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Socio-economic differentials in peripheral biology: Cumulative allostatic load

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This chapter focuses on evidence linking socio-economic status (SES) to "downstream" peripheral biology. Drawing on the concept of allostatic load, we examine evidence linking lower SES with greater cumulative physiological toll on multiple major biological regulatory systems over the life course. We begin by reviewing evidence linking lower SES to poorer trajectories of aging in multiple, individual physiological systems, followed by evidence of the resulting cumulative, overall burdens of physiological dysregulation seen among those of lower SES. The role of cumulative physiological dysregulation in mediating SES gradients in morbidity and mortality is then examined. We conclude with discussion of the question of interactions between SES (and other such environmental factors) and genetic endowment, and their potential consequences for patterns of physiological activity—an area of research that appears poised to contribute significantly to our understanding of how social conditions "get under the skin" to affect health and aging.

Keywords: SES; allostatic load; peripheral biology

Introduction

Building on the previous chapter's focus on socio-economic status (SES) differences in central (brain) aging and function, this chapter examines evidence regarding SES impacts on "downstream" peripheral biology. We discuss the brain-mediated influences of SES on patterns of activity as well as aging of major peripheral physiological regulatory systems, including the autonomic nervous system, cardiovascular, metabolic, and inflammatory processes, presenting evidence for SES gradients in parameters of each of these major systems. Drawing on the concept of allostatic load (AL), we also examine the cumulative impact of SES across these multiple biological systems and parameters. Such a multisystems view of the impact of SES on rates of aging of peripheral biology provides a different and complementary perspective to that of SES effects on individual physiological systems. Although lower SES is nearly always associated with poorer trajectories of physiological aging when individual biological parameters are examined, the gradients are generally relatively modest while larger gradients are frequently evident when examining "cumulative" measures, representing multisystems indices of physiological aging, suggesting that lower SES is associated with more rapid aging of all major systems. We review the growing evidence for both the more modest SES gradients in individual systems/parameters as well as the recent literature focusing on cumulative indices of physiological dysregulations across multiple systems. We also examine the small, but growing, literature focused on testing the role of such cumulative physiological dysregulation in mediating observed SES gradients in risks for a range of diseases, disability, and mortality.

We also provide a brief overview of the latest work testing for interaction effects between SES (and other such environmental factors) and genetic endowment and their resulting impact on patterns of physiological activity—an area of research that appears poised to contribute significantly to a more substantive understanding of how social conditions

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"get under the skin" to affect health and aging over the life-course. Above and beyond providing clearer understanding of the physiological routes through which SES impacts health and aging, research on links between SES and peripheral biology can also contribute to the development of more evidence-based programs and policies to reduce current social inequalities. Information on peripheral biology could be used, for example, as an intermediate "outcome," for tracking the more immediate, and hopefully beneficial impacts of such policies and programs.

Socioeconomic status gradients in patterns of activity in major regulatory systems

As the McEwen and Gianaros chapter outlines, growing evidence points to significant SES differences in brain development and function, beginning at the earliest stages of life and continuing across the life-course. Such differences in brain development and function impact, and indeed regulate, downstream peripheral biology through cortico-limbic pathways, including known interconnections between structures such as the prefrontal cortex, hippocampus and amygdala, and more downstream regulation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS), orchestrated in large part through the hypothalamus and adrenal gland.[1–5] In the following sections, we examine evidence linking SES to differences not only in such downstream HPA and SNS activity (*e.g.*, circulating levels of cortisol, norepinephrine (NE), and/or epinephrine) but also in additional related regulatory systems reflecting cardiovascular, metabolic, and inflammatory parameters.

Table 1 provides an overview of major biological systems and their respective parameters that are our focus in light of their known associations with increased risks for major health outcomes.

The negative health consequences of high *blood pressure* (particularly systolic) have been recognized for decades, including higher death rates, the onset of cardiovascular disease, and the loss of both physical and cognitive functioning.[6–9] Several studies have also found that high resting heart rate is associated with increased mortality risk (see Ref. 10 for review). *Metabolic parameters,* including higher total serum and LDL cholesterol, lower HDL cholesterol, and higher relative weight, are also recognized risk factors for poor health outcomes including mortality, cardiovascular disease, and functioning loss.[7,11–14] Elevated glucose levels—as indexed by fasting glucose or more integrated assessments of glucose metabolism such as glycosylated hemoglobin (HgA1c)—have also been related to heart disease risk;[15] to higher mortality;[16] and to poorer cognitive[17–20] and physical function.[8] It is important to note that even modest elevations in these biomarkers are associated with adverse outcomes, even when they do not meet accepted thresholds for clinical intervention.[21,22]

Dysregulations in HPA axis activity, particularly chronically elevated cortisol, have been related to increased risks for range of health problems, including obesity,[23] hypertension, diabetes

Table 1. Major biological regulatory systems

System	Parameters commonly assessed
Cardiovascular	Diastolic/systolic blood pressure
	Heart rate/pulse
Metabolism	Glucose, glycosylated hemoglobin
	Insulin
	Lipids (total, HDL, LDL cholesterol)
	Relative weight (BMI, WHR)
Hypothalamic-pituitary-adrenal (HPA) axis	Cortisol; dehydroepiandrosterone sulfate (DHEA-S)
Autonomic nervous system	
Sympathetic nervous system (SNS)	Norepinephrine, epinephrine
SNS/Parasympathetic balance	Heart rate variability
Inflammation	C-reactive protein, IL-6

mellitus type 2, lipid imbalance, atherosclerosis,[24–26] accelerated brain aging,[27] hippocampal atrophy, and cognitive impairment,[28–31] loss of bone mineral density,[32–34] sarcopenia,[35] and immune dysfunction.[36] Similarly, more chronic elevations in SNS activity can raise blood pressure and heart rate that promotes atherosclerosis, and appears to be independently associated with cancer mortality.[37]

Exposure to chronically elevated inflammation processes has also been increasingly recognized as a significant health risk with links to increased risks for osteoporosis,[38,39] cardiovascular disease,[40–45] and cognitive decline.[46–48]

As reviewed in McEwen and Gianaros chapter, these peripheral processes also have feedback loops to the brain such that downstream physiological activity frequently has significant impacts on "brain health" as well. For example, dysregulation of metabolism as in Type 2 diabetes has deleterious effects on the brain.[49] Elevated HPA and cardiovascular parameters have also been linked to poor cognitive functioning in many studies.[29,31,49–54] Accumulating evidence also indicates that inflammatory processes in the body are associated with reductions in volume of a key brain structure, the hippocampus[55] as well as poor sleep[56] (for additional details see chapter by McEwen and Gianaros). From our perspective, a significant and central feature of these biological processes is the degree to which they not only relate to major health risks but also exhibit gradients by SES. A growing body of evidence documents consistent SES gradients for nearly all of these biological risk parameters—with lower SES groups exhibiting higher levels of risk. Much of the earliest work presented evidence for these SES gradients in adults[12,57] but more recent work has shown that these same SES gradients are evident as early as the first 5 years of life,[58–60] as well as throughout childhood,[59,61–65] early adolescence,[66–68] and into early adulthood.[69–73] Figure 1A and B illustrate these gradients, showing levels of glycosylated hemoglobin (HgA1c)—an index of overall glucose metabolism over the past 6–8 weeks[74]—by SES as indexed by the poverty income ratio (PIR), an index of household income relative to the federally defined poverty level.

As shown in Figure 1A, gradients in HgA1c levels are seen even as early as ages 1–5, with those from lower income (lower PIR) households showing higher prevalence of elevated HgA1c levels compared with children from higher income (higher PIR) families; Figure 1B documents that these gradients continue throughout adulthood as well. As shown in Figure 2, similar SES gradients are seen for a wide array of additional biological risk factors, including blood pressure, total and HDL cholesterol, and C-reactive protein (CRP) with lower SES associated with a higher prevalence of "high risk" values for all of these parameters—"high risk" being defined based clinically accepted criteria.[75–80] Indeed, a large body of evidence documents SES gradients for nearly all major peripheral biological parameters, including those reflecting HPA axis regulation,[60,62,66,70,72,81–85] SNS activity,[60,71,72,81,83,85] heart rate variability (an index of autonomic balance),[60,86–88] resting blood pressure,[61,66,69,83,89–92]

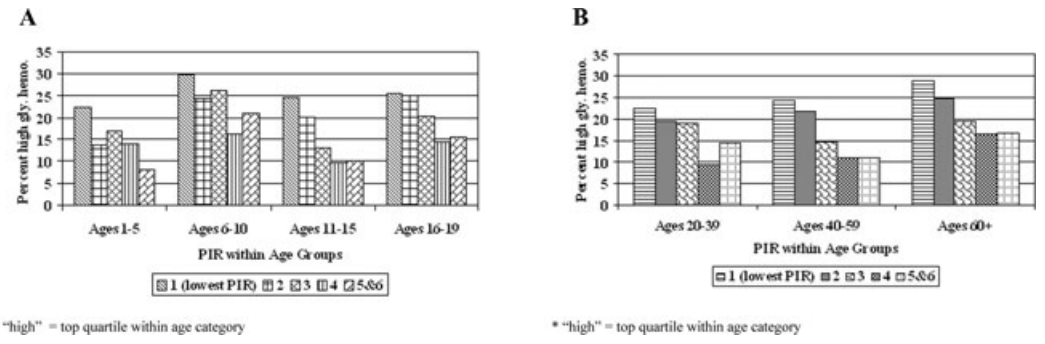

Figure 1. (A) High glycodylated hemoglobin* by Poverty Income Ration (PIR). SES gradients based on PIR in relation to glucose regulation among children (*i.e.*, ages 19 and under). (B) High glycosylated hemoglobin* by PIR. SES gradients based on PIR in relation to glucose regulation in adults (*i.e.*, ages 20 and above)—NHANES III (1988–1994).[1] PIR reflects the ratio of respondents' reported household income to the federally defined poverty level for those living in the respondent's area of residence and with a household size similar to the respondent's.

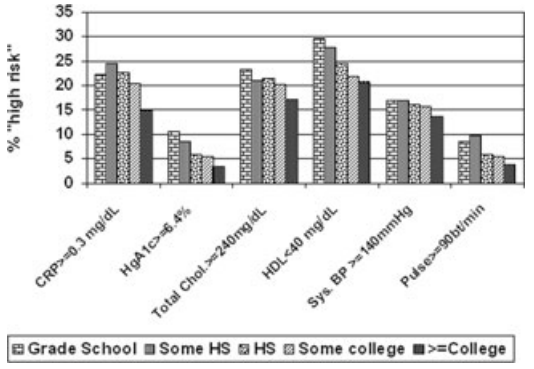

Figure 2. Education gradients in "percent with high risk values" for components of allostatic load.

and reaction to challenge (see Ref. 93 for review), lipids/metabolic risks,[72,90,92,94–102] inflammation,[73,94,103–109] and relative weight and fat distribution patterns (*i.e.*, body mass index, waist-hip ratio).[90,92,95,110] In addition to the foregoing evidence linking individual SES to major biological risk parameters, evidence also points to impacts from more macro-level, neighborhood-level SES (*e.g.*, Refs. 111,112).

Cumulative biological "wear and tear" (that is, allostatic load)

The concept of "allostatic load," introduced in the early 1990s by McEwen and Stellar,[113] proposes a multisystems view of the cumulative physiologic toll that may be exacted on the body over the course of a lifetime of efforts to adapt to life's demands.[113] The concept of allostatic load is itself derived from Sterling and Eyer's[114] concept of allostasis, meaning "stability through change"; allostasis refers to the physiological imperative that "an organism must vary parameters of its internal milieu and match them appropriately to environmental demands" (p. 638). This view of internal physiology emphasizes its constant dynamism, stressing that healthy functioning requires on-going adjustments of the internal physiologic milieu, with physiologic systems exhibiting fluctuating levels of activity as they respond and adapt to environmental demands. Moreover, each mediator involved in allostasis is part of a nonlinear network in which each mediator has biphasic effects on physiological outcomes and also has reciprocal regulatory influences on other mediators.[115]

Allostasis thus emphases the idea of optimal operating ranges of physiologic systems in contrast to the earlier homeostatic idea of optimal set-points. It also acknowledges that few homeostatic networks are solely under local regulation but rather are importantly regulated centrally by the brain (see also McEwen and Gianaros chapter). As such, our perceptions and cognitive-emotional responses to environmental stimuli can, and do, influence patterns of physiological activity and reactivity as, for example, when our blood pressure rises in anticipation of standing.[114]

The concept of allostatic load derives from a longer-term, cumulative view of the process of allostasis and the consequences of dysregulation in patterns of response to environmental demands (*i.e.*, responses that no longer operate within optimal ranges). The premise is that while relatively short-term fluctuations in levels of physiologic activity are necessary for the body to respond successfully to stimuli (*e.g.*, the fight or flight response in the face of various types of danger), excessive fluctuations either in terms of the extent, duration or frequency (*e.g.*, responding to perceived "danger" everywhere) can result in wear and tear on the body's regulatory systems. This wear and tear is manifested in progressive dysregulations in the system's ability to maintain levels of system parameters within "normal operating ranges" in terms of resting levels (*e.g.*, seated blood pressure or fasting glucose) and dynamic patterns of response (*e.g.*, extent and duration of response). Allostatic load represents the cumulative physiological toll (*i.e.*, the extent of such dysregulation) across multiple systems over time. It reflects both a multisystem and life-span orientation, visualizing disease risks as resulting from the individual's cumulative exposure over time to the "wear and tear" associated with elevations in physiologic activity across the body's multiple regulatory systems.

The idea that cumulative levels of "stress" may have deleterious effects on health and longevity has long intrigued investigators, dating back to early work on homeostasis[116,117] and continuing with the work of Selye[118–120] and others[121] on the pathological consequences of excessive physiologic activation. Much of this work has tended to focus on the effects of stress and dysregulation in specific, individual biological parameters.[122–127] The concept of allostatic load proposes that biological

risk can be more effectively conceptualized from a more cumulative, multisystems view and that such a concept can better contribute to our understanding of health outcomes—a view that is consistent with known multifactorial etiologies of most pathology. In part, this view stems from the realization that these individual mediators are coupled together in nonlinear networks and cannot be independent of each other.[115]

Selye himself wrote that "life is largely a process of adaptation to the circumstances in which we exist..(and)..the secret of health and happiness lies in successful adjustment to the ever-changing conditions on this globe; the penalties of failure in this great process of adaptation are disease and unhappiness" (pp. xv–xvi,[120]). Allostatic load might then be viewed as an index of the relative degree of "failure" at a physiologic level—*i.e.*, a marker of the cumulative, physiologic costs of previous efforts to cope with life's slings and arrows. It is the price that the body may ultimately pay for dysregulated patterns of physiological response to adaptational demands (*e.g.*, patterns of under- or over-responding). As an "historical" index of prior physiologic toll, allostatic load also provides the background setting for current and future patterns of physiological response to stimuli and thereby contributes significantly to health risks.

Allostatic load differs from more traditional concepts of biological risk in two ways. The first is its focus on "the sum total of physiological dysregulation across systems"—a view closer to the reality of known system interconnections than approaches that focus on the role of one or another regulatory system. And, the second is its inclusion of relatively more modest forms of dysregulation in the accounting of biological risk. This view of biological risk proposes that relatively modest dysregulation (*e.g.*, somewhat elevated BP and/or more frequent or prolonged elevations in response to stimuli) when cumulated across multiple systems may have significant impacts on health risks, even if none of the individual effects would be deemed either statistically or clinically "significant" in and of themselves. The sum of these effects is nonetheless hypothesized to exert a cumulative wear and tear on systems.

As a cumulative phenomenon, allostatic load is postulated to develop over the life course, with individuals accumulating AL at different rates. Both the initiation and progression of such dysregulation is postulated to be driven by individual differences in the frequency of exposure to real and perceived challenges and differences in their patterns of physiological responses to these challenges. Factors that may influence characteristic patterns of reactivity (*i.e.*, maximum change from basal levels and duration of the response) include such things as (1) *age* (*e.g.*, prolonged neuroendocrine responses at older ages have been found in some studies[124,128] though not all (see Epel *et al.*, 2007[129] for review), as well as decreased vagal tone at rest,[130] decreased cardiovagal baroreflex sensitivity,[131] and impaired functional immune responses to challenges, such as vaccination[132]); (2) *genetic influences (e.g.*, certain polymorphisms being associated with greater physiological dysregulation in the face of stressful conditions[133,134]); (3) *lifestyle/behavioral influences* (*e.g.*, hyper-reactivity of HPA, SNS, blood pressure, and glucose among the less physically fit and overweight individuals,[135–141] and among those consuming greater sugar/glucose;[142–144] smoking has also been associated with increased acute HPA and SNS reactivity[145,146] but longer-term blunted HPA responses to acute stress[147] while alcohol consumption has been associated with increased HPA reactivity[148,149] along with decreased blood pressure and heart rate response to acute stress[150]); (4) *psychological influences* (*e.g.*, hyper-reactivity of cardiovascular and HPA systems among those with poorer self-esteem,[151] poorer self-efficacy beliefs,[152,153] more passive coping[154], and greater hostility or Type A personality attributes[155–158]); (5) *inter-personal/social influences* (*e.g.*, greater HPA, SNS, and cardiovascular reactivity under conditions of social isolation and social conflict;[159–161]); and (6) *chronic stressor experience* (*e.g.*, greater SNS reactivity and lower functional immune activity to acute stressor experiences in those with a higher level of background stress;[162] although lower levels of endocrine and immune reactivity have also been observed[163]).

Though supported by less empirical evidence, additional factors likely to influence the frequency of reactivity include: (1) *environmental exposures* (*e.g.*, neighborhoods where you live and work); (2) *individual differences in what is perceived as "threatening."* Indeed, the latter is perhaps the most uniquely "human" feature of our stress responses. Specifically, the capacity of our brains to imagine

scenarios (*e.g.*, potential outcomes of situations) contributes a special feature to human stress responses, so that in the extreme case, one could experience prolonged stress responses solely due to perceptions/beliefs regardless of the actual, objective presence of danger or stressors. Conversely, some individuals may respond only minimally if at all to what most would view as major life challenges. Indeed, such individual differences in the interpretation of situations can result in dramatically different patterns of response at all levels (cognitive/emotional, behavioral, and physiological). Over time, as a result of individual differences in exposure to different situations and stimuli, and individual differences in cognitive/emotional reactions to these stimuli, population differences in allostatic load are postulated to develop. Older individuals will generally have more cumulative load; but within any given age group, there will be a range of allostatic loads that reflect differences in prior exposures and reactions to one's life-time experiences.

Empirical efforts to operationalize allostatic load

Though attracting considerable attention and enthusiasm from a theoretical/conceptual point of view, the multifaceted nature of allostatic load has proven to be difficult to operationalize in any straightforward or accepted, "gold standard" way. Despite continued work using various methodologies,[164–169] debate continues regarding how best to capture the multiple and inter-connected features of AL,[165,170] including questions regarding the range and scope of physiological measurements that should be included (*e.g.*, which systems and which aspects of these systems) as well as methods for summarizing such information into one or more "cumulative indices." As highlighted in the Evans and Kim chapter, these debates show remarkable parallels to earlier debates on development of cumulative indices of childhood psychosocial and environmental risk factors, including concerns about the use of indices that "cumulate" effects of different systems or domains into a single score (thereby obviating the ability to ascertain the impact of individual components) as well as concerns regarding the use of simple summative approaches that fail to account for the potentially differential impact of different components of risk (see Refs. 134,171 for overviews). As Rutter and others have shown, however, simple summative indices appear to capture the essential cumulative nature of such childhood risk factors and the cumulative number of such risks appears to predict outcomes more strongly than specific risk factors or combinations of such factors (see Refs. 134,172 for review). Other fields have also employed similar approaches to capture the combined impacts of multiple forms of child abuse[173,174] and environmental risks.[175]

Initial efforts to operationalize AL followed a similar approach,[176] using a straightforward summative methodology. Such an approach also shares similarities with other indices of cumulative biological risk that combine information on multiple risk factors into a single score, including the metabolic syndrome[177,178] (which is calculated as a simple sum with equal weighting for all contributing factors) and Framingham Risk Score[179] (which is calculated with differential weight for component items). These latter cumulative scores—like their analogs in the childhood psychosocial risk literature—have been shown to predict outcomes better than their individual components.[179] Indeed, use of such cumulative assessment is now recommended for clinical decision-making related cardiovascular disease risk management.[80,180] Drawing on available data from the MacArthur Study of Successful Aging[181] for an initial set of data on 10 biological parameters—resting systolic and diastolic BP; waist-hip ratio; total and HDL cholesterol; glycosylated hemoglobin; urinary free cortisol, NE, and epinephrine; dehydroepiandrosterone sulfate (DHEA-S), reflecting four major regulatory processes (HPA, SNS, cardiovascular, and metabolic)—we constructed an initial index of AL by simply summing the number of parameters for which the individual had a value that placed them in the top quartile (or bottom quartile for HDL cholesterol and DHEA-S) of that parameter's distribution within the MacArthur cohort.[176] It is important to note that this original set of 10 parameters was not meant to be comprehensive nor was it offered as a fixed/standard measure of AL, rather it was an initial attempt to operationalize AL using available data. Indeed, subsequent work from this study has been able to augment the panel of AL components with additional information on parameters of inflammation (CRP, interleukin-6 (IL-6))—the goal being to optimize our assessment of overall AL by incorporating information regarding the multiple regulatory systems involved in

allostatic "adaptive" processes. This "inclusive" approach to operationalizing AL contrasts with that of many of the more traditional and targeted risk indices such as those developed to predict risks for cardiovascular disease where selection of a specific set of component physiological parameters is based on their known contribution to risks for the specific outcome in question. Operationalization of AL, by contrast, seeks to achieve an index that—as comprehensively as possible—reflects the overall total cumulative burden of physiological dysregulations in allostatic processes across as many regulatory systems as possible. Thus, the focus in terms of measuring AL is on capturing a multisystems array of information regarding the multiple major regulatory systems involved in adaptive "allostatic" processes rather than prediction of one or another specific outcome.

The choice of "top risk quartile" as our criterion for counting a given parameter was based on two considerations. First, this allowed for a common definition of "higher risk" for all of the components of our summary score; use of "clinically defined higher risk" guidelines was not feasible as such guidelines did not (and still do not) exist for many of the constituent parameters (*e.g.*, 12-h overnight urinary free cortisol, NE, and epinephrine (EPI)). Second, given the original design of the MacArthur study (*i.e.*, enrollment of a cohort of relatively high functioning 70–79 years old), our chosen criteria provided an assessment of which individuals within this cohort exhibited relatively "higher risk" profiles compared with their counterparts in the cohort. We also elected not to define gender-specific definitions as we would then be unable to compare men and women in the cohort based on a common definition.

Using this simple count index, analyses of the MacArthur Study data demonstrated that baseline AL was associated with significantly increased risks for a range of major outcomes, including risks for mortality, incident and recurrent cardiovascular disease, cognitive and physical decline. These associations were found both with respect to an initial 2.5 year follow-up period[176] as well as a longer 7-year period,[164] and the effects were found to result from the contributions of multiple regulatory systems represented in the index,[164] providing support for the cumulative nature of the risks reflected in such a summary index of AL. Subsequent work has shown that these associations are replicated when a variety of alternative scoring methods that incorporate more complex and detailed scoring algorithms are used to create indices of AL, including canonical correlation analyses,[169] grade-of-membership[166,167,182] and recursive partitioning.[168] The rationale for moving to these more complex scoring systems is their ability to incorporate more detailed information on specific values for the various component physiological parameters (rather than simply "counting" whether or not one's value is above or below a defined threshold value). And, in some cases (*e.g.*, recursive partitioning), their ability to account for potential nonlinearities in risk (*i.e.*, interactions between component physiological parameters). To date, however, evidence on their relative performance in predicting outcomes as compared to simpler count indices remains sparse. Available comparative data suggest that more complex scoring systems that incorporate greater information are, as expected, more strongly related to outcomes.[166] (Seeman and Karlamangla unpublished data) However, the "gains" in predictive ability appear to be relatively modest. For example, data from the MacArthur Aging Study suggests that the original simple count index captures a majority of the relevant health risk information—*e.g.*, correlations with decline in cognitive and physical function of 0.12 and 0.30, respectively, for the count index as compared with correlations of 0.17 and 0.39 based on the canonical AL index (Karlamangla and Seeman, unpublished data). Though suggestive, such comparative data remains sparse and the question of how best to approach cumulative scoring of AL remains a topic of significant interest and discussion. More comparative work is clearly needed to better evaluate the relative "gains" from more complex scoring systems such as canonical correlations, grade-of-membership, and recursive partitioning, before any "best practice" guidelines can be offered with respect to scoring of AL.

SES gradients in cumulative biological "wear and tear" (that is, allostatic load)

Empirical research has also provided evidence of the cumulative nature of AL across the life-course[183] as well as evidence supporting the hypothesis that the added stresses and resource constraints associated with lower SES are associated with faster accumulation of AL (*i.e.*, greater age-specific burdens of

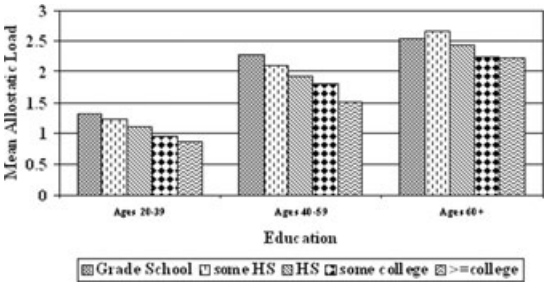

Figure 3. Total allostatic load by education. SES and total allostatic load among adults—NHANES III (1988–1994).

AL). Data from the MacArthur Study again provided the initial evidence to support this hypothesis, documenting not only the hypothesized SES differences but also the contribution of these SES-associated differences in AL to explaining observed SES gradients in mortality.[85] Building on this initial evidence, Singer and Ryff[184] demonstrated that both adult and childhood SES contributed to observed differences in AL for adults in their early 1960s.

Consistent with the hypothesis that lower SES is associated with faster accumulation of AL (*i.e.*, greater "wear-and-tear" on physiological regulatory systems), SES related gradients emerge as early as the first 5 years of life and persist throughout childhood, adulthood, and older age.[58,83,85,185–187] Analyses of nationally representative U.S. data for adults aged 20 and over from the National Health & Nutrition Survey (NHANES) have also documented these same SES gradients in AL[188–190] and the faster age-specific accumulation associated with poverty.[191] Figure 3 illustrates both of these trends, showing SES gradients in each of three adult age groupings as well as the greater cumulative AL among those of lower SES within each of these age groups. Although SES gradients in accumulated AL narrow in the oldest age group, consistent with the hypothesis that all are susceptible to age-associated increases in AL, it is important to note that higher SES older adults exhibit levels of AL that are similar to levels experienced in lower SES adults during middle-age. Also, consistent with evidence linking cumulative exposure to lower SES conditions to increased health risks (see Cohen *et al* chapter), one of the few studies to examine SES histories in relation to AL found that greater exposure to lower SES (*e.g.*, reporting low SES as a high school student and as an older adult) was associated with the highest levels of AL while consistently high SES was associated with the lowest levels of AL.[184] Among those reporting changes in SES, increases in SES from childhood to adulthood were associated with levels of AL closer to the "consistently high SES" group while downward mobility was associated with levels closer to the "consistently low SES" group.[184]

A much smaller AL literature speaks to the question of whether and how much such cumulative profiles of biological risk actually mediate SES differentials in health outcomes. Several published reports provide evidence supporting the role of multiple biological systems in mediating SES differentials in mortality.[12,57,85,174] Consistent with the basic concept of AL (focusing on the known co-occurrence of biological risks), examination of specific biological parameters or regulatory systems/processes provides more modest evidence of mediation, with the most extensive/complete mediation seen when the broadest array of biological systems are taken into account. Analyses from the MacArthur Study of Successful Aging, for example, document that the total AL index mediates some 35% of the education gradient in mortality while none of its component items or subscales accounts for anything close to this, with most accounting for under 15%.[85] Preliminary evidence also suggests that links between SES and AL are at least partially explained by SES-related gradients in factors such as health behaviors[85] but additional work is needed to elucidate more fully the ways in which SES contributes to the accumulation of AL.

Future directions

To date, research on AL has largely focused on testing of main effects of SES. However, a small but growing body of evidence suggests that future research should consider potential moderating effects of SES with respect to the impacts of other psychosocial and/or environmental "stressors/stimuli" on physiological parameters and accumulation of AL. Current evidence, for example, suggests that lower SES may synergize with other stressors, potentiating the negative impact of "stressors" on accumulation of AL.[67,83,192,193] Availability of psychosocial resources may also convey greater relative benefits in the context of lower SES. For example, sense of control is more strongly associated with better health among

those of lower SES[194] while presence of supportive social ties was strongly related to more positive reports of psychological well-being in lower SES groups.[195] Though as yet not linked to biological parameters, one might hypothesize that in addition to these better self-reports of health, those of lower SES who enjoy such psychosocial resources will be found to exhibit lower cumulative AL than might otherwise be expected. Investigation of these potentially important modifiers of overall SES effects on biology will be an important next steps in understanding the multiple and complex pathways through which SES affects peripheral biology and ultimately morbidity and mortality.

The question of gene-by-environment interactions is another rapidly developing area of research where important new findings are likely in coming years. To date, a small but growing body of evidence points to significant interactions between genetic endowment and environmental conditions, with different genetic profiles rendering individuals more or less responsive to environmental conditions.[134] Significantly, these interactions appear to be a persistent feature across the life-course. Adverse early childhood conditions, for example, have been found to increase the genetic contribution to patterns of morning cortisol rise[196] as well as cortisol reactivity to an unfamiliar situation[197] with MZ twins showing increased concordance as compared with DZ twins. Adverse early childhood conditions have also been shown to exacerbate the genetic liability of a polymorphism in the 5-HTT serotonin transporter gene, resulting in heightened risks for depression.[133,198] Poorer childhood conditions have also been associated with differences in neural responses to negative emotional stimuli[199] as well as differences in physiological reactivity to challenge in college-aged students.[84] At older ages, reported loneliness, a marker of impoverished social conditions, has been shown to synergize with transcriptional control pathways resulting in overexpression of gene bearing pro-inflammatory Nf-κB/Rel transcription factors and under-expression of genes bearing antiinflammatory glucocorticoid response elements.[200]

A third direction for future work is to more fully evaluate the role of biological processes in mediating SES links to health. Here, it will be important to balance our interest in understanding specific biological pathways with the reality that these pathways are multiple and interacting. Consequentially, a focus on one or another pathway, while illuminating with respect to that pathway's individual role, will not provide the needed level of understanding as to how SES "gets under the skin" to impact major health outcomes. As the data reviewed above clearly highlight, SES gets under the skin in multiple inter-related ways as a function of its multiple influences on our brain's cognitive-emotional processes and their related peripheral biological consequences. It is the cumulative total of these biological effects that likely accounts for the broad and consistent gradients seen for SES with multiple health outcomes. Only through a more comprehensively multisystems approach to modeling biological mediation of SES effects on health can we hope to reach a true picture of these processes. Work on one such multisystems concept—allostatic load—has already highlighted the added value of a multi-systems view of the biological pathways mediating SES influences on health, showing that a more comprehensive assessment of biological risks associated with SES (*i.e.*, our index of AL) does the best job of explaining observed SES gradients in mortality risk.[85] Though a gold standard approach to developing such cumulative biological indices has yet to be determined, evidence to date clearly points to the value of finding ways to evaluate the multiple, cumulative impacts of SES on our physiology if we are to gain a true understanding of how the consistent and persistent SES gradients in nearly all health outcomes come to be—and have any hope of altering these SES-related health disparities.

Policy

Evidence linking lower SES conditions to greater/faster cumulative dysregulation in nearly all major biological systems provides clear evidence of the health toll such socio-economic conditions exact. Such evidence underscores the need for broader, societal level interventions to reduce health disparities associated with socio-economic disparities. Importantly, testing the effectiveness of any such interventions must include relatively shorter-term outcomes that can provide early evidence that the policy or program in question is having desired impacts. Peripheral biological parameters represent a potentially valuable category of such "intermediate" or short-term outcomes. Because such parameters are known risk factors

for major disease outcomes but have shorter time horizons than do more downstream disease outcomes in terms of their responsiveness to changing conditions, such parameters might be used as a more immediate outcome to track and evaluate the effects of policies or programs designed to reduce health disparities. Importantly, efforts to use biological parameters as "intermediate" outcomes should avoid a narrow focus on one or another biological parameter or system and incorporate assessments of the multiple biological systems likely to be positively impacted by these interventions. Evidence of positive trends in peripheral biological risk profiles (reflecting positive trends in multiple parameters/systems) would hopefully support the maintenance of such a policy/program so that longer-term disease outcomes would ultimately be seen to be affected as well. For example, shift work[201] and short-turn around time for air crews on trans-meridianal flights[202] have health and cognitive effects that could be ameliorated by work policies. Indeed, one could argue that current efforts to evaluate many programs targeted at reducing health disparities by relying only on evidence for changes in disease outcomes (and frequently failing to see such changes in what are generally relatively short time horizons), may have failed to identify what are actually effective programs by using outcomes with time horizons that are not appropriately matched to evaluation periods. With their likely shorter time horizon, peripheral biological profiles would appear to be good candidates for such shorter-term evaluations—providing early evidence of the impact of a program or policy on risk profiles that are known to predict longer-term disease risks. Evidence that a policy/program appears to be generating positive trends in peripheral biological parameters would hopefully allow for the continuation of such a policy/program for sufficient time to see impacts on longer-term disease outcomes.

Conflicts of interest

The authors declare no conflicts of interest.

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