed in our second study would provide a comprehensive demonstration of our framework.

Overall, our findings were supportive of these expectations. The latent cluster analysis identified three groups of high, average, and low exposure to socioeconomic stressors, with the high-stress group (26% of the sample) reporting the highest exposure to early-life stressors, the lowest levels of parental support, and the worst general health outcomes, and the low-stress group (12% of the sample) reporting the lowest exposure to early-life

stressors, the highest levels of parental support, and the best general health outcomes. By contrast, the average-stress group (62% of the sample) reported relatively moderate levels across these variables. We also found that our results from the second study were replicated, where participants with high and low exposure to socioeconomic stressors both exhibited stronger protective effects from nature exposure, while participants with average exposure to socioeconomic stressors exhibited weaker and non-significant associations.

In turn, these findings provide seminal insights into our prior studies. First, they emphasize the predictive power of our framework, especially following the integration of the evolutionary-developmental perspectives [25–28]. Second, they highlight that even if groups in lower and higher socioeconomic positions are both particularly sensitive to the health-protective effects of nature exposure, these protective effects could be even more pronounced for groups in lower socioeconomic positions with higher early-life stressor exposure, given the heightened risk of disease in this population [29,30]. Third, they outline that the proportion of individuals who are environmentally sensitive in higher socioeconomic positions could be significantly less than the proportion of individuals who are environmentally sensitive in lower socioeconomic positions. Collectively, these findings provide crucial insights as to why emerging epidemiological evidence indicates that groups in low socioeconomic positions exhibit greater health benefits from nature exposure, relative to their more privileged counterparts, and underscore important implications for research and public health.

[2] Research & Public Health Implications

Overall, the evidence attained from this program of research supports the idea that increased environmental sensitivity induced by early life stress could be at least one plausible mechanism underpinning epidemiological evidence that groups in low socioeconomic positions exhibit more pronounced health benefits from nature exposure [1–7]. This provides a causal claim to strengthen the argument that increasing access to nature for disadvantaged communities could be a strategic target to reduce health disparities [43–46]. Importantly, nature-based interventions offer a promising approach;

they are passive, promoting health without requiring behavioral change; they are sustainable, often with low maintenance costs, and they can be implemented through public health policy for lasting impacts [47–50].

If future research corroborates our findings, this could have widespread and far-reaching implications for public health and environmental health research, particularly in elucidating the differential impacts of physical and social environmental factors across diverse populations and socioeconomic gradients. Overall, our findings emphasize the importance of considering "person x environment" interactions when designing and implementing public health initiatives. To date, public health initiatives have predominantly considered the effects of socioenvironmental factors on population-level health outcomes, without considering how individual differences in environmental sensitivity modify these effects. This distinction is critical, as the majority of individuals in a population are likely to be non-sensitive [25,27,51,52], masking the effects for the smaller proportion of individuals who are especially sensitive to the risks and benefits of their environment. This has resulted in missed opportunities for targeted interventions that leverage individual differences in environmental sensitivity to more effectively maintain and improve population-level health outcomes.

When considering our findings in the context of our framework, this could necessitate a significant shift in how we conceptualize "susceptibility" in public health research. Traditionally, susceptibility has been primarily understood as heightened neurobiological sensitivity to the health risks of adverse environments, which could be a function of early-life exposures. However, our findings suggest a more nuanced understanding: that the same early-life exposures that increase sensitivity to adverse environments might also increase sensitivity to protective and supportive environments. Therefore, this bidirectional responsiveness might be more accurately conceptualized as "total environmental sensitivity" rather than the unidirectional distinction of "susceptibility". This reconceptualization ultimately proposes that individuals identified in various investigations as being more reactive to adverse conditions might also be more responsive to protective and supportive conditions. In other words, susceptible individuals may have a wider range of reaction

norms, covering the total gamut of environmental exposures, whereas non-susceptible individuals may have a much narrower range of reaction norms, responding less to adverse and protective environmental exposures. Therefore, certain aspects of what is currently recognized as "susceptibility" from an environmental health perspective might in some cases be better framed as increased sensitivity to both adverse and protective environments.

While this idea is grounded within the concept of differential susceptibility in developmental psychology [51–54], the evidence supporting this idea has prominently centered on social environments. To our knowledge, the evidence obtained from this program of research is the first to elucidate that differential susceptibility might also extend to protective physical environments. This could provide opportunities for more effective interventions through altering and improving physical environments with the intention of promoting positive well-being outcomes, which has been less of a focus in public health research. In this regard, our findings also suggest that urban planning initiatives should prioritize close-to-home nature-based interventions in disadvantaged communities (e.g., public parks, green corridors, neighborhood gardens), especially considering that groups in low socioeconomic positions often experience environmental injustices, including neighborhood-level inequities in their access to nature exposure [55]. Our virtual reality findings also provide implications for simulated nature-based approaches that might be remarkably simple but effective, including windows with nature views, greening walls, and indoor plants [56–58]. Just imagine if by orienting beds toward windows in a community clinic, we could improve the recovery time of patients; if by greening walls, we could reduce the burden of air pollution for families living near highways; and if by redesigning the landscapes of public housing communities, we could reduce disparities in health between groups in lower versus higher socioeconomic positions.

When considering our findings in the context of our framework, this also could necessitate a significant shift in how we conceptualize "resilience" in public health research. Traditionally, while some people are regarded as being especially susceptible to the risks of adverse environments, due to their neurobiological predispositions, other people lacking these predispositions who do not succumb to these risks are considered to be resilient. Through

a differential susceptibility lens "resilience" is something of a misnomer, as people who are more resilient to the risks of adverse environments are also more (resilient?) to the benefits of protective environments [51–54]. Unfortunately, many studies informed by the traditional understanding of resilience are not well-positioned to examine differential susceptibility to the total environment, as protective environments in these contexts often just reflect the absence of adversity, and beneficial outcomes often just reflect the absence of disease or dysfunction [59]. The result has been an imbalanced approach to research, yielding significantly more knowledge about dysfunction rather than adaptive function, making it challenging to attain a full account of the subject matter. Rather, our findings support an alternative "adaptation-based" approach to resilience, one that aims to cultivate environments that leverage the unique strengths of susceptible individuals to promote positive well-being outcomes [60].

[3] Future Directions

While the evidence obtained from this program of research is promising, additional research is needed to investigate the generalizability of the present findings to other populations and other outcomes. Studies with longitudinal designs are also needed to support causal modeling, especially considering that proposed theoretical mediation is central to our framework (e.g., early life stress mediates the association between child poverty and susceptibility to stress, which in turn could moderate the effect of adverse and protective environments on adult health outcomes). While we controlled for a range of relevant covariates to eliminate the most plausible alternative explanations and confounders (e.g., childhood socioeconomic status, adult-life stressor exposure, physical activity and weight loss), systematic assessments of other potential confounders will be helpful.

Even though data obtained from geographical information systems are reliable measures of nature exposure [61], these measures do not distinguish between different types or account for the quality of the exposure, which could be important moderating factors. Using more innovative approaches such as global position systems and smartphone tracking [62], wearable sensors and watches [63], and machine learning algorithms and street-view

imagery [64] would be helpful to better link nature exposure to personal experiences (e.g., level of engagement, duration of the exposure, engaging with one exposure over another [65]). In this regard, it is also important for future researchers to consider other relevant exposures, such as the quality of the neighborhood (e.g., housing conditions, crime rates, access to amenities, walkability, cleanliness, air quality, aesthetics, noise and traffic) which could have interactive effects with nature exposure [66–69].

Regarding stress assessments, it is crucial for researchers to consider the strengths and weaknesses of the measures used. Stress is a complex construct that represents a neurobiological response to adverse socioenvironmental exposures "stressors", which differ in their subjective severity, frequency, timing, and duration, can occur in different life domains (e.g., relationships, finances) and have various social-psychological characteristics (e.g., interpersonal loss, physical danger) [20]. While simple measures such as the Adverse Childhood Experience Questionnaire [12] seem to be effective in differentiating between pathogenic and non-pathogenic adaptations to stressors [29,30], they also treat all stressors as equal, making it unclear what is actually being measured. To better understand stress and health relationships, a precursor for environmental sensitivity research, we encourage researchers to use more sophisticated interview-based measures that do account for these complexities, such as the Stress and Adversity Inventory for Adults (STRAIN [24]).

In terms of statistical power, it is important for researchers to consider the distinction between proximal and distal indicators of environmental sensitivity. Proximal indicators (e.g., neurobiological correlates of susceptibility to stress) share a direct pathway between the indicator and outcome, increasing statistical power and reducing the risk of unmeasured confounders [8]. By contrast, distal indicators (e.g., early life stress, socioeconomic status) share a more indirect pathway between the indicator and outcome, which can reduce statistical power and increase the risk of unmeasured confounders. It is also important to recognize that the use of proximal versus distal indicators corresponds to the pathways being tested. In other words, a pro-inflammatory immune state could be a measure of environmental sensitivity specific to groups with higher exposure to early-life stressors

[14,15], while a precise measure of early-life stressor exposure could capture multiple phenotypes of environmental sensitivity along the continuum of early life stress [27,28].

Another important consideration for future research relates to the distribution of early life stress within a sample, especially considering that the association between early life stress and environmental sensitivity is likely to be non-linear [25–28]. For instance, if most participants in a sample report low to average levels of early life stress, relative to the population, this might lead to the conclusion that early life stress decreases environmental sensitivity; and by contrast, if most participants report average to high levels of early life stress, this might lead to the conclusion that early life stress increases environmental sensitivity [70]. A better understanding of this non-linear association could be fundamental for resolving discrepancies in the biological embedding literature about whether early life stress induces hyper-reactivity or hypo-reactivity to stressors (for discrepancies related to cortisol reactivity, see Hosseini-Kamkar et al. 2021 [71]).

Although we have used typological language to describe environmentally sensitive versus non-sensitive individuals, this is just a linguistic convenience, and it would be a mistake to infer that environmental sensitivity is more categorical than continuous (e.g., the misassumption that non-sensitive individuals are completely immune to their environmental influences; instead these individuals might simply need intensification of the intervention to experience results similar to those achieved among environmentally sensitive individuals [51]). Rather, we argue that it makes the most sense to conceptualize environmental sensitivity along a continuous dimension, with specific thresholds that represent the theoretical boundaries of homogeneous response patterns; thresholds which themselves may vary considerably across individuals, groups, and populations. To support research in this area, we encourage the use of statistical approaches such as Johnson-Neyman intervals [72] which retain the moderator on a continuous scale to identify thresholds of significant versus non-significant effects (e.g., sensitive versus non-sensitive individuals).

Expanding the concept of differential susceptibility to physical environments also raises important nuances to the question of whether differential susceptibility is “domain general” or “domain specific” [73]. For instance, while a core argument of our framework

is that sensitive individuals are more responsive to both social and physical environmental exposures, it is entirely possible that some individuals are more sensitive to one domain versus another, and even on one neurobiological system versus another. Domain specificity aligns with the widely embraced idea that different neurobiological systems respond to different environmental inputs and influence different developmental outputs [27]. At the same time, a certain degree of domain generality is required to regulate adaptive developmental outputs that ultimately form different responsivity patterns [27]. This suggests that domain specificity could be more common at a granular level (e.g., the individual components within a neurobiological system), while domain generality could be more common at a global level (e.g., the hierarchical organization of the stress response system: encompassing the autonomic, neuroendocrine, neuroimmune, cardiometabolic systems [74]). Efforts to better understand the domain specificity versus generality of neurobiological responses to social and physical environmental exposures represent an important area for further research.

Future researchers are also encouraged to measure the complete range of environmental exposures, ranging from truly adverse (not just the absence of protective) to truly protective (not just the absence of adverse) [59]. While the focus of the current program of research was specifically on protective physical environments (ranging from protective [high levels of nature exposure] to neutral [the absence of nature exposure]), demonstrating that individuals who are more sensitive to the protective effects of nature exposure are also more sensitive to the harmful effects of adverse physical exposures would have provided an even stronger claim that differential susceptibility also extends to physical environments. To advance this arm of our framework, the principal investigator and co-investigators of this program of research are currently working on additional studies, using data from the same participants, to demonstrate that early life stress also increases sensitivity to the adverse effects of traffic-related air pollution (e.g., Olvera-Alvarez et al., 2025 [75]). The culmination of this work will be a framework paper, highlighting both experimental and observational evidence that individuals with high exposure to early-life stressors are more sensitive to both the health benefits of nature exposure and the health risks of air pollution.

[4] Ethical Disclaimers

Even though this program of research focuses on the positive effects of early life stress, we are not arguing that it is a good thing for children to grow up in poverty or under stressful conditions. Harsh environments often harm or even kill children, and it is well-established that early life stress is associated with the leading causes of morbidity and mortality among adult populations [29,30]. Rather, we are arguing that the detrimental effects of childhood adversity are very real, but this is only half the story, and more researchers should be asking: "how can we leverage the unique strengths and abilities that develop in response to adverse environments?"

We are also not arguing that individuals in lower socioeconomic positions are bad parents who treat their children harshly. Rather, the burden of high early-life stressor exposure among these groups is primarily characterized by household dysfunctions that are beyond the control of the family (e.g., poor housing conditions, neighborhood deprivation, frequent relocations, food insecurities, restrictive work schedules [31,32]). In other words, this burden is not a "family issue" but the result of social inequities that should not be considered as unmodifiable facts of life.

In contrast to the dominant perspective in the resilience literature, we are also not arguing that the solution to adversity is bolstering an individual's resilience. This rhetoric occupies the dangerous ground of "fixing" what is "wrong" with susceptible people, when in reality, their neurobiology is appropriately responding to adversity through processes maintained during our natural selective history [76] (just as someone living in a mold-infested building would develop coughing and sneezing to expel harmful spores). Instead, we argue that rather than "blaming" the susceptible person, intervention efforts should focus on improving environmental conditions.

This program of research also has important implications for researchers in identifying subsets of a population who would be the most responsive to interventions, and for clinicians and policymakers in obtaining more realistic estimates of the effectiveness of these interventions. As stated before, this could lead to the development of more targeted

interventions, and in some cases, candidates may be selected using environmental sensitivity screens [51]. However, we are not arguing that interventions should be exclusively targeted toward sensitive individuals. Rather, we need to ensure a baseline standard of care for everyone, and use these screens to tailor interventions in a way that leverages individual differences in environmental sensitivity to promote health equity.

[5] Relevance to Nursing

Environmental factors have long been recognized as integral to health in nursing, dating back to Florence Nightingale's impetus on creating healing environments for the patient's mind, body, and spirit [77]. In fact, Nightingale was a pioneer in linking the physical environment to the health and well-being of her patients and her legacy provides a strong foundation for modern nurses to lead the design of healthcare in a way that harnesses the healing power of the total environment [78]. From fresh air to sunlight, integrating natural elements into healthcare settings is a maturing field of fundamental importance to nurses. While there is an extensive field of literature on the health benefits of natural environments, dating back to the earliest civilizations [79], the contemporary renaissance of this field was a study led by nurses [56] who found that patients recovering from surgery had shorter postoperative hospital stays, better vital signs, and fewer symptoms when assigned to rooms with window views of nature versus urban buildings.

Importantly, the Integrative Model of Environmental Sensitivity incorporates and extends this perspective, highlighting that the healing power of the total environment could be harnessed to reduce disparities in health across socioeconomic gradients [8–10]. This aligns with the overarching principles of nursing practice, to embrace holistic and person-centered approaches that provide all patients with equitable opportunities to achieve their full potential for health and well-being [80]. For instance, with a better understanding of individual differences in environmental sensitivity, nurse practitioners could help patients develop personalized care plans that harness the healing power of the environment, leveraging the unique strengths and abilities that develop in response to childhood adversity [60]. This reflects a nexus between patient-centered care and a next generation of trauma-

informed care, which recognizes that patients exposed to childhood adversity could be more sensitive to the risk-promoting and benefit-enhancing aspects of their environment.

[6] Summary, Implications, & Conclusion

The overarching objective of this program of research was to uncover potential causal mechanisms underpinning epidemiological evidence that groups in low socioeconomic positions exhibit more pronounced health benefits from nature exposure compared to more privileged groups. Establishing these mechanisms could ultimately reveal more effective strategies for addressing health disparities, as nature-based interventions offer a promising approach: they are passive, promoting health without requiring behavioral change; they are sustainable, often with low maintenance costs; and they can be implemented through public health policy to create lasting impacts.

To guide this inquiry, we developed the Integrative Model of Environmental Sensitivity, a theoretical framework for synthesizing knowledge from disparate literatures to better understand how individual differences in environmental sensitivity could be leveraged to reduce disparities in health across socioeconomic gradients. Central to this framework are two overarching ideas: (susceptibility to stress) groups in lower socioeconomic positions often face higher exposure to persistent psychosocial stressors in early life, inducing a lifelong susceptibility to stress through various neurobiological pathways; (environmental sensitivity) susceptibility to stress, traditionally understood as increased reactivity to stressors, could also encompass enhanced responsivity to health-protective exposures, inducing greater risks in adverse environments, but also greater benefits in protective environments.

Based on our framework, we operationalized environmental sensitivity across three levels of analysis: a pro-inflammatory immune state as a neurobiological correlate of susceptibility to stress; early life stress as a causal antecedent of susceptibility to stress; and socioeconomic status as the broader context through which social and health relationships are shaped, serving as an upstream facilitator of susceptibility to stress. In the first study, we found that participants with a pro-inflammatory immune state exhibited greater auto-

nomic recovery from an acute stressor in a nature versus office environment, relative to less susceptible participants. This evidence broadly elucidates a physiological mechanism through which groups with high exposure to early-life stressors could derive greater health benefits from nature exposure. In the second study, we found that participants with higher exposure to early-life stressors exhibited more pronounced cardiometabolic benefits when living in greener neighborhoods, as compared to participants with relatively moderate exposures. This evidence reinforces the role of early life stress as a facilitator of the mechanistic pathway through which groups in low socioeconomic positions could derive greater health benefits from nature exposure. In the third study, we found that participants in lower socioeconomic positions reported the highest exposure to early-life stressors and also exhibited more pronounced cardiometabolic benefits when living in greener neighborhoods, as compared to participants in relatively moderate positions. This evidence reinforces the role of low socioeconomic position as an upstream facilitator of early life stress and in turn, the physiological mechanism that could promote greater health benefits from nature exposure.

Overall, our findings contribute to growing evidence and further support the idea that increasing access to nature within disadvantaged neighborhoods could be an effective strategy to reduce disparities in health across socioeconomic gradients. Specifically, our findings further underscore the importance of integrating protective physical environments into public health strategies, especially for groups with high exposure to early-life stressors, who are particularly susceptible to health risks but also might stand to experience the greatest health benefits from nature exposure. In turn, future research in line with the Integrative Model of Environmental Sensitivity could lead to a better understanding of how the total environment could be harnessed to more effectively reduce disparities in health among vulnerable populations. As the evidence supporting this framework continues to expand, it could inform more targeted interventions that leverage individual differences in environmental sensitivity to promote health equity, ultimately providing more nuanced, strategic, and socioeconomically attuned approaches to public health.

References

1. Mitchell R, Popham F. Effect of exposure to natural environment on health inequalities: an observational population study. Lancet. 2008;372: 1655–60. doi:10.1016/S0140-6736(08)61689-X

2. Mitchell RJ, Richardson EA, Shortt NK, Pearce JR. Neighborhood environments and socioeconomic inequalities in mental well-being. Am J Prev Med. 2015;49: 80–4. doi:10.1016/j.amepre.2015.01.017

3. Brown SC, Lombard J, Wang K, Byrne MM, Toro M, Plater-Zyberk E, et al. Neighborhood greenness and chronic health conditions in Medicare beneficiaries. Am J Prev Med. 2016;51: 78–89. doi:10.1016/j.amepre.2016.02.008

4. Brown SC, Perrino T, Lombard J, Wang K, Toro M, Rundek T, et al. Health disparities in the relationship of neighborhood greenness to mental health outcomes in 249,405 U.S. Medicare beneficiaries. Int J Environ Res Public Health. 2018;15: 430. doi:10.3390/ijerph15030430

5. Rigolon A, Browning MHEM, McAnirlin O, Yoon HV. Green space and health equity: a systematic review on the potential of green space to reduce health disparities. Int J Environ Res Public Health. 2021;18: 2563. doi:10.3390/ijerph18052563

6. Nicholls N, Caryl F, Olsen JR, Mitchell R. Neighbourhood natural space and the narrowing of socioeconomic inequality in years of life lost: a cross-sectional ecological analysis of the Scottish Burden of Disease. J Epidemiol Community Health. 2022;76: 976–83. doi:10.1136/jech-2022-219111

7. Wang R, Dong G, Cao M, Zhou Y, Dong G-H. Exploring “equigenesis” in the associations between green space and kidney health among middle-aged and older adults using street view data. Innov Aging. 2024;8: igad130. doi:10.1093/geroni/igad130

8. Eisen AM, Bratman GN, Olvera-Alvarez HA. Susceptibility to stress and nature exposure: unveiling differential susceptibility to physical environments; a randomized controlled trial. PLoS One. 2024;19: e0301473. doi:10.1371/journal.pone.0301473

9. Eisen AM, Cedeño Laurent JG, Spengler JD, Slavich GM, Olvera-Alvarez HA. Susceptibility to stress and nature exposure: evidence on the positive effects of early life stress. PLoS One. 2025. Manuscript submitted for publication.

10. Eisen AM, Cedeño Laurent JG, Spengler JD, Slavich GM, Olvera-Alvarez HA. Susceptibility to stress and nature exposure: demonstrating the Integrative Model of Environmental Sensitivity. PLoS One. 2025. Manuscript submitted for publication.

11. Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test'–a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology. 1993;28: 76–81. doi:10.1159/000119004

12. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998;14: 245–58. doi:10.1016/s0749-3797(98)00017-8

13. Adler NE, Epel ES, Castellazzo G, Ickovics JR. Relationship of subjective and objective social status with psychological and physiological functioning: preliminary data in healthy white women. Health Psychol. 2000;19: 586–92. doi:10.1037//0278-6133.19.6.586

14. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol Bull. 2011;137: 959–97. doi:10.1037/a0024768

15. Nusslock R, Miller GE. Early-life adversity and physical and emotional health across the lifespan: a neuroimmune network hypothesis. Biol Psychiatry. 2016;80: 23–32. doi:10.1016/j.biopsych.2015.05.017

16. Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, et al. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. Proc Natl Acad Sci U S A. 2009;106: 14716–21. doi:10.1073/pnas.0902971106

17. Miller GE, Chen E. Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. Psychol Sci. 2010;21: 848–56. doi:10.1177/0956797610370161

18. McEwen CA, Gregerson SF. A critical assessment of the Adverse Childhood Experiences Study at 20 years. Am J Prev Med. 2019;56: 790–4. doi:10.1016/j.amepre.2018.10.016

19. Anda RF, Porter LE, Brown DW. Inside the adverse childhood experience score: strengths, limitations, and misapplications. Am J Prev Med. 2020;59: 293–5. doi:10.1016/j.amepre.2020.01.009

20. Slavich GM. Stressnology: the primitive (and problematic) study of life stress exposure and pressing need for better measurement. Brain Behav Immun. 2019;75: 3–5. doi:10.1016/j.bbi.2018.08.011

21. Crouch E, Radcliff E, Strompolis M, Srivastav A. Safe, stable, and nurtured: protective factors against poor physical and mental health outcomes following exposure to adverse childhood experiences (ACEs). J Child Adolesc Trauma. 2019;12: 165–73. doi:10.1007/s40653-018-0217-9

22. Brinker J, Cheruvu VK. Social and emotional support as a protective factor against current depression among individuals with adverse childhood experiences. Prev Med Rep. 2017;5: 127–33. doi:10.1016/j.pmedr.2016.11.018

23. Olvera Alvarez HA, Provencio-Vasquez E, Slavich GM, Laurent JGC, Browning M, McKee-Lopez G, et al. Stress and health in nursing students: the Nurse Engagement and Wellness Study. Nurs Res. 2019;68: 453–63. doi:10.1097/NNR.0000000000000383

24. Slavich GM, Shields GS. Assessing lifetime stress exposure using the Stress and Adversity Inventory for Adults (Adult STRAIN): an overview and initial validation. Psychosom Med. 2018;80: 17–27. doi:10.1097/PSY.0000000000000534

25. Boyce WT, Ellis BJ. Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. Dev Psychopathol. 2005;17: 271–301. doi:10.1017/s0954579405050145

26. Ellis BJ, Essex MJ, Boyce WT. Biological sensitivity to context: II. Empirical explorations of an evolutionary-developmental theory. Dev Psychopathol. 2005;17: 303–28. doi:10.1017/s0954579405050157

27. Del Giudice M, Ellis BJ, Shirtcliff EA. The Adaptive Calibration Model of stress responsivity. Neurosci Biobehav Rev. 2011;35: 1562–92. doi:10.1016/j.neubiorev.2010.11.007

28. Ellis BJ, Oldehinkel AJ, Nederhof E. The Adaptive Calibration Model of stress responsivity: an empirical test in the Tracking Adolescents' Individual Lives Survey study. Dev Psychopathol. 2017;29: 1001–21. doi:10.1017/S0954579416000985

29. Merrick MT, Ford DC, Ports KA, Guinn AS, Chen J, Klevens J, et al. Vital signs: estimated proportion of adult health problems attributable to adverse childhood experiences and implications for prevention - 25 states, 2015-2017. MMWR Morb Mortal Wkly Rep. 2019;68: 999–1005. doi:10.15585/mmwr.mm6844e1

30. Jones CM, Merrick MT, Houry DE. Identifying and preventing adverse childhood experiences: implications for clinical practice. JAMA. 2020;323: 25–6. doi:10.1001/jama.2019.18499

31. National Academies of Sciences, Engineering, and Medicine, Health and Medicine Division, Board on Population Health and Public Health Practice, Committee on Community-Based Solutions to Promote Health Equity in the United States. The root causes of health inequity. In: Baciu A, Negussie Y, Geller A, Weinstein JN, editors. Communities in action: pathways to health equity. Washington DC: National Academies Press; 2017. pp. 99–184.

32. National Academies of Sciences, Engineering, and Medicine, National Academy of Medicine, Committee on the Future of Nursing 2020–2030. Social determinants of health and health equity. In: Flaubert JL, Menestrel SL, Williams DR, Wakefield MK, editors. The future of nursing 2020-2030: charting a path to achieve health equity. Washington DC: National Academies Press; 2021. pp. 38–51.

33. Kim P, Evans GW, Chen E, Miller G, Seeman T. How socioeconomic disadvantages get under the skin and into the brain to influence health development across the lifespan. In: Halfon N, Forrest CB, Lerner RM, Faustman EM, editors. Handbook of life course health development [Internet]. Cham (CH): Springer; 2018. doi:10.1007/978-3-319-47143-3_19

34. Evans GW, Chen E, Miller G, Seeman T. How poverty gets under the skin: a life course perspective. In: King RB, Maholmes V, editors. The Oxford handbook of poverty and child development. New York: Oxford University Press; 2012. pp. 13–36.

35. Shonkoff JP, Boyce WT, McEwen BS. Neuroscience, molecular biology, and the childhood roots of health disparities: building a new framework for health promotion and disease prevention. JAMA. 2009;301: 2252–9. doi:10.1001/jama.2009.754

36. Taylor SE. Mechanisms linking early life stress to adult health outcomes. Proc Natl Acad Sci U S A. 2010;107: 8507–12. doi:10.1073/pnas.1003890107

37. Danese A, McEwen BS. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. Physiol Behav. 2012;106: 29–39. doi:10.1016/j.physbeh.2011.08.019

38. Agorastos A, Pervanidou P, Chrousos GP, Baker DG. Developmental trajectories of early life stress and trauma: a narrative review on neurobiological aspects beyond stress system dysregulation. Front Psychiatry. 2019;10: 118. doi:10.3389/fpsyt.2019.00118

39. Evans GW, Kantrowitz E. Socioeconomic status and health: the potential role of environmental risk exposure. Annu Rev Public Health. 2002;23: 303–31. doi:10.1146/annurev.publhealth.23.112001.112349

40. Evans GW. The environment of childhood poverty. Am Psychol. 2004;59: 77–92. doi:10.1037/0003-066X.59.2.77

41. Evans GW, Gonnella C, Marcynyszyn LA, Gentile L, Salpekar N. The role of chaos in poverty and children's socioemotional adjustment. Psychol Sci. 2005;16: 560–5. doi:10.1111/j.0956-7976.2005.01575.x

42. Evans GW, Kim P. Childhood poverty, chronic stress, self-regulation, and coping. Child Dev Perspect. 2013;7: 43–8. doi:10.1111/cdep.12013

43. Hartig T. Green space, psychological restoration, and health inequality. Lancet. 2008;372: 1614–15. doi:10.1016/S0140-6736(08)61669-4

44. Craig JM, Prescott SL. Planning ahead: the mental health value of natural environments. Lancet Planet Health. 2017;1: e128–e129. doi:10.1016/S2542-5196(17)30068-2

45. Badland H, Pearce J. Liveable for whom? Prospects of urban liveability to address health inequities. Soc Sci Med. 2019;232: 94–105. doi:10.1016/j.socscimed.2019.05.001

46. Xian Z, Nakaya T, Liu K, Zhao B, Zhang J, Zhang J, et al. The effects of neighbourhood green spaces on mental health of disadvantaged groups: a systematic review. Humanit Soc Sci Commun. 2024;11: 1–19. doi:10.1057/s41599-024-02970-1

47. Wolf KL, Measells MK, Grado SC, Robbins AST. Economic values of metro nature health benefits: a life course approach. Urban For Urban Green. 2015;14: 694–701. doi:10.1016/j.ufug.2015.06.009

48. Brochu P, Jimenez MP, James P, Kinney PL, Lane K. Benefits of increasing greenness on all-cause mortality in the largest metropolitan areas of the United States within the past two decades. Front Public Health. 2022;10: 841936. doi:10.3389/fpubh.2022.841936

49. Wilson J, Xiao X. The economic value of health benefits associated with urban park investment. Int J Environ Res Public Health. 2023;20: 4815. doi:10.3390/ijerph20064815

50. Frumkin H, Bratman GN, Breslow SJ, Cochran B, Kahn PH, Lawler JJ, et al. Nature contact and human health: a research agenda. Environ Health Perspect. 2017;125: 075001. doi:10.1289/EHP1663

51. Ellis BJ, Boyce WT, Belsky J, Bakermans-Kranenburg MJ, van Ijzendoorn MH. Differential susceptibility to the environment: an evolutionary–neurodevelopmental theory. Dev Psychopathol. 2011;23: 7–28. doi:10.1017/S0954579410000611

52. Boyce WT. Differential susceptibility of the developing brain to contextual adversity and stress. Neuropsychopharmacology. 2016;41: 142–62. doi:10.1038/npp.2015.294

53. Ellis BJ, Del Giudice M. Beyond allostatic load: rethinking the role of stress in regulating human development. Dev Psychopathol. 2014;26: 1–20. doi:10.1017/S0954579413000849

54. Belsky J, Pluess M. Beyond risk, resilience, and dysregulation: phenotypic plasticity and human development. Dev Psychopathol. 2013;25: 1243–61. doi:10.1017/S095457941300059X

55. Rigolon A, Browning M, Jennings V. Inequities in the quality of urban park systems: an environmental justice investigation of cities in the United States. Landsc Urban Plan. 2018;178: 156–69. doi:10.1016/j.landurbplan.2018.05.026

56. Ulrich RS. View through a window may influence recovery from surgery. Science. 1984;224: 420–21. doi:10.1126/science.6143402

57. Park S-H, Mattson RH. Effects of flowering and foliage plants in hospital rooms on patients recovering from abdominal surgery. HortTechnology. 2008;18: 563–8. doi:10.21273/HORTTECH.18.4.563

58. Park S-H, Mattson RH. Ornamental indoor plants in hospital rooms enhanced health outcomes of patients recovering from surgery. J Altern Complement Med. 2009;15: 975–80. doi:10.1089/acm.2009.0075

59. Belsky J, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. Psychol Bull. 2009;135: 885–908. doi:10.1037/a0017376

60. Ellis BJ, Bianchi J, Griskevicius V, Frankenhuis WE. Beyond risk and protective factors: an adaptation-based approach to resilience. Perspect Psychol Sci. 2017;12: 561–87. doi:10.1177/1745691617693054

61. Rhew IC, Vander Stoep A, Kearney A, Smith NL, Dunbar MD. Validation of the normalized difference vegetation index as a measure of neighborhood greenness. Ann Epidemiol. 2011;21: 946–52. doi:10.1016/j.annepidem.2011.09.001

62. Merry K, Bettinger P. Smartphone GPS accuracy study in an urban environment. PLoS One. 2019;14: e0219890. doi:10.1371/journal.pone.0219890

63. Ates HC, Nguyen PQ, Gonzalez-Macia L, Morales-Narváez E, Güder F, Collins JJ, et al. End-to-end design of wearable sensors. Nat Rev Mater. 2022;7: 887–907. doi:10.1038/s41578-022-00460-x

64. Larkin A, Hystad P. Evaluating street view exposure measures of visible green space for health research. J Expo Sci Environ Epidemiol. 2019;29: 447–56. doi:10.1038/s41370-018-0017-1

65. Holland I, DeVille NV, Browning MHEM, Buehler RM, Hart JE, Hipp JA, et al. Measuring nature contact: a narrative review. Int J Environ Res Public Health. 2021;18: 4092. doi:10.3390/ijerph18084092

66. Ji JS, Zhu A, Lv Y, Shi X. Interaction between residential greenness and air pollution mortality: analysis of the Chinese Longitudinal Healthy Longevity Survey. Lancet Planet Health. 2020;4: 107–15. doi:10.1016/S2542-5196(20)30027-9

67. Juul V, Nordbø ECA. Examining activity-friendly neighborhoods in the Norwegian context: green space and walkability in relation to physical activity and the moderating role of perceived safety. BMC Public Health. 2023;23: 259. doi:10.1186/s12889-023-15170-4

68. Huang W, De Roos AJ, Kondo MC, Clougherty JE, Zhao Y, Schinasi LH. Gender and violent crime modify associations between greenspace and cardiovascular disease mortality in Philadelphia, PA. Health Place. 2024;90: 103372. doi:10.1016/j.healthplace.2024.103372

69. Belcher RN, Murray KA, Reeves JP, Fecht D. Socioeconomic deprivation modifies green space and mental health associations: a within person study. Environ Int. 2024;192: 109036. doi:10.1016/j.envint.2024.109036

70. Ellis BJ, Boyce WT. Biological sensitivity to context. Curr Dir Psychol Sci. 2008;17: 183–7. doi:10.1111/j.1467-8721.2008.00571.x

71. Hosseini-Kamkar N, Lowe C, Morton JB. The differential calibration of the HPA axis as a function of trauma versus adversity: a systematic review and p-curve meta-analyses. Neurosci Biobehav Rev. 2021;127: 54–135. doi:10.1016/j.neubiorev.2021.04.006

72. Lin H. Probing two-way moderation effects: a review of software to easily plot Johnson-Neyman figures. Struct Equ Model. 2020;27: 494–502. doi:10.1080/10705511.2020.1732826

73. Belsky J, Zhang X, Sayler K. Differential susceptibility 2.0: are the same children affected by different experiences and exposures? Dev Psychopathol. 2022;34: 1025–33. doi:10.1017/S0954579420002205

74. Godoy LD, Rossignoli MT, Delfino-Pereira P, Garcia-Cairasco N, de Lima Umeoka EH. A comprehensive overview on stress neurobiology: basic concepts and clinical implications. Front Behav Neurosci. 2018;12: 127. doi:10.3389/fnbeh.2018.00127

75. Olvera-Alvarez HA, Cedeño Laurent JG, Eisen AM, Campen MJ, Slavich GM, Kubzansky LD, et al. Early life stress moderates the association between traffic exposure and circulating inflammatory biomarkers. Brain Behav Immun. 2025. Manuscript submitted for publication.

76. Ellis BJ, Del Giudice M. Developmental adaptation to stress: an evolutionary perspective. Annu Rev Psychol. 2019;70: 111–39. doi:10.1146/annurev-psych-122216-011732

77. Selanders LC. The power of environmental adaptation: Florence Nightingale's original theory for nursing practice. J Holist Nurs. 2010;28: 81–8. doi:10.1177/0898010109360257

78. Gregory DD, Stichler JF, Zborowsky T. Adapting and creating healing environments: lessons nurses have learned from the COVID-19 pandemic. Nurse Lead. 2022;20: 201–07. doi:10.1016/j.mnl.2021.10.013

79. Glacken CJ. Traces on the rhodian shore: nature and culture in western thought from ancient times to the end of the eighteenth century. Berkeley: University of California Press; 1967.

80. National Academies of Sciences, Engineering, and Medicine, National Academy of Medicine, Committee on the Future of Nursing 2020–2030. The future of nursing 2020-2030: charting a path to achieve health equity. Flaubert JL, Le Menestrel S, Williams DR, Wakefield MK, editors. Washington DC: National Academies Press; 2021.