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Allostatic Load and Its Impact on Health: A Systematic Review

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Abstract
Introduction: Allostatic load refers to the cumulative burden of chronic stress and life events. It involves the interaction of different physiological systems at varying degrees of activity. When environmental challenges exceed the individual ability to cope, then allostatic overload ensues. Allostatic load is identified by the use of biomarkers and clinical criteria. ***Objective:*** To summarize the current knowledge on allostatic load and overload and its clinical implications based on a systematic review of the literature. ***Methods:*** PubMed, PsycINFO, Web of Science, and the Cochrane Library were searched from inception to December 2019. A manual search of the literature was also performed, and reference lists of the retrieved articles were examined. We considered only studies in which allostatic load or overload were adequately described and assessed in either clinical or non-clinical adult populations. ***Results:*** A total of 267 original investigations were included. They encompassed general population studies, as well as clinical studies on consequences of allostatic load/overload on both physical and mental health across a variety of settings. ***Conclusions:*** The findings indicate that allostatic load and overload are associated with poorer health outcomes. Assessment of allostatic load provides support to the understanding of psychosocial determinants of health and lifestyle medicine. An integrated approach that includes both biological markers and clinimetric criteria is recommended.

Introduction

The concept of allostatic load was introduced by McEwen and Stellar in 1993 [1] and refers to the cost of chronic exposure to fluctuating or heightened neural and neuroendocrine responses resulting from repeated or chronic environmental challenges that an individual reacts to as being particularly stressful. It derives from the definition of allostasis as the ability of the organism to achieve stability through change [2], and the view that healthy functioning requires continual adjustments of the internal physiological milieu [3].

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Table 1. Clinical criteria for allostatic overload (A through B are required)

Criterion A	The presence of a current identifiable source of distress in the form of recent life events and/or chronic stress; the stressor is judged to tax or exceed the individual coping skills when its full nature and full circumstances are evaluated
Criterion B	The stressor is associated with one or more of the following features, which have occurred within 6 months after the onset of the stressor: 1. At least two of the following symptoms: difficulty falling asleep, restless sleep, early morning awakening, lack of energy, dizziness, generalized anxiety, irritability, sadness, demoralization 2. Significant impairment in social or occupational functioning 3. Significant impairment in environmental mastery (feeling overwhelmed by the demands of everyday life)

The definition of allostatic load [1, 4, 5] reflects the cumulative effect of experiences in daily life that involve ordinary events (subtle and long-standing life situations) as well as major challenges (life events), and also includes the physiological consequences of the resulting health-damaging behaviors, such as poor sleep and circadian disruption, lack of exercise, smoking, alcohol consumption and unhealthy diet. When environmental challenges exceed the individual ability to cope, then allostatic overload ensues [3, 6] as a transition to an extreme state where stress response systems are repeatedly activated and buffering factors are not adequate [7].

Situations that may lead to the development of allostatic load/overload are: (a) exposure to frequent stressors that may determine a status of chronic stress and repeated physiological arousal; (b) lack of adaptation to repeated stressors; (c) inability to shut off the stress response after a stressor is terminated; (d) allostatic response not sufficient to deal with the stressor [8, 9].

In response to environmental demands, different physiological systems interact at varying degrees of activity [1]. The neuroendocrine and immune systems respond to internal or external challenges and promote adaptation to threats or adversities [5, 8]. The hypothalamic-pituitary-adrenal axis plays a key role in the pathophysiology of allostatic load [5, 10]. Brain architecture and neurochemical functions are affected by both genomic and nongenomic mechanisms [11, 12]. Adjustments in the immune system (e.g., leukocytes, cytokines, inflammation) do occur, with immunosuppressive effects in the long run [13]. Alterations in body functions involving cardiovascular and gastrointestinal systems, endocrine-metabolic balances and sleep may ensue [5, 10, 14, 15].

Characterization of allostatic load has been carried out by two distinct approaches. One is concerned with the use of biomarkers that reflect physiological derangements; the other is a clinical approach targeted to the more severe end of the spectrum of associated symptomatology, subsumed under the rubric of allostatic overload.

Several studies have focused on identifying allostatic load through biological markers [5, 7, 14, 16–25]. Seeman et al. [16, 17] identified 10 biological parameters: cortisol, dehydroepiandrosterone (DHEA), epinephrine, norepinephrine, cholesterol, glycosylated hemoglobin, resting systolic and diastolic blood pressure, body mass index, and waist-hip ratio. The first four parameters have been considered as primary mediators of allostatic load because of their immediate correlation with adrenal function, whereas the remaining parameters were defined as secondary mediators [16, 17]. Biological markers of diseases resulting from a condition of allostatic load were defined as tertiary mediators [26]. Additional biomarkers (glucose levels, lipid profiles, interleukin-6, heart rate variability) have subsequently been recognized as having a role in the allostatic load response and were then included in a cumulative index of allostatic load, commonly known as the "allostatic load battery" [14, 17, 27]. This index of allostatic load was found to be a better predictor of mortality and decline in physical functioning than individual biomarkers alone [28–31], yet a number of limitations emerged due to the complexity and dynamic nature of this multisystem network [22].

While the biological perspective does not allow for a comprehensive understanding of allostatic load and overload and related clinical phenomena, a substantial contribution has come from clinimetrics, the science of clinical measurements [32, 33]. Clinimetric criteria for the determination of allostatic overload and the underlying experiential factors (Table 1), as well as a semi-structured interview, have been developed [6, 34] and included in the Diagnostic Criteria for Psychosomatic Research (DCPR) [35]. The interview can be supplemented by the PsychoSocial Index (PSI) [36, 37], a simple self-rated questionnaire, tailored to a busy clinical setting, for a comprehensive assessment of stress, psychological distress, abnormal illness behavior and well-being. The PSI may provide a quantitative measurement of the degree of allostatic load, with opportunity to monitor its course over time. Use of cut-off points for identifying allostatic overload is also possible [36, 37]. The interview and the PSI may contribute to formulating a global clinical judgment of individual assets and coping skills in dealing with current life situations. The clinimetric evaluation of allostatic overload may help identify a state that, by exceeding individual resources, could constitute a danger to health. Unlike in the DSM-5 diagnosis of adjustment disorder [38], the presence of a psychiatric disorder is not a source of exclusion from the criteria.

With this systematic review we try to summarize the current knowledge on allostatic load/overload and its clinical implications. Previous systematic reviews [29, 30, 39, 40] were concerned with specific aspects such as health disparities, workforce, socioeconomic position and psychosocial resources.

Methods

Search Strategy

The methods used fulfilled the PRISMA guidelines [41]. Published articles concerning allostatic load/overload were identified by searching in PubMed, PsycINFO, Web of Science, and the Cochrane Library from inception to December 2019. Search terms included "allostatic load" or "allostatic overload." Only published articles in the English language and involving human subjects were considered for inclusion. A manual search of the literature was also performed, and reference lists of the retrieved articles were examined for further studies not yet identified.

Study Selection

We considered only those studies in which allostatic load or overload were adequately described and assessed in either clinical or non-clinical adult populations. Biological evaluation of allostatic load should be based on at least 3 biological markers. Allostatic overload was determined according to clinimetric criteria. Studies involving pediatric or adolescent populations were excluded.

Data Extraction

The first two authors (J.G. and M.L.) independently performed the search, screened titles and abstracts, assessed the full text of articles appearing potentially relevant, and selected studies meeting the eligibility criteria. In case of disagreement, a consensus was reached through discussion with the senior authors (N.S. and G.A.F).

Data Synthesis

All selected original investigations were reported in the systematic review. Other studies (e.g., articles not primarily focused on allostatic load and studies not involving adults) were not included. The most relevant reviews were cited in the introduction and discussion.

Results

The initial search strategy provided 3,633 published articles that were screened for potential inclusion in the review (online suppl. Fig. S1; for all online suppl. material, see www.karger.com/doi/10.1159/000510696). A total of 524 full-text articles were assessed for eligibility, 267 of which were included in the systematic review.

General Population Studies

Sociodemographic Correlates

Several studies focused on the association between sociodemographic variables and allostatic load [18, 19, 22, 23, 42–58].

Low socioeconomic status was associated with high levels of allostatic load [59–68]. The findings were confirmed by other investigations where high socioeconomic position appeared to be related to low allostatic load [45, 53, 69–72]. Similarly, income level was negatively related to allostatic load in different populations [65, 73–76]. Perceived neighborhood quality may have an impact on allostatic load [77, 78], and high levels of allostatic load were reported by individuals living in impoverished [79–85] or segregated neighborhoods [86]. Nonetheless, adults who grew up in low socioeconomic status households showed lower levels of allostatic load when adapting to life stressors maintaining a focus on the future [87]. Factors such as renting one's home, having low income, and smoking were found to mediate the association between socioeconomic position and allostatic load [88] and explain socioeconomic disparities in allostatic load [88]. Parental socioeconomic position was found to be inversely associated with midlife allostatic load, and part of this association was mediated by education [89]. In a longitudinal community-based study on a multi-ethnic cohort of midlife women, high racial discrimination and hostility, low income, and low education significantly predicted high allostatic load levels [65].

In some studies, allostatic load was negatively associated with years of education [61, 73, 79, 90–92]. However, two investigations [93, 94], examining the mediating role of ethnicity in the relationship between allostatic load and educational attainment, found the highest levels of allostatic load among minorities with a college degree or more.

Ethnicity was associated with allostatic load, with Black Americans displaying higher levels of allostatic load compared to Whites [95–99]. Among immigrants, a positive association between allostatic load and duration of residence was found [100–102], whereas studies on age at immigration yielded mixed results [101, 102]. The relationship between perceived racial discrimination and allostatic load was found to be mitigated by the effect of educational attainment among African American women [103]. Differential associations between everyday versus institution-specific racial discrimination and allostatic load were found among black women [104]. Furthermore, higher allostatic load was shown by individuals reporting greater perceived racial [105] or social inequalities [63, 106], or adversities over the life course [107, 108]. In addition to perceived racial discrimination [65, 109–114], also acculturation stress [115] and weight discrimination [116, 117] were found to be associated with high levels of allostatic load.

There was an association between allostatic load and gender-related characteristics (e.g., androgynous and undifferentiated individuals, masculinity levels), as well as sexual orientation (i.e., lesbian, gay, and bisexual individuals) [118–122].

A negative association between allostatic load biomarkers and religious attendance has been reported [123]. Weekly religious service attendance was associated with lower allostatic load in older adults [124–126]. A significant inverse association between church attendance and all-cause mortality risk, partially explained by allostatic load, was also found [127].

Aging

Several studies have shown an association between allostatic load and frailty, a multidimensional loss of individual resources with aging [128–130]. Evaluation of data from two prospective population-based cohort studies [131] have suggested that several allostatic load parameters could be considered as a preclinical marker of frailty.

Allostatic load was associated with a decline in cognitive and physical functioning in older adults [16, 17, 130, 132–135], changes in brain structure with aging [136], brain-predicted age difference [137], and inversely related to white-matter and brain volume [138]. A potential link between an immune risk phenotype and allostatic load in very old adults was identified [139]. Allostatic load was also found to increase delirium in hospitalized elderly patients [140] and the risk of mortality [141, 142]. Data from a representative longitudinal study on older adults [143] showed that high allostatic load levels were associated with several personality characteristics (neuroticism, lower extroversion, lower conscientiousness) at baseline, and with declines in extroversion, conscientiousness, agreeableness and openness at a 4-year follow-up. Older adults with canine companionship displayed lower levels of allostatic load compared to those without [144].

Data from a large community-based study on participants aged 60 years and over showed a significant association between increased allostatic load levels and worsening of visual acuity, after adjustment for confounders [145]. Further, worse visual acuity increased mortality risk, with a potential mediating effect of allostatic load [145].

Work and Environment

Several studies showed that high levels of allostatic load were correlated with work-related stress [108, 114, 146–151], poor quality job [152] and burnout syndrome [153, 154], but no significant associations were found in other studies [155–158]. A negative association between allostatic load and heart rate variability in males employed full-time was reported [159]. Allostatic load was related to insufficient recovery from work stress in women [160], job demand and reorganization at workplace [150, 161, 162], self-employment [163] and effort-reward imbalance that is regarded as the core dimension of the burnout syndrome [146, 164]. In a study on civil service workers [165], a non-linear, stable association between negative emotional response to major life events and allostatic load was observed.

In two cross-sectional studies, greater vegetated land cover near residence was associated with low allostatic load levels [166, 167]. Conversely, living in an unhealthy environment may have deleterious effects on health. Lead exposure [168, 169], perception of pollution [170], dangerous traffic [125], household crowding [171], and environmental riskscapes [172] may contribute to allostatic load increased levels. Furthermore, poor indoor environmental quality could raise allostatic load [173], whereas better housing conditions and satisfaction with own house appeared to reduce allostatic load [125].

Early Life Events

Adverse childhood experiences, including child abuse and maltreatment, were found to be associated with high levels of allostatic load in adulthood [174–180]; only in one study [181] childhood socioeconomic status and stress exposure in adulthood were found to predict allostatic load, while adverse childhood experiences were not.

Perceived social support across the life span partially mediated the association between child maltreatment and allostatic load in adulthood [182]. As to family environment, some studies reported the association between either harsh parenting in adolescence [183], lower family support [184], or negative family interactions [185, 186] and allostatic load in adulthood. Conversely, emotional and instrumental support in childhood [187], warmth within the family [174], and parental academic involvement [188] appeared to be associated with lower allostatic load in adulthood. Allostatic load in adulthood seems to be related also to avoidant attachment patterns [189] and predicted by adult anxious attachment style [190].

Well-Being and Coping Strategies

Cross-sectional data derived from a multidisciplinary prospective population-based cohort study showed an inverse association between allostatic load and positive affects, after adjusting for confounders, with a stronger association in women than men [191].

As to well-being dimensions, data from the Midlife in the United States (MIDUS) survey showed that greater purpose in life predicted lower levels of allostatic load at a 10-year follow-up [192], while studies on positive relationships and social support yielded mixed results [50, 193–196]. In a longitudinal study on middle-aged healthy women, allostatic load at baseline was found to be a negative predictor of sense of coherence at a 6-year follow-up [197].

In a cross-sectional analysis of data from a large community-based study on African American adults [198], women, but not men, using disengagement coping styles displayed significantly higher allostatic load scores. Among self-employed individuals, problem-focused coping strategies were negatively associated with allostatic load [163]. Cognitive reappraisal was indirectly associated with lower allostatic load, whereas the tendency to use emotion suppression was indirectly associated with greater allostatic load [199]. Further, a significant inverse association was found between intrinsic capacity (i.e., physical and mental skills acquired and modified throughout life) and allostatic load among older adults [200].

Caregiving

Caring for an ill and/or disabled person (i.e., caregiving) represents a risk factor for developing allostatic load, which, in turn, may affect individual health status [151]. The number of negative life events among caregivers of patients with Alzheimer disease was found to be related to allostatic load [201]. Caregivers of patients with Alzheimer disease showed higher levels of allostatic load compared to controls, and this association was mitigated by personal sense of mastery [202]. Parents of children with developmental disorders had lower allostatic load when reporting higher positive affects in a controlled study [203].

Consequences on Physical Health

A number of studies addressed the relationship between allostatic load and health status and outcomes [204–208], including chronic conditions [209], disabilities [210], pain [211, 212], and mortality [17, 24, 56, 213–218].

Poor self-rated health, a measure of actual health status as perceived by an individual, was associated with markers of allostatic load, such as increased cytokine levels [219], higher body mass index and worse lipid profiles [220]. A negative association between self-rated health and allostatic load has been documented by other studies [206, 221–223], and ethnicity seemed to play a mediating role [223].

Allostatic load was found to be related to leukocyte telomere length [224]. Levels of vitamin D [225] and serum carotenoid concentrations [226] appeared to be inversely associated with allostatic load.

Lifestyle Habits

Physical activity was found to be associated with lower allostatic load [227–229], whereas poor sleep quality [230–233], unhealthy diet and overweight [52, 218, 228, 234–239], alcohol consumption [52, 92, 228, 229, 240] and smoking habits [241] were associated with high allostatic load levels.

Cardiovascular Diseases

Allostatic load was linked to increased risk for cardiovascular diseases, particularly coronary heart disease [242], ischemic heart disease [243] and peripheral arterial disease [244].

A clinimetric evaluation of allostatic overload by specific criteria [6, 34, 35] was performed in a number of studies in cardiac settings. In outpatients with essential hypertension and coronary heart disease [245], the presence of allostatic overload was characterized by a higher disease-related emotional burden, poor psychosocial functioning and high rates of psychopathology. Similarly, in patients with atrial fibrillation [246], allostatic overload was associated with increased psychological distress (e.g., depressive and anxiety disorders). In a study on patients undergoing implantable cardioverter defibrillator implantation [247], 16.2% reported moderate allostatic overload, while 4.3% reported severe allostatic overload. The presence of allostatic overload before implantation was the only significant predictor of subsequent negative cardiac outcomes, including complications and death after implantation. In patients with congestive heart failure, prevalence of allostatic overload was as high as 32.9%

[248], with a significant association with hyperglycemia among cardiac risk factors. In essential hypertension, 32.5% of patients reported allostatic overload and displayed significantly higher levels of psychological distress and a greater prevalence of psychosomatic syndromes [249]. The presence of allostatic overload among hypertensive patients was associated with lower levels of well-being and quality of life [249], unlike in a previous study that used different criteria [250].

Diabetes

Patients with type 2 diabetes experienced higher allostatic load and greater depressive and hostile symptoms compared to controls [251]. They were found to display a disruption of multisystem responses to stress, as indicated by systolic and diastolic blood pressure, heart rate, total cholesterol, salivary cortisol, and plasma IL-6 levels. Similarly, among patients with type 2 diabetes, allostatic load was associated with high systolic and diastolic blood pressure, and glycated hemoglobin [252].

Gynecology and Obstetrics

There was an association between early age at menarche, retrospectively ascertained, and allostatic load [253].

Allostatic load in early pregnancy was significantly higher in a sample of women with preeclampsia compared to controls, suggesting a possible role of chronic stress in the development of this condition [254]. Although some studies reported that allostatic load among pregnant women may contribute to adverse pregnancy and birth outcomes [255–257], research findings appear to be rather controversial [81, 258, 259].

Musculoskeletal Disorders

In a cross-sectional study, greater allostatic load levels were associated with lower spine bone mineral density and lower femoral neck strength values [260].

Symptom frequency and intensity were associated with higher levels of allostatic load among chronic fatigue syndrome patients compared to controls [261–263]. In this condition, polymorphisms in angiotensin-1-converting enzyme linked to allostatic load were reported [264].

A recent preliminary study on female outpatients with fibromyalgia found a prevalence allostatic overload, based on clinimetric criteria, as high as 25% of the sample [265].

Neurological Disorders

Depressive symptoms after traumatic brain injury appeared to be related to chronic stress [266] and perceived stress [267]. In a sample of individuals with a first unprovoked seizure or newly diagnosed epilepsy, allostatic load was associated with a higher risk of seizures [268].

In a recent study [269], allostatic overload based on clinimetric criteria was one of the most frequent psychosomatic diagnoses among patients with either episodic or chronic migraine.

Cancer

Women with breast and ovarian cancer displayed elevated basal cortisol levels and decreased acute cortisol reactivity compared to healthy controls [270]. Among patients with breast cancer, black women reported higher levels of allostatic load compared to both white patients and control subjects [271], after adjusting for confounders. Allostatic overload was more common among cancer survivors (52%) than healthy controls (33%) [272].

A randomized controlled trial reported the clinical utility of a mentor-based supportive-expressive program designed to help women with metastatic breast cancer, that obtained significant improvements in allostatic load parameters as well as in affective symptoms and quality of life [273].

Periodontal Diseases

Data from a large community-based investigation [243] and a subsequent study [274] provided support for the association between allostatic load and periodontal diseases. Further, children of mothers with increased allostatic load were significantly more likely to have dental caries, suggesting the role of maternal stress in child oral health [275].

Consequences on Mental Health

A clinimetric assessment in the general population [276] revealed that subjects with allostatic overload had significantly higher levels of self-rated stress, psychological distress and abnormal illness behavior than those without. The clinimetric criteria for allostatic overload were able to discriminate the presence of psychological distress in another sample of the general population as well [277]. In a primary care setting [278], allostatic overload was the most frequently reported psychosomatic syndrome according to the DCPR [35]; it was associated with significantly greater psychological distress, lower well-being and impaired quality of life.

Mood and Anxiety Disorders

Several studies showed a significant association between depressive and anxiety symptoms and allostatic load [279–283], not confirmed by others [233, 284–286]. In the association between childhood physical abuse and depression in adulthood, allostatic load appeared to have a mediating role [287]. In a prospective study [288], reaction time in adolescence was found to be predictive of depressive symptoms in adulthood, with a mediating effect of cumulative allostatic load. Data from a large community-based study showed that high allostatic load was more strongly associated with depression among white women and black men than among their respective counterparts, with differences across gendered race groups [282]. In emergency patients primarily diagnosed with mood or anxiety disorders [283], higher levels of allostatic load were found than in those diagnosed with personality disorders.

In a study on older adults, higher levels of allostatic load were associated with both affective and somatic depressive symptoms [280] and were prospectively associated with depressive symptoms at a 3-year follow-up in another [279]. Among older euthymic bipolar disorder patients [289], allostatic load was found to be associated with delayed memory performance.

Post-Traumatic Stress Disorder

Allostatic load helped to understand the association between maternal post-traumatic stress disorder (PTSD) and birth outcomes (i.e., pregnancy complications, preterm birth) [290]. Mothers of pediatric cancer survivors were found to display significantly higher levels of allostatic load compared to control mothers of healthy children, and those meeting criteria for PTSD reported the highest allostatic load levels [291, 292]. In adults with early life traumas, neuroendocrine biomarkers of allostatic load were significantly related to early life stress and subsequent PTSD development [293]. In a study on women veterans reporting multiple sexual assaults during childhood and civilian and military life, higher allostatic load levels were detected compared to women reporting sexual assault in only one life circumstance [294].

Psychotic Disorders

Allostatic load was associated with cortical thickness [295] and fornix microstructure [296] in schizophrenic patients. It seemed to have a role early in the course of schizophrenia and in greater severity of positive psychotic symptoms in its early stages [297], as well as in the chronic course of the disease [298]. Accordingly, higher levels of allostatic load were found in patients at their first psychotic episode [299, 300] and at acute relapse of schizophrenia [301] compared to control subjects. Allostatic load appeared to be inversely related to psychosocial [299] and cognitive functioning [301] in psychotic patients.

Alcohol Dependence

The combined contribution of hypothalamic-pituitary-adrenal reactivity and environmental stressors to relapse severity in alcohol-dependent men following treatment was investigated [302]. Greater levels of ongoing life stress strengthened the relationship between adrenocortical sensitivity and post-treatment drinking. Environmental stressors increased relapse intensity [302].

Discussion

Most research on allostatic load relies on biomarkers that express a state of body systems, but do not provide information on the underlying individual causes. Moreover, substantial heterogeneity exists across studies as to the type and number of parameters to be considered. It seems that use of clinimetric tools can increase the number of people screened, set the use of biomarkers in a clinical context, and broaden dissemination of measures to prevent or decrease the negative impact of toxic stress on health.

The findings indicate that higher allostatic load and overload are associated with poorer health outcomes in both general and clinical populations. The results provide support to the clinical utility of the trans-diagnostic identification of allostatic load and overload in a variety of settings, with a number of potential applications.

Consideration of allostatic load may increase the predictive power of the assessment procedure and may contribute to the understanding of many symptoms that are commonly encountered in clinical practice, but that, in a predominantly disease focused model, fail to receive adequate attention and care [303, 304]. Clinical assessment of allostatic overload may help to demarcate important differences in patients who otherwise seem deceptively similar because they share the same medical diagnosis, as it was found to be the case in cardiovascular diseases [242–244], particularly congestive heart failure [248], atrial fibrillation [246] and hypertension [249]. Allostatic load acknowledges the burden of different phases of medical disorders. Examples are provided by the post-hospital syndrome, a period of enhanced vulnerability to disease and to adverse events [305]; difficulties related to the process of recovery or rehabilitation [306]; and the cumulative long-standing chronic disease impairment [307]. In general, psychological distress was reported in subjects displaying allostatic overload [276–278], which could also be linked to the onset and course of psychiatric disorders [297, 308, 309].

General population studies indicate that allostatic load is increased by low socioeconomic status, living in impoverished neighborhoods, low educational attainment, ethnicity and racial discrimination [39, 93]. Further, most of the studies indicate a relationship between high levels of allostatic load and work-related stress (including caregiving) with the ensuing risk of burnout syndrome [151, 153, 154]. In this regard, allostatic overload has been used as a conceptual framework for understanding the physical and psychological state of medical health workers facing the COVID-19 pandemic [310, 311]. In older adults, allostatic load was found to be associated with a decline in cognitive and physical functioning, and with frailty, as a multidimensional loss of individual resources [128–132]. Adverse experiences in childhood, including child abuse and maltreatment, were found to predict high levels of allostatic load later in life [15, 312]. Altogether, individual psychological well-being and coping styles may modulate the association between socio-demographic factors and allostatic load [87], and higher psychosocial resources were linked to lower allostatic load [40, 194]. Environmental factors, such as work and living conditions, play an important role in determining allostatic load [125, 149, 162], but their modification is often not taken into account. Work conditions are modifiable factors to be targeted by specific interventions [313]. Work reorganization and stress management in employees may reverse allostatic overload and stimulate physiological regeneration processes and recuperation [313]. Inclusion of allostatic load in the clinical assessment allows to view illness within the interaction between the individual and the surrounding environment.

Allostatic load was associated with health-damaging lifestyle habits, such as lack of physical activity, unhealthy diet and poor sleep, in several investigations [52, 228, 229, 233, 239]. The metabolic syndrome, which may be frequently associated with allostatic load [17], is an important example of the devastating effects of harmful lifestyles and of the need to prevent its occurrence as early as possible in life [314]. Individuals may try to counteract manifestations of allostatic overload by the use of medications (e.g., sleeping pills). However, the adverse iatrogenic effects [315] may cause a state of "pharmacological allostatic load" [27] and medications do not entail solution to problems they are used for. Promoting lifestyle modifications and pursuit of psychological well-being, whose importance is increasingly recognized in clinical medicine [316] and psychiatry [317], may provide more enduring effects. Psychotherapeutic strategies aimed at improving coping with stressful situations [304, 318–320] may also be of value. The clinical diagnosis of allostatic overload may be helpful in a comprehensive approach that seeks to understand how the interactions among genetics, mind, body, behavior and the environment affect both the risk of disease and the response to treatment [321]. However, we still lack studies that employ both clinimetric criteria and biological markers. Such investigations would shed some light on the correspondence between clinical and biological parameters, and provide a determination of the state of allostatic overload better than either criteria used alone. In this context, consideration of components that may buffer the impact of stress may be important [313]. In clinimetric terms, this translates into consideration of psychological well-being and euthymia [317, 322]. McEwen [314] has emphasized how coping with daily life challenges is continuously shaping both brain circuitry and systemic physiology, which, in turn, determine lifestyle choices in terms of protective or damaging health behaviors. Such adaptive changes may trigger epigenetic mechanisms [314, 323] that modulate physiological and psychological sensitivity and are relevant for regenerative processes [313]. Consideration of the impact of allostatic load on health also calls for a multidisciplinary organization of health care to overcome the artificial boundaries among medical specialties, based mostly on organ systems (e.g., cardiology, endocrinology) that appear more and more inadequate in dealing with symptoms and problems which cut across organ system subdivisions [303, 324, 325].

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

All authors conceived the project. J. Guidi and M. Lucente performed the searches and collected the data. All authors analyzed the data, drafted and revised the paper.

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