Recent Advances in the Assessment of Allostatic Load and Its Health Impacts: A Postprint

Authors: Li Yiru, Yuhong Li, Li Yuhong

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Abstract

Stress is recognized as a significant factor in disease etiology, and chronic stress can induce severe disruption of physiological systems. Allostatic load, as a composite index for assessing physiological dysregulation across multiple systems under chronic stress, plays an important role in health onset and development. This paper systematically and comprehensively reviews the relevant concepts, assessment methods, and health impacts of allostatic load, revealing a significant correlation between allostatic load and health. However, there remains no unified standard for the selection of biomarkers and algorithms for allostatic load in domestic and international research, which constitutes a future research direction.

Full Text

Preamble

Progress in Methods for the Assessment of Allostatic Load and Its Impact on Health

LI Yiru, LI Yuhong*
School of Nursing, Anhui Medical University, Hefei 230601, China
*Corresponding author: LI Yuhong, Professor; E-mail: liyuhong@ahmu.edu.cn

Abstract

Stress is considered a critical factor leading to disease, and continuous stress can cause severe disruption to the body' s physiological systems. Allostatic load, as a comprehensive indicator for assessing physiological dysregulation across multiple systems under chronic stress, plays a significant role in the occurrence and

development of health outcomes. This article systematically and comprehensively reviews the relevant concepts, assessment methods, and health impacts of allostatic load, revealing a clear correlation between allostatic load and health. However, there remains no unified standard for the selection of biomarkers and algorithms for allostatic load in domestic and international research, which represents an important direction for future investigation.

Keywords: Stress, psychological; Allostasis; Allostatic load; Allostatic load indices; Health; Biomarkers

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Literature Search Strategy

A computerized search was conducted across PubMed, Web of Science, CNKI, Wanfang Data, and VIP databases using Chinese search terms including "stress," "chronic stress," "allostasis," "allostatic load," and "health," as well as English terms such as "Stress," "chronic stress," "Allostasis," "Allostatic load," "AL," and "health." Boolean operators AND/OR were employed to retrieve Chinese and English literature on allostatic load assessment methods and their health impacts from database inception to February 2023. Inclusion criteria were: (1) systematic reviews, meta-analyses, review articles, and research studies published within the past 5–10 years; (2) research content involving allostatic load assessment methods (biomarkers and clinical standard assessment) or the impact of allostatic load on health, encompassing both psychological and physiological aspects; and (3) human subjects. Exclusion criteria were: (1) studies without full text or where full text could not be obtained; and (2) duplicate publications.

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1. Concepts of Allostatic Load

The concept of allostasis was proposed by Sterling and Eyer in 1988 to reflect the impact of stress on the human body. During stress, the body maintains homeostasis through physiological system adjustments; when the body cannot adapt to external stressors and homeostasis becomes dysregulated, allostasis occurs. To further measure the degree of impact of allostasis on the body, McEwen and Stellar introduced the concept of allostatic load in 1993. When exposed to repeated or chronic stressors over the long term, the human neuroendocrine, cardiovascular, and immune systems produce fluctuating or heightened responses, and the cumulative wear on the body caused by prolonged exposure to these responses is termed allostatic load. This definition reflects the cumulative effects of both everyday events and major life challenges, as well as the physiological consequences of resulting health-damaging behaviors. Unlike other physiological dysregulation studies, allostatic load posits that dysregulation occurs across multiple physiological systems. When an individual is exposed to stress, acute

stress systems (parasympathetic nervous system) and chronic stress systems [hypothalamic-pituitary-adrenal (HPA) axis] are activated. The acute stress system releases norepinephrine and epinephrine, while the chronic stress system controls cortisol release. Over time, these stress mediators—whether at high or low levels—lead to long-term changes in secondary outcomes (such as blood pressure, glucose metabolism, and immune system function), subsequently resulting in negative physical and mental health outcomes.

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2. Assessment Methods for Allostatic Load

Currently, allostatic load assessment primarily employs biomarker assessment and clinical standard assessment methods.

2.1 Biomarker Assessment Method

2.1.1 Allostatic Load Indices (ALIs) Allostatic load represents physiological damage and dysregulation across multiple systems under chronic stress, typically estimated using composite indicators of biomarkers representing neuroendocrine, metabolic, cardiovascular, and immune systems to quantify the degree of allostatic load during stress states. Compared with single biomarkers, ALIs better predict health outcomes. The earliest ALIs were proposed based on the MacArthur Study of Successful Aging, which included 10 biomarkers: four primary mediators—serum dehydroepiandrosterone sulfate (DHEA-S), 12-hour urinary cortisol excretion, and 12-hour urinary norepinephrine and epinephrine excretion levels—representing biochemical changes in the neuroendocrine system during stress response activation; and six secondary mediators—systolic and diastolic blood pressure, waist-to-hip ratio, serum high-density lipoprotein (HDL) and total cholesterol levels, and plasma total glycohemoglobin levels—representing structural remodeling of receptor sites in cardiovascular and metabolic systems resulting from chronic activation of the stress response. This study laid the foundation for subsequent ALI construction.

With advances in allostatic load research, additional ALIs have been proposed. Some scholars have calculated ALIs by measuring 15 biomarkers, primarily including cardiovascular markers (systolic blood pressure, diastolic blood pressure), anthropometric indicators (BMI, waist-to-hip ratio), inflammatory markers (high-sensitivity C-reactive protein, fibrinogen, albumin), glucose homeostasis parameters (fasting glucose, insulin), blood lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), and steroids (cortisol, serum DHEA-S). Others have employed up to 24 biomarkers across seven physiological systems to estimate ALIs. While no consensus has been reached on ALI standards, most scholars use one or more primary mediators (such as cortisol, epinephrine) and inflammatory mediators, along with multiple secondary mediators (such as blood pressure and cholesterol), to construct ALIs.

The National Health and Nutrition Examination Survey (NHANES) has added to or deleted from the biomarkers in the MacArthur Study of Successful Aging, with 21 studies encompassing 26 different biomarkers and ALIs comprising 7–14 biomarkers. Most researchers comprehensively evaluate allostatic load levels primarily based on cardiovascular, metabolic, and immune systems, with the 12 most frequently used biomarkers representing these systems including: cardiovascular system (average of three resting systolic blood pressure measurements, average of three resting diastolic blood pressure measurements, pulse rate), metabolic system (glycated hemoglobin, serum albumin, serum creatinine, total cholesterol, HDL, serum triglycerides, BMI), and immune system (high-sensitivity C-reactive protein, white blood cell count).

2.1.2 Allostatic Load Scoring Currently, no consensus has been formed on allostatic load scoring algorithms in domestic and international research. Approximately 52.5% of studies employ the sample distribution high-risk quartile cutoff method, 11.1% use clinical cutoff values, and the remainder utilize other algorithms.

The sample distribution high-risk quartile cutoff method establishes a high-risk threshold for each biomarker in subjects, with the highest quartile used for all markers except HDL and serum albumin, which use the lowest quartile. According to the cutoff criteria for each indicator, scores are dichotomized where "1" represents high risk and "0" represents low risk, with total allostatic load calculated by summing individual indicator scores.

The clinical cutoff method assigns a score of 1 to each marker that meets or exceeds clinically established cutoff values, with scores below cutoff receiving 0, to calculate a total clinical allostatic load score. Based on historical literature, differences in morbidity and mortality between groups emerge when allostatic load scores reach 3–4 or above. Consequently, most studies consider allostatic load scores of 3 or 4 and above to indicate high allostatic load.

Using clinical cutoff values to determine allostatic load levels yields results no different from the high-risk quartile distribution method. However, not all biomarkers have established clinical cutoff values, and clinical cutoffs are prone to measurement sensitivity issues and cannot accurately explain all positive allostatic load cases. Therefore, the sample distribution high-risk quartile method is currently the preferred approach for allostatic load calculation in most research.

2.2 Clinical Standard Assessment Method

While biomarker measurement of allostatic load can objectively reflect physiological allostatic load levels following long-term cumulative chronic stress, its complexity and dynamic nature impose certain limitations on results. Fava et al. proposed a clinical standard method for measuring allostatic load, which was incorporated into the Diagnostic Criteria for Psychosomatic Research (DCPR) in 2017. In the revised DCPR, allostatic load is assessed based on stressors

(Criterion A) and clinically relevant manifestations associated with stressors (Criterion B). High allostatic load is identified when both Criterion A and Criterion B conditions are met. The revised DCPR diagnostic criteria for allostatic load are presented in Table 1 .

In summary, biomarkers are objective indicators for measuring allostatic load levels, reflecting a state of the body' s physiological systems and representing the preferred method for most researchers. However, no unified standard currently exists for biomarker selection and algorithms. Clinical standard assessment, as a novel evaluation method, compensates for the lack of potential individual experience information inherent in biomarker measurement by employing explicit standard criteria and subjective evaluation to comprehensively assess individual allostatic load levels based on recent life events, chronic stressors, and psychological status. No studies have yet combined both approaches, and future research should consider integrated methods employing both biomarkers and clinical standards to evaluate allostatic load.

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3. Impact of Allostatic Load on Health

3.1 Impact on Mental Health

3.1.1 Allostatic Load and Depression Over 350 million people worldwide suffer from depression, whose occurrence and development are associated with long-term stress responses. Multiple studies have demonstrated a relationship between allostatic load and depression. A longitudinal study found a bidirectional association between allostatic load and depressive symptoms in older adults, where high allostatic load increased the risk of depressive symptoms five years later, and conversely, depressive symptoms also led to elevated allostatic load levels five years later. Research has also indicated that childhood trauma (such as physical abuse) is associated with adult depression risk, a relationship mediated by allostatic load. Childhood trauma may induce physiological dysregulation, and long-term cumulative allostatic load can affect specific brain regions (such as the hippocampus, amygdala, and prefrontal cortex), predisposing individuals to depression.

The association between allostatic load and depression also exhibits gender and racial differences. Bey et al. found that in men, hypertension and low serum protein levels could predict depression onset, while in women, high cholesterol was associated with depression development. An NHANES-based survey revealed that the association between high allostatic load and depression was stronger in white women than in black women. Although these studies demonstrate that the allostatic load-depression relationship varies by gender and race, findings across studies remain inconsistent. Therefore, future research requires larger samples to elucidate gender and racial differences in the association between allostatic load and depression.

3.1.2 Allostatic Load and Schizophrenia Allostatic load measures cumulative stress on the body and reflects a composite index of chronic stress-induced wear, contributing to understanding the pathophysiological processes and pathogenesis of schizophrenia. First, allostatic load levels are significantly higher in schizophrenia patients compared to healthy populations, particularly in first-episode schizophrenia patients. Higher allostatic load indices correlate with more severe positive symptoms and more pronounced declines in psychosocial functioning, and may even lead to cognitive dysfunction in individuals with high familial psychiatric risk and psychiatric patients. Second, scholars investigating the association between allostatic load and subcortical brain region structures in schizophrenia patients found that choroid plexus enlargement was significantly associated with high allostatic load. Additionally, high allostatic load contributes to reduced cortical thickness and cognitive deficits in schizophrenia patients, with the left superior frontal gyrus being the most significant mediating cortical region through which allostatic load affects cognitive function in schizophrenia patients. In summary, allostatic load is associated with schizophrenia and can influence its development by reducing cortical thickness and altering subcortical brain region structures.

3.1.3 Allostatic Load and Other Mental Health Disorders Allostatic load also shows associations with post-traumatic stress disorder (PTSD) and anxiety disorders. Research indicates that PTSD may lead to dysregulation of physiological systems (such as HPA axis dysfunction, immune system dysregulation, and metabolic dysfunction), resulting in adverse physical health outcomes, with changes in neuroendocrine and immune system biomarkers showing clear associations with PTSD. Studies have found that mothers with PTSD exhibit higher allostatic load levels compared to mothers without PTSD, related to increased BMI, norepinephrine, and cortisol levels. In adults with early life trauma, allostatic load neuroendocrine biomarkers are significantly associated with PTSD development in adulthood. The HPA axis, as the primary neuroendocrine axis regulating stress responses, may contribute to psychiatric disorders such as depression and anxiety disorders when its function is dysregulated. Research has found that anxiety disorder patients may exhibit higher allostatic load levels compared to patients diagnosed with personality disorders, potentially related to dysregulation of cortisol, interleukin-6, and heart rate.

3.2 Impact on Physical Health

3.2.1 Allostatic Load and Sleep Sleep is essential for health and well-being, and stress represents a significant cause of sleep problems. Allostatic load, as a physiological mechanism model describing the relationship between stress and disease, has been proposed to understand the adverse health effects of sleep disorders. Compared to normal sleepers, individuals with sleep disorders or excessively long sleep duration exhibit significantly higher allostatic load levels. A study on college student sleep found that both insufficient sleep and evening chronotype were associated with high allostatic load. However, recent research

has identified that good sleep can serve as a moderating factor buffering the impact of psychosocial stress on cardiovascular system indicators of allostatic load (BMI, blood pressure/mean arterial pressure, and heart rate).

3.2.2 Allostatic Load and Cardiovascular Disease Allostatic load reflects comprehensive wear across multiple physiological systems, and research demonstrates that high allostatic load is associated with increased cardiovascular disease incidence. In coronary heart disease populations, increased disease risk is mediated by overall allostatic load or elevated allostatic load metabolic system indicators, where higher scores for metabolic system indicators (such as waist circumference, total cholesterol, HDL) correlate with higher coronary heart disease incidence. Studies have also found that allostatic load mediates the relationship between educational status and coronary heart disease incidence. In atrial fibrillation patients, research on implantable cardioverter defibrillator recipients indicated that 16.2% exhibited moderate allostatic load and 4.3% showed severe allostatic load. Among patients with essential hypertension, 32.5% had high allostatic load levels and demonstrated higher psychological stress levels and psychosomatic syndrome prevalence. Furthermore, allostatic load can predict cardiovascular disease mortality and even all-cause mortality, with high allostatic load increasing cardiovascular disease mortality by 31% and all-cause mortality by 22%.

Current research on allostatic load and cardiovascular disease primarily focuses on elderly populations, with fewer studies on young adults. However, WHO reported in 2017 that 17.9 million people died from cardiovascular disease globally, with approximately 22% of adults aged 18 and older having elevated blood pressure. The 2019 Chinese White Paper on Cardiovascular and Cerebrovascular Health in Young and Middle-aged Populations revealed a clear trend toward younger onset of cardiovascular and cerebrovascular diseases in China, with 15.3% of individuals aged 20–29 already being patients or at high risk. Therefore, future research should increase investigation into pathogenic mechanisms of cardiovascular disease in young populations and explore whether allostatic load measurement can predict cardiovascular disease and mortality risk in young people.

3.2.3 Allostatic Load and Metabolic and Immune Diseases Research indicates that excessive allostatic load can induce insulin resistance, leading to type 2 diabetes development. A study on type 2 diabetes found that 79.6% of diabetic patients exhibited high allostatic load, and longer diabetes duration was associated with higher allostatic load levels. A systematic review on the relationship between primary allostatic load mediators and metabolic syndrome revealed that high allostatic load may adversely affect the neuroendocrine system, contributing to metabolic syndrome development, with elevated cortisol and reduced serum DHEA-S levels showing associations with metabolic syndrome. Evidence also suggests that stress effects across multiple systems may increase allergic and non-allergic airway inflammation. In a study on allostatic

load and adolescent asthma, boys with high allostatic load had four times higher asthma risk compared to boys with low allostatic load, potentially related to increased total cholesterol, glucose, and cortisol levels.

3.2.4 Allostatic Load and Other Chronic Diseases The link between allostatic load and health outcomes also manifests in chronic diseases such as cancer. Increased hormone levels (epinephrine, norepinephrine, glucocorticoids) induced by chronic stress can accelerate cancer development, thereby increasing cancer prevalence and mortality risk. A cross-sectional study found that higher allostatic load levels in metastatic lung cancer patients were associated with adverse social determinants (low income, stressful life events) and increased mortality risk. In breast cancer patients, higher prediagnostic allostatic load was associated with poorer tumor differentiation and larger tumor diameter, further explaining the role of stress in the development and progression of chronic diseases such as cancer. Additionally, in chronic kidney disease, end-stage renal disease patients may experience higher allostatic load levels.

In summary, the impact of allostatic load on health has received widespread attention, with scholars investigating increasingly broad research areas. However, allostatic load levels are dynamic, and health damage is influenced by multiple factors such as unhealthy lifestyles, low social support, poor economic status, and age. Developing targeted interventions to reduce allostatic load occurrence will be a focus of future research. Notably, although allostatic load-related research has continued to increase in recent years, consensus has not yet been reached regarding biomarker selection for physiological systems representing allostatic load and allostatic load scoring methods, creating substantial heterogeneity in interpretation and comparison of allostatic load measurement across studies. Therefore, future research requires further work to determine optimal standardized methods for assessing allostatic load.

Author Contributions

LI Yiru was responsible for literature review, table preparation, manuscript drafting, and revision. LI Yuhong was responsible for manuscript revision and final approval, with overall responsibility for the article and supervision.

Conflict of Interest

The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.