frontiers | Frontiers in Environmental Health

TYPE Mini Review
PUBLISHED 13 March 2025
DOI 10.3389/fenvh.2025.1466951

OPEN ACCESS

EDITED BY
Araceli Camargo,
Centric Lab, United Kingdom

REVIEWED BY
Shady Abohashem,
Massachusetts General Hospital and Harvard Medical School, United States

*CORRESPONDENCE
Ilona Jaspers
ilona_jaspers@med.unc.edu

†PRESENT ADDRESS
Ilona Jaspers,
NIEHS/NHLBI, Research Triangle Park,
NC, United States

RECEIVED 18 July 2024
ACCEPTED 25 February 2025
PUBLISHED 13 March 2025

CITATION
Bailey A and Jaspers I (2025) The next SABV—stress as a biological variable.
Front. Environ. Health 4:1466951.
doi: 10.3389/fenvh.2025.1466951

The next SABV—stress as a biological variable

Aleah Bailey[1,2] and Ilona Jaspers[1,2,3,4*†]

[1]Curriculum in Toxicology and Environmental Medicine, University of North Carolina, Chapel Hill, NC, United States, [2]Center for Environmental Medicine, Asthma, and Lung Biology, University of North Carolina, Chapel Hill, NC, United States, [3]Department of Pediatrics, School of Medicine, University of North Carolina, Chapel Hill, NC, United States, [4]Department of Microbiology and Immunology, School of Medicine, University of North Carolina, Chapel Hill, NC, United States

The 2015 policy to incorporate sex as a biological variable (SABV) enhanced biomedical research and allowed for better predictions to be made regarding clinical outcomes and environmental health risks. This review aims to make a case for the next SABV—stress as a biological variable. While the body is equipped to respond to acute stress, chronic stress can overwork physiologic systems, leading to allostatic load, or progressive wear and tear on the brain and body. Allostatic load has many implications on immune, cardiovascular, and metabolic function, and alters xenobiotic metabolism of environmental and pharmaceutical chemicals. However, historically disadvantaged communities and populations are at an increased risk of harm due to elevated exposure to psychosocial stressors and environmental pollutants. Therefore, the unique biological responses among populations that experience this double hit should be considered in toxicology risk assessments. Among current approaches, allostatic load measurements are optimal as a framework that captures health disparities and a tool that quantifies cumulative stress burdens that can be integrated into health data for better risk predictions.

KEYWORDS

allostatic load, stress, health disparities, environmental susceptibility, risk assessment

1 Introduction

In 2015, the National Institutes of Health (NIH) released the sex as a biological variable (SABV) policy to address the historical exclusion of female humans and animals from biomedical research. Many environmental health studies have demonstrated that sex is an important biological variable that influences xenobiotic exposure, metabolism, and health effects. In Rebuli et al., for example, we identified sex-specific inflammatory responses to woodsmoke exposure, that were not discernable when analyzing aggregate data (1). As a result of the SABV policy, which requires researchers to factor sex into both human and vertebrate animal study design, better predictions can be made regarding clinical outcomes and environmental health risks. However, stress, which affects all bodily systems and is another major biological variable that influences individual-level susceptibility to both clinical and environmental outcomes, is not considered in the design of clinical and pre-clinical studies. While the body is equipped to manage small or infrequent doses of stress, chronic stress can alter bodily processes, making individuals more vulnerable to other stressors, including environmental chemicals. Because of the broad impacts of stress on the body and the presence of persistent psychosocial stressors in minority and low-income communities, it is vital to understand how stress modifies responses to xenobiotic exposures, ranging from environmental exposures to pharmaceutical drugs, to improve comprehensive risk

assessments. Additionally, as climate-related changes drive increased environmental exposures, it is crucial to integrate stress into environmental research to fully capture the complexities of environmental health risks and disparities. Therefore, this review discusses the importance of stress as a biological variable and the use of allostatic load to integrate chronic stress-related dysregulation into toxicology and risk assessments.

2 The biology of stress and allostatic load

The neuroendocrine stress response is implicated in the physiological effects of chronic stress. Stressful stimuli activate the sympathetic-adrenal-medullary (SAM) to release catecholamines, primarily epinephrine and norepinephrine, from the adrenal medulla which interact with alpha- and beta-adrenergic receptors in the central nervous system and smooth muscle cells to exert a "fight or flight" response characterized by increased blood pressure, heart rate, cardiac output, oxygen consumption and lipolysis among other physiological responses (2). The hypothalamus-pituitary-adrenal (HPA) axis is also stimulated to produce corticotrophin-releasing hormone, which triggers adrenocorticotropic hormone (ACTH) synthesis from the pituitary gland. ACTH acts on adrenal glands to release glucocorticoids, primarily cortisol, into circulation. Glucocorticoids affect various systemic processes in response to stress, including altering lipid and glucose metabolism and immune responses according to the duration and intensity of exposure. While SAM and HPA activation is an adaptive response following acute stress, prolonged exposure to psychosocial and environmental stressors can chronically activate the HPA axis and stress responses, leading to excess glucocorticoid and catecholamine production and downstream adverse effects on immune, cardiovascular, metabolic, and nervous systems (3). Over time, chronic stressors impair the body's capacity for effective regulation and adaptation, increasing the risk for maladaptive responses, and allostatic load, the progressive physiological 'wear and tear' on the brain and body that pre-dispose individuals to disease through deterioration of physical and mental health. As sub-clinical changes to organ systems persist, allostatic overload occurs in which chronic stress results in morbidities and mortality (4, 5).

Traditionally, stress was defined as a threat to homeostasis, or the dynamic equilibrium maintained by physiological systems through immediate, short-term adjustments to restore balance to a fixed set point. However, allostasis, introduced by neuroscientist Peter Sterling and epidemiologist Joseph Eyer, expands on this concept by emphasizing the body's ability to achieve stability through adaptive changes in response to stress. Unlike homeostasis, which relies on adhering to a limited set point, allostasis describes the adaptive mechanisms that allow physiological systems to function within a dynamic operating range in response to stress (6, 7). However, both homeostasis and allostasis fail to account for the long-term effects of chronic stress, which causes long-term activation of allostatic processes. Over time, chronic or prolonged stress exert wear and tear on organs and tissues, where they are unable to recover from or adapt to ongoing stress. As a result, the body begins brace for prolonged exposure to stress by operating at new, altered set points (6, 8, 9). Allostatic load (AL) was defined by neuroscientist Bruce McEwen and physiological psychologist Eliot Stellar to encompass this stress-induced strain on the body that predisposes individuals to disease (Figure 1B) (6).

Allostatic load is both a framework and a tool to measure the effects of cumulative stress on the body. Teresa Seeman and colleagues were the first to develop an operational method for allostatic load which involved measuring biomarkers across various systems and integrating those markers into a composite score (10). These biomarkers include primary mediators (epinephrine, norepinephrine, cortisol, and DHEA-S), which have direct correlation with adrenal function, and secondary mediators, which represent the organ effects of stress on cardiovascular (systolic and diastolic blood pressure) and metabolic (waist-hip ratio, total cholesterol-HDL ratio, glycosylated hemoglobin, HDL cholesterol) systems. Higher allostatic load scores, measured in a cohort of older men and women, correlated with increased risk for poorer cognitive and physical function, cardiovascular disease, and mortality (10). These results were corroborated in a 5-year follow up study that also showed composite allostatic load scores were a better predictor of mortality and declines in physical functioning than metabolic markers or primary markers alone (11). Allostatic load continues to serve as an objective measure of cumulative stress in research and has been studied in the context of various physical and mental health outcomes including ageing, increased risk for cardiovascular diseases, diabetes, preeclampsia, musculoskeletal disorders, depression, epileptic seizures, cancer, anxiety disorders, and health risk behaviors (5, 12).

3 Allostatic load as a risk for immune, metabolic and cardiovascular diseases

As illustrated in Figure 2, the physiological wear and tear from allostatic load can increase susceptibility to other physical and chemical stressors, including environmental pollutants, by impairing immune function, and increasing risks for metabolic and cardiovascular diseases (13). Allostatic load is characterized by the excess production or release of primary stress hormones, which regulate the immune system through mediating leukocyte distribution. Epinephrine and norepinephrine act together to mobilize immune cells into the bloodstream and epinephrine and cortisol influence the trafficking of immune cells to specific tissues or sites of injury (14). However, stress induced immune responses depend on the duration and severity of the stress response (3). Under acute stress, energy stores are mobilized, and the immune system ramps up as the body prepares for wound healing or defense against invading pathogens (15). This is characterized by the mobilization of leukocytes into the blood from various compartments, including spleen, bone marrow, lung, and lymph nodes, and the subsequent redistribution of

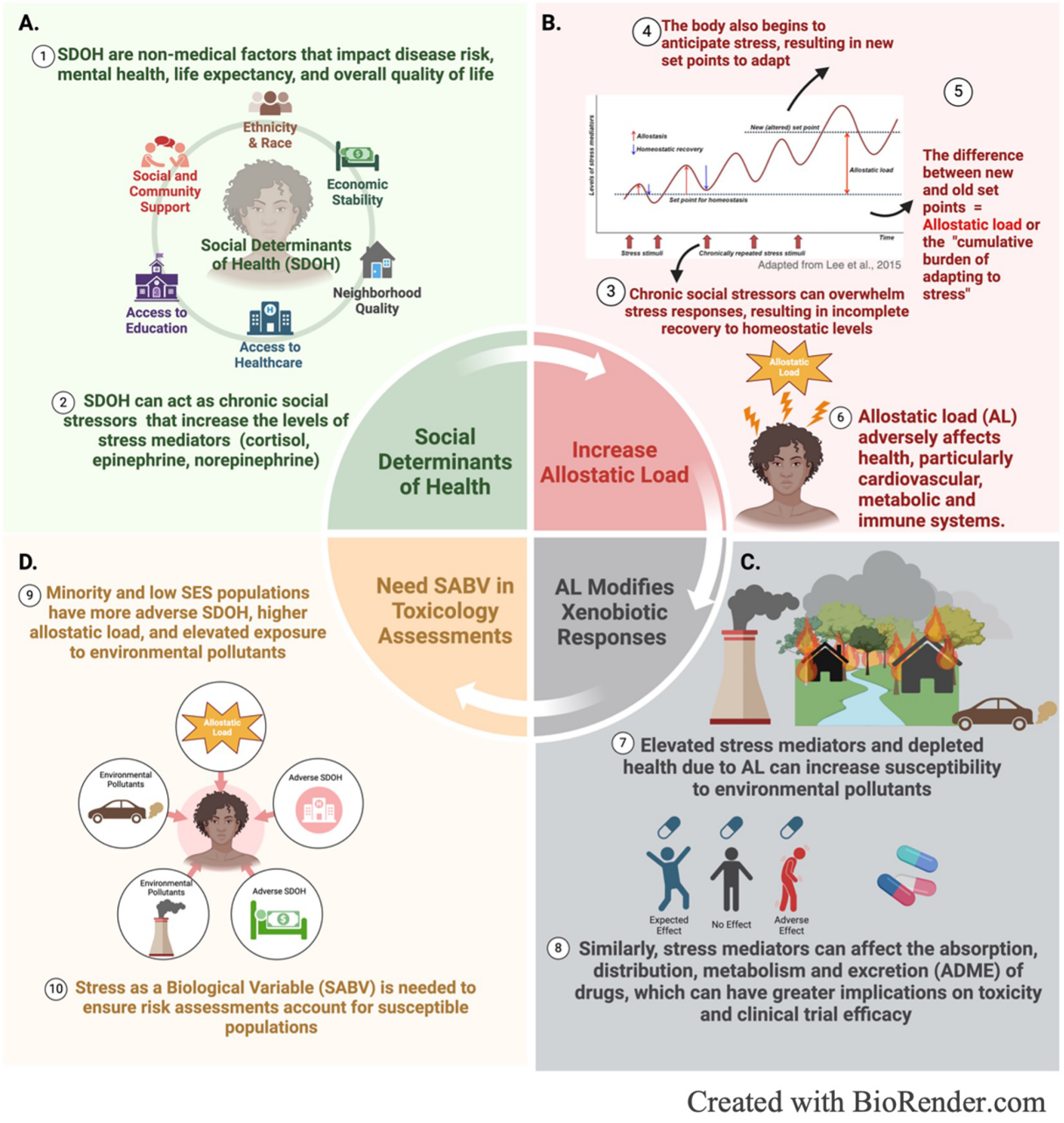

FIGURE 1
Graphical depictions of the interplay between (A) social determinants of health, (B) allostatic load, (C) environmental exposures and (D) stress induced susceptibility to environmental pollutants.

leukocytes to tissues and organs where they recruit other immune mediators, such as cytokines. After the initial trafficking of immune cells, blood monocytes, lymphocytes, T helper cells, cytotoxic T cells, B and NK cells continue to decrease while blood neutrophil counts increase (14, 16). In contrast, chronic stress reduces the number of circulating lymphocytes and reduces immune cell responsivity, which may indicate glucocorticoid resistance (14). Additionally, chronic stress has been shown to suppress other immune mediators, including cell mediated immunity, antibody production, NK cell activity, and leukocyte proliferation, which is believed to be induced by chronic inflammation (17, 18). Compromised immune function can increase susceptibility to environmental exposures, which also have various harmful effects on the immune system, including generating oxidative stress that damage DNA or cellular proteins, activating pro-inflammatory pathways, or suppressing immune cell activity (19–21) (Figure 2).

Additionally, glucocorticoids have regulatory effects on cardiovascular and metabolic systems (22). For the cardiovascular system, glucocorticoids increase sensitivity to catecholamines, such as epinephrine and norepinephrine, which elevate heart rate and blood pressure, and directly affect the renin-angiotensin-aldosterone

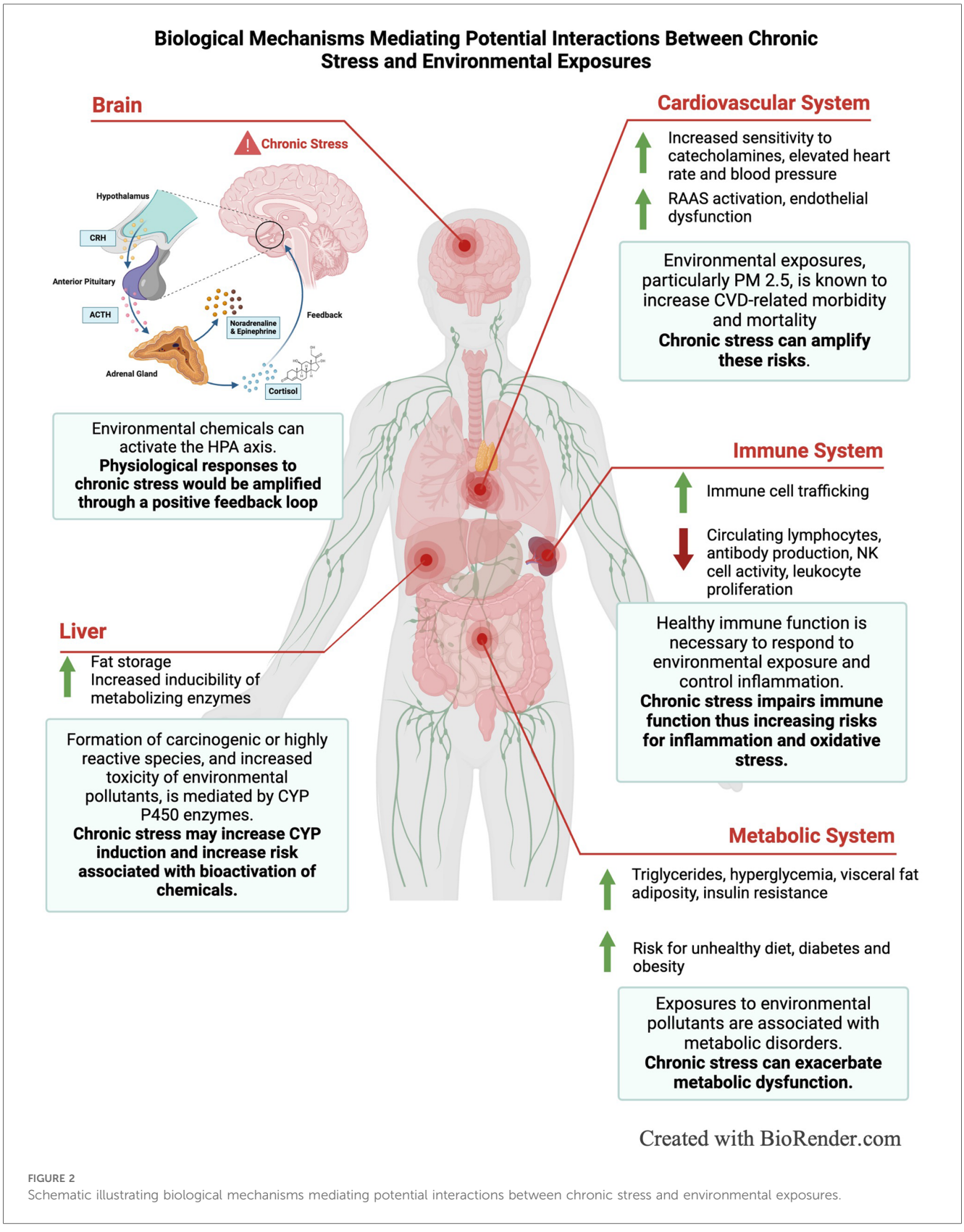

FIGURE 2
Schematic illustrating biological mechanisms mediating potential interactions between chronic stress and environmental exposures.

system (RAAS), which regulates blood volume, electrolyte balance, and endothelial function (22, 23). Excess glucocorticoids can also lead to metabolic syndrome, characterized by high blood pressure, obesity, low HDL cholesterol, elevated triglycerides, and hyperglycemia (24). Specifically, glucocorticoids drive changes in eating behaviors, promoting the consumption of less nutrient, but more palatable foods, increase visceral fat deposition in the liver and vascular tissue, and contribute to insulin resistance and

elevated blood glucose levels (25, 26). Therefore, in a state of allostatic load, excess glucocorticoid production disrupts normal metabolic and cardiovascular function, driving the development of Type-2 diabetes, hypertension, obesity, atherosclerosis and cardiovascular-specific mortality (25, 27–29). Because chronic stress and environmental chemicals act through similar mechanisms, co-exposure amplifies their cumulative impact on cardiovascular and metabolic systems (3, 30, 31). This is demonstrated by studies linking transportation noise, a prevalent socioeconomic stressor, and air pollution to major adverse cardiovascular events (MACE) (32, 33). Chronic environmental stressors, such as transportation noise, stimulate stress-related neurobiological activity, including increased amygdala metabolic activity, which is central to stress perception (34–36). Elevated amygdala activity increases arterial inflammation, a critical driver of cardiovascular disease and metabolic conditions such as hypertension, type-2 diabetes and obesity (35, 37). Air pollution, such as PM 2.5, also exacerbates arterial inflammation and promotes leucopoietic tissue activity, contributing to MACE risk (38, 39). Air pollution also increases risks for metabolic diseases such as diabetes and stroke (39). When combined, exposure to both stressors and pollutants amplify these harmful pathways, significantly increasing susceptibility to cardiovascular and metabolic diseases (33). The combined impact of transportation noise and elevated PM 2.5 highlights how chronic stress amplifies susceptibility to environmental exposures, compounding their effects on already compromised systems and increasing the risk of harm.

4 Stress and xenobiotic metabolism

In addition to increasing environmental susceptibility through modifying organ function, stress can also modify xenobiotic metabolism through altering cytochrome P-450 (CYP) enzymes, the primary enzymes involved in the metabolism of endogenous and exogenous chemicals (Figure 1C) (40). Glucocorticoids are known regulators of CYP enzymes, specifically belonging to the CYP1A family, which metabolizes polycyclic aromatic hydrocarbons, persistent organic pollutants present in air, water, and soil (41, 42). Cortisol suppresses the hypothalamic-pituitary-thyroid (HPT) axis through stimulating the release of somatostatin, which inhibits the secretion of thyrotropin releasing hormone (TRH) and thyroid stimulating hormone (TSH), modifying thyroid-mediated regulation of CYPs. Somatostatin also suppresses growth hormone secretion, which further down-regulates insulin-like growth factor-1 and, thus, alters insulin-mediated regulation of CYP enzymes (43). Catecholamines are also capable of modifying CYP enzymes through alpha- and beta-adrenergic receptor pathways (40). Animal studies have demonstrated that psychological stress suppressed CYP1A2 in rat liver and upregulated CYP2A5 in mice (42). Another study showed stress increased the inducibility of CYP1A1 and CYP1A2 by Benzo[a]pyrene, a polycyclic aromatic hydrocarbon prevalent in urban and industrial areas (44–46). The consequences of altered CYP function depend on the location of the enzyme and the activity of the parent compound; however, a major risk is the potential of induced enzymes to accelerate the formation of carcinogenic or highly reactive species, increasing the toxicity of the parent compound (47) (Figure 2). Overall, more research is needed to elucidate the role of stress in modifying xenobiotic metabolism and assess differences between the effects of acute and chronic stress.

Factors that alter the expression and function of metabolizing enzymes can also affect the pharmacodynamics of various drugs. Glucocorticoids can affect drug absorption by influencing gastrointestinal function and blood flow. Stress decreases blood flow to visceral organs while increasing blood flow to working muscles, which may decrease drug absorption by the GI track for orally administered drugs and increase absorption for drugs administered intramuscularly (43). Additionally, because distribution occurs most rapidly into tissues with increased blood flow and least rapidly in tissue with decreased blood flow, changes in blood flow can alter the distribution of drugs from circulation into target tissues (48). Further, because cortisol mobilizes free fatty acids, which have a strong binding affinity for the same binding sites as drugs on human serum albumin, it may displace drugs from albumin binding sites, increasing the amount of unbound drug in circulation, which can result in subtherapeutic or toxic plasma concentrations of drugs (49–51). This effect has been reported for various drug types including anesthetics, anticoagulants, and antibiotics (48). Pharmacologic implications of stress may influence clinical trial success and drug efficacy and safety, especially among racial and ethnic groups that have higher circulating levels of glucocorticoids and higher baseline allostatic load.

5 Disparities in allostatic load and social determinants of health

Many studies have reported racial, ethnic, and socioeconomic disparities in allostatic load, which are driven by "weathering," the hypothesis that minority populations experience early health deterioration because of socioeconomic disadvantage (27, 52–56). This accelerated health decline is often overlooked in research studies, which can misinform health and disease predictions. For example, one study observed that cohort selection bias in the Study of Women's Health Across the Nation (SWAN) resulted in poor age of onset predictions for cardio-metabolic diseases, which were significantly lower for Black and Hispanic women compared to White women (57). Weathering is an outcome of experiencing adverse social determinants of health (SDOH), non-medical factors (neighborhood quality, access to education and health care, economic stability, and social and community support) that impact disease risk, mental health, life expectancy, education and development, productivity, economic stability, and overall quality of life (Figure 1A) (58–62). Adverse SDOH are the legacy of discriminatory practices, such as redlining and disinvestment, which created housing, economic, educational and health inequalities in minority communities that are still felt today (63, 64). Historically redlined neighborhoods across the U.S. are not only associated with current markers of

neighborhood disadvantage and elevated social stressors (discrimination, crime, violence, and noise), but also correlate with elevated exposure to pollutants (63, 65). Therefore, allostatic load is useful for capturing the weathering effects of SDOH to assess how they affect pollutant susceptibility and responses.

6 Allostatic load as a risk for susceptibility to environmental pollutants

Because of the effects allostatic load has on xenobiotic metabolism, immune dysfunction, and cardiometabolic health, it is plausible that allostatic load increases susceptibility to environmental pollutants. This is further supported by epidemiological studies reporting a link between adverse psychosocial experiences, toxicant exposures, and greater risks for adverse health outcomes. A study in infants reported that prenatal exposure to both air pollution and maternal stress were associated with lower orienting and regulation (OR) at 4 months, which predicted lower competence and increased behavioral problems at 12 months (66). Other studies have found strong associations between air pollution and asthma in children exposed to community violence (67, 68). Similar associations were observed among children from mothers with less than a high school education, black children, and children living in geographic areas with a higher percentage of black residents (69). Additionally, in adults, strong associations have been found between high psychosocial stress, $PM_{2.5}$ exposure and systolic blood pressure (70). Among the most impactful studies highlighting the link between allostatic load and environmental disparities is a study associated with the Baltimore Housing Mobility Program, which was designed to address historic and contemporary housing discrimination. This study demonstrated that removing factors causing allostatic load, by moving families from high to low poverty neighborhoods with increased access to resources (food, safe schools, etc.), decreased symptoms and improved disease outcomes in children with asthma (71). Interestingly, indoor $PM_{2.5}$ and PM_{10} concentrations, as well as levels of allergens, were less associated with changes in asthma outcomes than markers of stress. These examples underscore the impact stressful events, before and during one's lifespan, can have on susceptibility to environmental exposures and suggest that interventions addressing causes of allostatic load can significantly improve environmental health disparities.

7 Operationalizing allostatic load

Currently, operationalizing allostatic load is limited by the substantial variability in scoring approaches used throughout the literature. Since the introduction of the allostatic load score, the number of primary and secondary biomarkers included in allostatic load indices has grown from the original 10 to approximately 60, with individual scores now incorporating a variable range of 6–25 biomarkers (72). Most commonly, biomarkers are converted into dichotomous variables using high-risk quartiles to assign risk. Typically, biomarkers in either the highest or lowest 25% of the sample distribution are deemed high-risk and assigned a value of 1, while "low-risk" biomarkers are assigned a value of 0. The total allostatic load score then reflects the sum of high-risk biomarkers for an individual (73). Calculating high-risk quartiles based on the sample distribution may skew results by baselessly weighing biomarkers from certain biological systems more than others. Additionally, because the sample distribution is study-specific, results can vary significantly across studies due to study demographics, making it harder to compare findings or establish thresholds for high allostatic load (73). Alternatively, some studies use clinically-relavant cutoffs to dichotomize biomarkers into high vs. low risk and compute scores. However, many biomarkers lack established clinical cutoffs and this approach may fail to detect subclinical changes that are characteristic of allostatic load (73). Less common approaches include calculating the sum or average of biomarker Z-scores and summing dichotomous systems-level scores to generate an overall allostaic load score (73). Because biomarker Z-scores are weighted based on its deviation from the mean, biomarkers with greater deviation will have a greater weight and impact on the overall allostatic load score without proper justification (5). Translating allostatic load scores into meaningful interpretations poses another challenge. Allostatic load scores are often reported as either continuous variables or categories (low, medium, or high) using a variety of approaches, such as assigning scores above the median, or in the highest quartile, as high or using arbitrary thresholds based on score distributions (73). Despite these limitations, the utility of allostatic load justifies greater efforts to develop standardized methods. To improve the validity and comparability of allostatic load, researchers suggest using a core set of biomarkers to improve comparability. An individual participant data (IPD) meta-analysis identified a panel of five biomarkers—resting heart rate (RHR), high density lipoprotein (HDL), waist-to-height ratio (WtHR), C-reactive protein (CRP), and hemoglobin A1C (HbA1C)- that predicted health outcomes and mortality similar to longer allostatic load measures (74). Using a small set of biomarkers consistently across studies is a first step toward standardizing allostatic load scoring. This framework can be re-evaluated with additional markers as new research emerges.

8 Integrating allostatic load in toxicology risk assessments

Integrating allostatic load into environmental exposure assessments is an emerging area of research. Previous studies have commonly used high-risk thresholds to calculate allostatic load scores, followed by regression models to examine relationships between allostatic load and environmental pollutants such as PFAS, traffic-related air pollution, and PM 2.5 (75–77). More complex approaches, like multilevel mixed-effects generalized linear models, have been used to examine associations between residential greenspace and allostatic load (78). Association studies provide valuable insight into the relationship between stress and pollutant health effects; however, mechanistic studies are needed to

better understand the underlying factors that contribute to increased susceptibility. Animal models have proven useful for studying stress-induced susceptibility to air pollutants (79). In these models, allostatic load can be integrated using tools like the rat cumulative allostatic load measure (rCALM) to explore stress and pollutant interactions (80, 81). In human exposure studies, allostatic load can be incorporated as critical variable, much like sex, to better understand its role in stress-induced susceptibility. By evaluating the mechanisms described earlier, researchers can gain insight into how allostatic load interacts with environmental exposures to influence health outcomes. Furthermore, longitudinal studies on allostatic load would help characterize the development of allostatic load over a lifespan as well as potential consequence of persistent exposures. For example, a longitudinal study by Mair et al., found that long-term proximity to petrochemical plants in Texas City was associated with higher allostatic load, particularly among women (82). Together, these approaches will help to enhance the precision of risk evaluations and guide more targeted interventions for vulnerable populations.

As allostatic load assessments become increasingly standardized and research on the environmental risks linked to allostatic load continues to grow, there is a greater opportunity to integrate these assessments into clinical practice. This integration can enhance patient evaluations, identify underlying stress-related health risks, and inform more personalized interventions to improve both mental and physical health. Incorporating allostatic load into clinical settings will also allow for a more comprehensive understanding of patients' health, not only addressing the physical symptoms, but also the psychological and environmental factors that contribute to health and well-being (83).

9 Discussion

In summary, epidemiological and experimental evidence support the relationship between stress and greater susceptibility to chemical stressors. Therefore, it is important to consider more rigorously stress as a biological variable in toxicological studies. Allostatic load is a powerful framework and tool that captures health disparities and socioeconomic disadvantages, while providing a cumulative stress score that can be integrated into risk assessments. Allostatic load overcomes the limitations of traditional stress assessment methods, including questionnaires, which are susceptible to bias or underreporting among racial and ethnic minorities, or using a single measure of cortisol, which naturally operate on a day-night rhythm and fail to account for the downstream effects of stress on the body (84, 85). Additionally, it is important that allostatic load is integrated into health data, to assess how chronic stress modifies biology and disease. The consequences of not accounting for allostatic load include having poorly representative research cohorts that fail to provide cumulative risk assessments for environmental and pharmaceutical chemicals. Therefore, future work is needed to refine allostatic load score measurements, establish a framework for incorporating allostatic load into risk assessment studies and clinical settings, and uncover the mechanisms underlying stress-induced susceptibility.

Author contributions

AB: Conceptualization, Visualization, Writing – original draft, Writing – review & editing. IJ: Conceptualization, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. AB was supported by the Environmental Protection Agency Cooperative Agreement with the University of North Carolina at Chapel Hill (UNC) CR 84033801, a pre-doctoral traineeship [National Research Service Award T32 ES007126] from the National Institute of Environmental Health Sciences, National Institutes of Health. This work was supported in part by a grant to UNC Chapel Hill from the Howard Hughes Medical Institute through the Gilliam Fellows Program.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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