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Mitochondrial Nexus to Allostatic Load Biomarkers

A recent study by Wiley, Gruenewald, Karlamangla, and Seeman modeling multisystemic allostatic load (AL) was

published in *Psychosomatic Medicine* (1). The observations reported in this article are consistent with the accumulating evidence published in this journal supporting the role of additive dysregulated biological and physiological processes in a wide range of diseases (2–5). We applaud this article and, here, with the objective of identifying proximal biological processes underlying AL, examine these findings in connection with cellular and mitochondrial biology.

For more than two decades, AL has been indexed using numerous stress-related biomarkers (6) and used as a tool to monitor multisystemic physiological dysregulations and predict disease risk (7). In their analysis of nationally representative data from the Midlife in the United States II Biomarker Project cohort ($N = 1,255$), Wiley et al. demonstrated that a bifactor model comprising 23 biomarkers loaded simultaneously onto a common AL factor as theorized by the AL model. Moreover, the underlying factor model for AL (i.e., “which biomarker contributes most to AL”) was consistent across a broad age range (34–84 years) and in both women and men. To accomplish this, Wiley et al. analyzed seven unique physiological system-specific factors including the following: i) sympathetic nervous system, ii) parasympathetic nervous system, iii) hypothalamic-pituitary-adrenal (HPA) axis, iv) inflammation, v) cardiovascular, vi) glucose, and vii) lipids. Each significantly contributed to the final AL score.

As investigators in psychosomatic medicine aim to integrate psychosocial, biological, and behavioral factors to understand mind-body processes, AL has proven useful as a heuristic model (2). However, its acceptance and implementation in various areas of medicine has been hampered by the lack of understanding regarding its underlying biological underpinnings. The question “What does AL actually measure?” is still under debate. This timely refinement of the model by Wiley et al. addresses long-standing AL measurement issues (2) and represents a step toward identifying which physiological systems contribute most directly and most significantly to overall AL.

In tracing the causal chain from systems to cells, we note that physiological functions are in part determined by cellular and subcellular processes. For example, studying genetic defects and polymorphisms causing disease teaches us that events at the molecular and subcellular level can trickle *up* to influence the function of complex organ systems such as the HPA axis (8). Thus, subcellular factors can contribute to the state of physiological dysregulation that defines AL.

In seeking to integrate knowledge about the underlying biology for individual AL biomarkers, we found it particularly noteworthy that the analysis by Wiley et al. (1) revealed that “overall, the largest factor loadings for the common AL factor were from biomarkers from the inflammation, glucose, and lipid systems.” This is in contrast to biomarkers that represent the sympathetic nervous system (e.g.,

epinephrine), parasympathetic nervous system (e.g., heart rate variability), and cardiovascular systems (e.g., systolic blood pressure), which did not load as strongly on an overall AL factor but loaded instead onto their system-specific factors.

At the subcellular level, glucose, lipids, and inflammatory biomarkers share a common origin. Compared to various other AL biomarkers, these are “proximal” and directly linked to a specific cellular component that is essential to energy production and signaling—the mitochondrion. Mitochondria are endosymbiotic organelles with their own genome involved in cellular energy production and signaling. To produce energy, they use or “burn” circulating energy substrates (9). This in turn fuels cellular activities such as action potentials in neurons, gene expression, hormone biosynthesis, DNA repair, and cellular replication, among other processes relevant to health and disease.

The ultimate fate of blood glucose and lipids is their oxidation at the level of mitochondria (Fig. 1). Glucose is metabolized first by glycolysis and generally followed by oxidative phosphorylation in mitochondria. Mitochondrial oxidation is also the major route to “burn off” or consume lipids. This in part explains why mitochondrial dysfunction is associated with hyperglycemia and hyperlipidemia in diabetes and why behaviors like exercise that increase energy metabolism in mitochondria decrease blood glucose and lipids (10). Mitochondria may also secrete signaling peptides that promote glucose homeostasis systemically (11). Thus, the link between mitochondria and glucose and lipid

biomarkers that Wiley et al. show contributes substantially to AL appears deeply rooted in cellular bioenergetics.

Likewise, defective mitochondria can both directly and indirectly promote inflammation (Fig. 1). The direct route involves the release of mitochondrial proteins and mitochondrial DNA in the blood. Because mitochondria evolved from bacteria and still carry several vestigial features of the bacterial ancestry, mitochondria-derived molecules are recognized as foreign, or immunogenic, by the immune system. Under conditions of stress, including oxidative stress, bacteria-like mitochondrial components can leak into systemic circulation and trigger systemic inflammatory pathways (12). On the other hand, the indirect route involves the release of immunogenic molecules and signaling molecules in the cell cytoplasm, in combination with oxidative stress that activates transcription factors (e.g., nuclear factor kappa-light-chain-enhancer of activated B cells, high mobility group box 1 protein) inducing proinflammatory gene expression programs and the release of cytokines (13). Together, these mechanisms link stress at the level of mitochondria to systemic circulating levels of glucose, lipids, and inflammatory AL biomarkers (14).

The study by Wiley et al. (1) also represents an opportunity to reflect on the driving forces and causal pathways underlying AL. The AL model was originally centered on stress hormones (e.g., cortisol) as key deregulators of multisystemic functioning. As we move beyond a cortisol-centric view of AL toward systemic perspectives, three notions must be considered. First, the interrelationships between individual

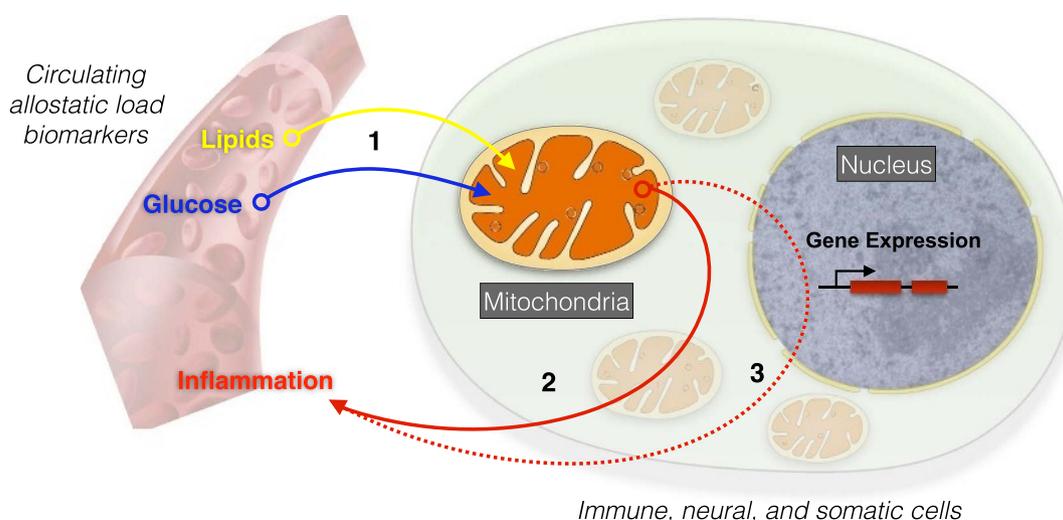


FIGURE 1. Relationship between mitochondrial function and glucose, lipids, and inflammation. Allostatic load biomarkers are influenced by mitochondrial activities. (1) Glucose and lipids are used as fuels and directly metabolized by mitochondria, effectively removing them from the circulation when mitochondria are functioning normally. Conversely, dysfunctional mitochondria may cause elevated circulating glucose and lipid levels, contributing to allostatic load. Dysfunctional or damaged mitochondria also produce (2) damage-associated molecular pattern molecules including circulating cell-free mitochondrial DNA that directly promote inflammation by activating the immune system, or (3) activate proinflammatory gene expression in the cell nucleus, leading to the production of proinflammatory cytokines in various cell types. Color image is available only in online version (www.psychosomaticmedicine.org).

biomarkers depend on the neuroendocrine and metabolic context in which they are present (15). This includes their direct reciprocal inhibitory/stimulatory effects and/or coupling with other systems. Second, AL indices generally include biomarkers assessed during fasting and resting conditions as originally defined (6). The inclusion by Wiley et al. of heart rate variability as part of Midlife in the United States II study, as well as the inclusion of stress reactive measures in other studies may represent useful additions to capture systems dynamics (16). Such measurements of resting, reactive, or physiological variability should contribute different information about physiological dysregulation, although it remains largely unclear how to interpret their contributions to AL. Lastly, common subcellular factors such as mitochondria may represent convergence points that simultaneously regulate multiple biomarkers (17). For example, studies of genetic manipulation of mitochondrial functions in animal models indicate that mitochondria simultaneously modulate metabolic, inflammatory, HPA and sympathetic-adrenal-medullary axes, as well as gene expression responses to psychological stress (18). This evidence positions mitochondria as modulators of systemic stress responses. More generally, it also suggests that subcellular factors regulate multisystemic biobehavioral processes contributing to translate stressors of various natures into variable health trajectories across the lifespan.

This “mitocentric” proposal might seem like yet another reductionist model that narrows complex physiological outcomes to more simple subcellular processes, possibly curtailing valuable opportunities to evaluate the health contribution of psychosocial and behavioral factors. To the contrary, we see this as an opportunity to expand psychosomatic medicine. Focusing on energy metabolism and mitochondria represents a new way to apply sensitive and biologically meaningful measures to detect the interactions among biopsychosocial factors. This is because mitochondrial functions i) directly respond to stress-related neuroendocrine mediators, ii) are modulated by behavioral factors such as physical activity and diet, iii) are partially regulated by genetic variants, and iv) exhibit age-related changes that parallel those of telomeres (14). Exploring mitochondrial functions in psychosomatic medicine therefore provides a useful theoretical and biological bridge to study the biobehavioral interactions that take place between individuals and their environment (17).

In summary, this letter outlines a proximal biochemical relationship between mitochondrial function and the biomarkers revealed by Wiley et al. (1) to exhibit the strongest statistical associations with a common AL factor, namely, glucose, lipids, and inflammation. This association is consistent with the notion that the accumulation of mitochondrial dysfunction as a result of chronic stress, or mitochondrial allostatic load, could represent an early event that increases AL and disease risk (14). Examining the biochemical connections linking AL biomarkers to quantifiable subcellular

processes may help to refine our understanding of the mechanisms by which chronic stressful experiences are translated, or biologically embedded, into measurable physiological dysregulation. In the long run, this should enable the psychosomatic research community to continue identifying and target novel modifiable pathways to promote resilience to stress and trauma and thus mitigate stress pathophysiology.

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Considering the Appropriateness of the Factor Analytic Operationalization of Allostatic Load

In a recent issue of *Psychosomatic Medicine*, Wiley et al. (1) made a valuable contribution to the discussion of the optimal measurement of allostatic load (AL). In the most comprehensive factor analytic investigation of AL to date, they found that a bifactor model with a general AL factor and seven physiological system factors fits better than a higher-order model in which the seven system factors loaded on the general AL factor. Similar models have been

applied by the author (T.B.) and others to operationalize AL (2–4). Here, we consider the primary theoretical assumptions underlying latent variable modeling, argue that the construct of AL is inconsistent with these assumptions, and propose alternate operationalizations of AL.

UNDERLYING CONSTRUCT (COMMON CAUSE)

A latent variable model is estimated based on the patterns of covariance in a set of variables. By including an AL general factor in a latent variable model, researchers are positing that an underlying construct is the common cause of the observed covariation in all of the modeled biological measures. Although the theoretical relation of the common cause or construct to the original variables differs in bifactor versus higher-order models, in either case, we must ask: What could this common factor be? Wiley et al. stated that the AL factor “[captures] the notion that there is an underlying process influencing multiple physiological systems” ((1): p. 4). However, the observation of a general factor estimated from inter-individual summary statistics (i.e., covariances) says little about what this process may actually be.

INDEPENDENCE CONDITIONAL ON THE LATENT TRAIT

A primary assumption of latent variable models is that once the effect of the latent factors has been accounted for, the measured variables—in this case, the biological measures—are independent. This is unlikely to be the case with AL measures. Levels of different biomarkers are linked causally to each other, rather than only through the common cause latent variable(s). For example, body mass index (BMI) has previously been used as a metabolic system AL biological measure (e.g., (2,5)). However, Mendelian randomization studies have found that increased BMI has a causal effect on levels of other metabolic biological measures as well as levels of AL biomarkers used to represent other physiological systems, such as blood pressure and inflammation (e.g., (6)). Thus, it is most likely that the biomarkers are not conditionally independent but are instead dynamically related in complex networks. Such networks can produce observed correlations between variables that have no common cause (7).

INTERCHANGEABILITY OF INDICATORS

A further assumption of the latent variable model is that the definition of the latent variable does not change when different sets of indicators are used (8). This holds because the indicators are affected by, but do not affect, the latent variable. Another key finding of Wiley et al. was that fitting models in which the biological measures from each of the 7 physiological systems were excluded caused no large changes in AL factor loadings (1). This method provides only a weak test of interchangeability. The stability of general intelligence factor loadings has long been a research