

Trends in Endocrinology & Metabolism

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Feature Review

Energy constraint on human health

Alexander Behnke ^{3,4,9}, Evan Shaulson ^{5,9}, Herman Pontzer ^{2,*}, Christopher P. Kempes ^{1,*}, and Martin Picard ^{5,6,7,8,*}

Evolved constraints to human energy transformation force the body–brain system to operate an economy of energy. To survive and thrive, an organism’s finite internal energy resources must be dynamically reallocated, forcing trade-offs from organelle to organism. Building on an energy trade-off framework integrating life history theory and cellular biology, we propose that energy trade-offs occur between three main classes of processes relevant to health: (i) vital, (ii) stress, and (iii) growth, maintenance, and repair (GMR). Competing demands for these processes exist within a hierarchy of energy needs where more ‘urgent’ vital- and stress-related functions are prioritized by suppressing longevity-promoting growth, maintenance, and repair processes. The energy constraint model of human health provides an energy-based framework to address health/disease dynamics across the lifespan.

Energy transformation, allocation, and trade-offs

Energy transformation is the fundamental driver of life. Animals consume oxygen and organic molecules to fuel **oxidative phosphorylation (OxPhos)** (see [Glossary](#)) that powers cellular, intercellular, physiological, and behavioral processes ([Box 1](#)). The central role that energy plays in the function of organisms has a long history that dates to the early comparisons of combusting flames and organisms [11]. Alongside the molecular and genetic revolutions of the 1950–1970s, there was also a revolution in bioenergetics that proved immensely informative. Beginning in the 1930s, the energetic revolution included discovering the tri-carboxylic acid (TCA) cycle [12], the proton motive force and chemiosmotic theory [13], the energetic yield of diverse metabolic pathways [14,15], the necessity and costs of maintenance [14], and the fundamentals of biological thermodynamics, entropy, energy flows, and energy budgets [11,16,17].

The role that energy plays in mammalian physiology and human health has also had a long and successful history of investigation [18–24]. **Energy constraint (EC)**—where energy limitations drive a certain behavior—is well-defined in biophysical and cellular systems [25,26] and has been described in physiological [23] and ecological [27] contexts, where it provides the most fundamental and parsimonious explanations for a variety of intra- and interspecies patterns involving reproduction, migration, and lifespan [28–34]. Specific cellular behaviors (e.g., the **Warburg effect**, where cells switch to anaerobic metabolism even when oxygen is plentiful to promote proliferation) are accurately accounted for by thermodynamic factors [25,35], which, under certain conditions, can supersede genetic and molecular programs [36]. These results across the ladder of life reveal that cells and organisms ‘compute’ and make decisions to deprioritize or shut off certain processes to favor others, that is, they perform trade-offs.

The instructive role of energy in relation to health is most clearly highlighted in cases where organisms fail to effectively transform energy, which leads to disease and death. As an example, in cases of mitochondrial diseases, impaired OxPhos capacity is incompatible with long healthy lives [37,38]. More generally, energetic/metabolic dysregulation defines most chronic diseases,

Highlights

Everything in biology costs energy, and over long time periods, there are evolutionarily imposed limits to energy transformation and dissipation.

Energy trade-offs arise when a normal process consumes more energy than it would under optimal conditions, thereby stealing energy from other processes.

Over time, energy trade-offs can impair health.

We propose a three-part division of processes: (i) vital, (ii) stress, and (iii) growth, maintenance, and repair, which exist along a hierarchy of energy needs.

The energy constraint framework suggests measurable features and helps understand clinical and physiological processes resulting from energy dynamics.

¹Santa Fe Institute, Santa Fe, NM, USA

²Department of Evolutionary Anthropology, Duke University, Durham, NC, USA

³Clinical & Biological Psychology, Institute for Psychology & Education, Ulm University, Ulm D-89082, Germany

⁴German Center for Mental Health (DZPG), partner site Mannheim-Heidelberg-Ulm, Ulm, Germany

⁵Department of Psychiatry, Division of Behavioral Medicine, Columbia University Irving Medical Center, New York, NY 10032, USA

⁶Department of Neurology, H. Houston Merritt Center for Neuromuscular and Mitochondrial Disorders, Columbia University Irving Medical Center, New York, NY 10032, USA

⁷New York State Psychiatric Institute, New York, NY 10032, USA

⁸Robert N. Butler Columbia Aging Center, Mailman School of Public Health, New York, NY 10032, USA

⁹Equal contributions.

Box 1. Energy transformation, consumption, and efficiency

Energy is transformed (not ‘produced’) from digested organic molecules and oxygen, providing the body–mind system with its total energy budget [1]. In respiring mitochondria, substrates such as pyruvate, ketone bodies, amino acids, and fatty acids are transformed into electron flow within the electron transport chain, which is harnessed to generate a flexible energetic resource: the electrochemical transmembrane potential [2]. Once energized, mitochondria deploy this finite resource to power the F_0F_1 ATP synthase to phosphorylate ADP into ATP—a process termed oxidative phosphorylation (OxPhos). In parallel with OxPhos, mitochondria perform dozens of other functions [3], notably contributing to intracellular and organism-wide signal transduction.

By releasing metabolites and hormones, mitochondria orchestrate gene expression locally within the cell they inhabit [4], and systemically by (re)directing energetic resources [5]. Different types of mitochondria populating different organs and cell types also perform essential anaplerotic functions required for GMR processes. Thus, mitochondria are at the crossroads of catabolic energy transformation and anabolic biosynthesis pathways, regulated by the redox status (NADH/NAD⁺ ratio) of the cell–mitochondria system.

Since the rate of energy transformation is limited, efficiency is imperative. The purpose of efficiency is to free up as much of the budget as possible for longevity-promoting, entropy-fighting processes and for supporting daily life. This is accomplished by the coordination of hundreds of cell types highly specialized for specific tasks, outsourcing dozens of functions to other cell subtypes [6]. Some cell types and organs specifically consume metabolic substrates that are uniquely synthesized by another organ [7], highlighting the interdependence among cells and organs, united as an energy-constrained social collective.

In any specialized cell type, only a limited subset of the genome needs to be ‘open’ and actively expressed. Because each gene incurs costs related to transcription and translation [8], active repression of genes, made possible by the cellular division of labor, affords exceptional energetic savings. In yeast, for example, metabolic cooperation via cell-to-cell metabolite sharing increases lifespan [9,10]. In the absence of competition from other molecular programs, specialized systems can thus direct their molecular and energetic budget in a focused and efficient manner through division of labor. Life can thus be sustained at the lowest energetic cost, freeing up energy to be invested into longevity-promoting GMR processes.

*Correspondence: herman.pontzer@duke.edu (H. Pontzer), ckempes@gmail.com (C.P. Kempes), and martin.picard@columbia.edu (M. Picard).

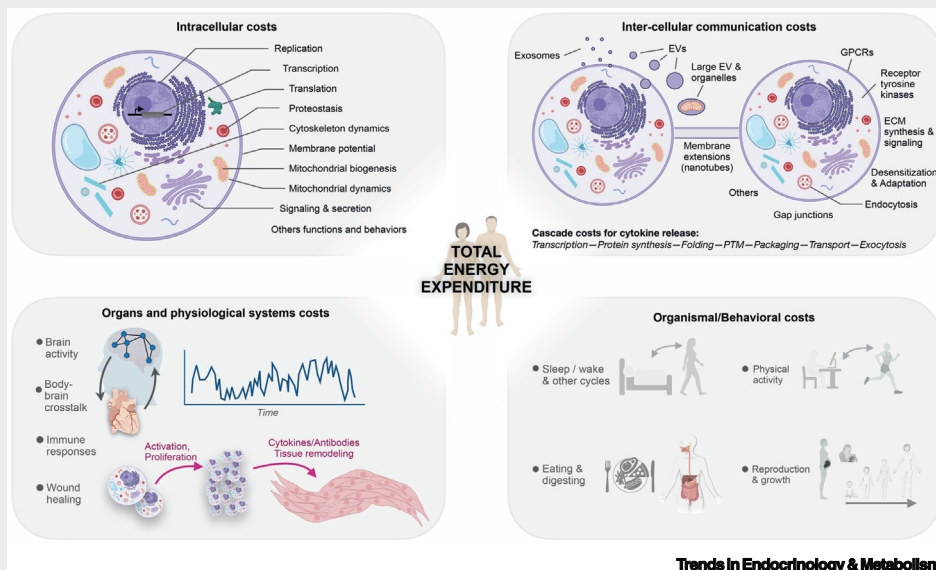


Figure 1. Energetic costs and multi-scale origin of energetic costs. Multiple nested processes contribute to whole-body energy expenditure, including molecular, cellular, physiological, and behavioral processes that are the basis of health and subjective experiences. ECM: extracellular matrix; EVs: extracellular vesicles; PTM: post-translational modifications; Abs: antibodies; GPCRs: g-protein coupled receptor.

including cancer [39], cardiovascular disease [40], neurodegenerative [41] and neuropsychiatric disorders [42], and aging [43]. Epidemiological evidence also implicates mitochondrial and metabolic processes as primary risk factors in age-related cognitive decline [44] and common chronic conditions [45], emphasizing the central role of energy in health and resilience.

Given these recent results, and the long history of energy studies in organisms, how do we: (i) recenter the importance of energy in human health, (ii) move to considerations of energy flow and allocation over different timescales, and (iii) use energy to think more integratively about health, disease prevention, and treatments?

Energy trade-offs are central in the field of life history theory, where researchers since the 1950s have investigated energy allocation strategies to address the competing demands of growth, reproduction, and maintenance [21,27]. While these concepts have informed important work on human biology and aging, they have not yet coalesced into a simple, integrative framework that connects molecular and cellular metabolism to biomedical concepts of health and aging. Here, we synthesize prior work on energy budgets from life history theory, comparative biology, and human energetics into a framework that is easily deployable in biomedical contexts, and we explicitly illustrate its application to specific health and disease states.

In this feature review article, we present a cross-cutting energetic principle that synthesizes past ideas and integrates organelle-to-organism levels of function to dynamically shape health across the lifespan (see Figure 1 in Box 1). The core idea of EC is that over a given duration, there is a finite rate at which organisms can transform or dissipate energy. Consequently, the brain–body system must operate an economy of energy in which an (effectively) fixed budget must be partitioned, shared, and competitively redirected according to a hierarchy of needs. Thus, only some processes can be fully active, forcing energy to be dynamically diverted away from acutely dispensable processes to fuel more ‘urgent’ or essential ones. This simple cross-cutting principle of EC leads to functional trade-offs that manifest at the level of subcellular, cellular, physiological, and behavioral processes. Over time, these trade-offs have consequences for aging and health. This model enables and stimulates holistic interdisciplinary hypotheses to address difficult biomedical challenges around human health.

Origins of finite energy budgets in organisms

Energy is the primary currency of life. Energy transformation is unleashed through biochemistry to bring the cellular hardware to life, countering the second law of thermodynamics that otherwise pushes life toward increasing entropy [1,46]. Energy has emerged as a ‘first principles’ way to understand numerous aspects of organism physiology across diverse species [22,24,26,28–34,47]. The framework we propose for human health is a relatively fixed energy budget, where all changes in activities represent reallocations of energy. This requires that the normal energy budget is already optimized (by evolutionary forces) and that there are no easily accessible improvements in efficiency. We briefly justify these ideas in the subsequent sections.

Darwin noted that natural selection will favor efficiency in the conversion of energy resources to support survival and, ultimately, reproduction [48]. Physical and chemical constraints set limits on the maximum efficiency that can be achieved by biological functions [49]. This implies that most functions cannot achieve greater efficiency, accounting for the impressive observed efficiency of many biological functions. For example, at the subcellular level, protein-synthesizing ribosomes operate exceptionally close to the physical limit [50], and ATP production by the ATP synthase occurs with ~99% efficiency [51]. As a result, humans conduct all resting activities at the same energy cost, lower than a 100 W light bulb [30].

A more recent idea is that the multiple physical and chemical constraints faced by organisms have caused evolution to find an optimal metabolic rate given trade-offs among unavoidable costs [52]. For example, the vascular system pumps blood through a network that minimizes energy dissipation [52]. Over evolutionary timescales, the benefits of delivering more blood-borne energy to

Glossary

Activity energy expenditure (AEE):

classic component of energy expenditure defined as energy expended on physical activity above basal/resting needs, including exercise and nonexercise movement, but excluding the energy costs associated with digesting and assimilating nutrients.

Allostatic load: cumulative physiological ‘wear and tear’ from chronic or repeated allostasis (and associated energy costs), often indexed by multisystem biomarkers.

Basal energy expenditure (BEE): minimum energy required to sustain basic functions at rest (postabsorptive); closely approximates basal metabolic rate; and is measured under strict conditions (fasting, early morning, and supine).

Energy constraint: functional limitation attributable to the limited energy budget, meaning that increased spending in one process is offset by reduced spending elsewhere over time.

Growth, maintenance, and repair (GMR): in the energy constraint model, refers to energetic investments in growth, maintenance, and repair processes (molecular, cellular, and physiological) that can be deferred short term but preserve function and longevity in the long term.

Hypermetabolism: energy expenditure above predicted needs (often defined as resting energy expenditure >10% above predicted), common in burns, trauma, infection, and sepsis.

Hypometabolism: energy expenditure below typical levels, often with reduced thermogenesis/body temperature (e.g., sleep, fasting, and torpor).

Interference effect: concurrent endurance plus resistance training can blunt strength/hypertrophy gains due to competing cellular priorities.

Life history theory: evolutionary framework emphasizing the finite energy/time allocated among growth, reproduction, and maintenance; trade-offs shape health and lifespan at the species level.

Oxidative phosphorylation

(OxPhos): ATP synthesis powered by electron transport to oxygen, which generates a proton gradient that powers the ATP synthase within mitochondria.

Relative energy deficiency in sport

(RED-S): low energy availability (underfueling relative to training load)

each cell are balanced against the energy costs of maintaining a higher throughput in vascular architecture (i.e., more blood vessels or greater cardiac output would cost additional energy). Heat dissipation also could contribute to such limitations [53]. These mechanisms manifest allometrically across species, predicting that metabolic rate mathematically scales with body mass raised to the exponent 0.75 ($M^{3/4}$), whereas linear scaling would have an exponent of 1 [52]. This means something counterintuitive: in larger animals, each cell exhibits lower energy demand than a comparable cell in a smaller mammal. But when combined with the idea of partitioning a fixed budget between two major purposes—maintenance of vital functions vs. growth or biomass accumulation—this allometric theory accurately explains ontogenetic growth curves [54], the rate of development, rate of aging, rate of cancer formation [55,56], and cell-level metabolic rates [57] across diverse mammals. Thus, an array of complex physiological dynamics can be explained by fairly simple ECs.

This also explains why a combination of selection pressure, physiological efficiency, and fundamental biophysical limits is at the origin of the finite energy budget that constrains living organisms [27]. The relative fixity of a species' energy budget is supported by evidence from many species. Across a wide range of species, patterns of evolved life history strategies indicate trade-offs in energy allocation to growth, reproduction, and maintenance [27]. For example, in laboratory studies of birds and rodents, when daily physical workload is experimentally increased, total daily energy expenditure typically remains constant [58]. This means that the additional energy expended to run, fly, or move is 'absorbed' by a reduction in other costs. Likewise, populations in the wild have similar daily energy expenditures for their body size as populations in captivity [59], and sedentary industrialized communities of humans have roughly the same daily expenditure as more active populations after controlling for body size [58,60]. Even with several-fold acute elevations in physical activity, humans and other animals maintain remarkably consistent rates of daily energy expenditure over the long term [61–65].

Given a fixed budget, every instance of a physiological function exceeding its typical allocation of energy implies that another function must receive less energy (Figure 1A). For example, a tissue fighting a toxin or damage will increase glucose consumption, decreasing glucose availability for repair in other tissues [67]. Increased functions in a given system imply other systems or functions must be turned off or slowed down. This EC framework offers a fresh lens for examining the well-known physiological trade-offs in humans, and an energetic framework to understand the stress–disease connection, which we discuss in the subsequent sections.

Evidence for limits on the total human energy budget

Fixed limit to human performance. One challenge to the EC perspective is that, at least over shorter time frames of minutes to days, the rate of energy expenditure is not rigidly fixed. Perhaps the clearest evidence for metabolic variation is during exercise, when a person's metabolic rate can reach approximately 20 times their basal expenditure [66]. Acute fluctuations in metabolic rate are not in conflict with the EC framework because the compensatory response to these perturbations and the resulting EC are expected to occur over longer time frames—in days to weeks or even months [68].

Even when all energetic resources are mobilized (food *ad libitum*, ample rest, psychological focus) for a singular purpose, human performance is still constrained within a metabolic ceiling, setting the limit for daily energy expenditure [66]. Maximum energy expenditure (energy/day) decreases as a function of the duration of the activity, with an asymptote at approximately 2.5 times basal metabolic rate [66,69] (Figure 1B). This means that over long time periods, we cannot simply eat more to increase our daily energy budget. In fact, overfeeding has deleterious health

causing multisystem impairment (metabolic, reproductive, bone, immune, and cardiovascular).

Sickness behavior: cytokine-driven fatigue, anorexia, social withdrawal, and reduced activity during illness, promoting defense and conserving energy.

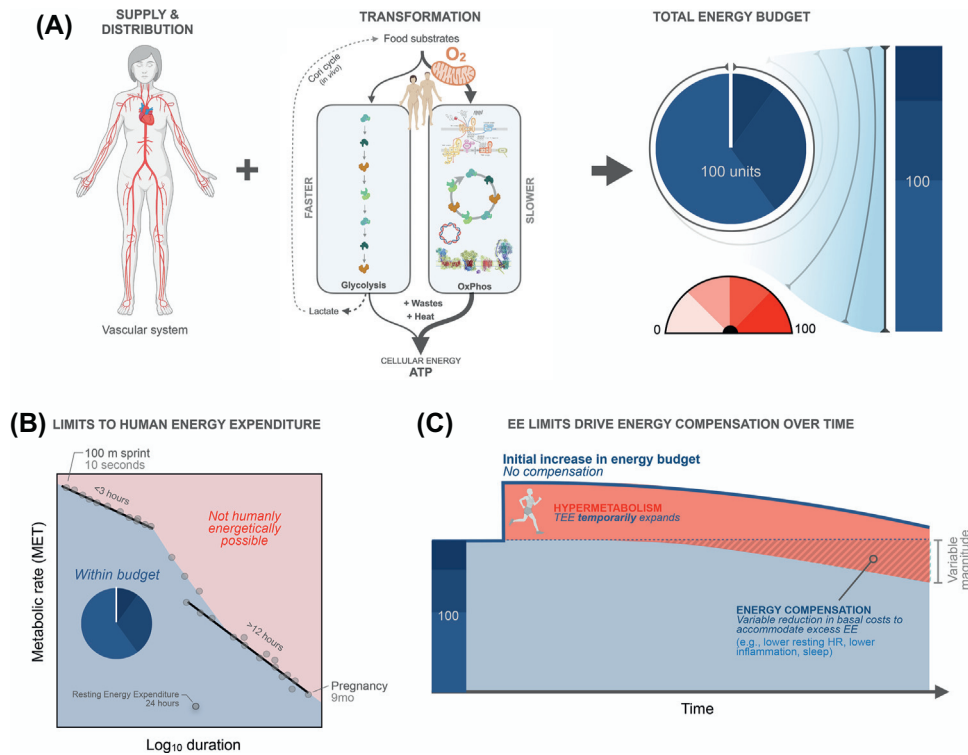
Stress costs: in the energy constraint model, added energy required for stress responses to challenges beyond baseline vital costs. To optimize survival, these costs are prioritized above growth, maintenance, and repair costs.

Thermic effect of food (TEF): a classic component of energy expenditure defined as the energy cost of digesting and assimilating food/nutrients (diet-induced thermogenesis).

Total energy expenditure (TEE): 24-h total energy transformed. Classically subdivided into three components: (i) resting/basal expenditure, (ii) activity-induced expenditure, and (iii) the thermic effect of food.

Vital costs: in the energy constraint model, baseline life-sustaining expenditures (maintaining ion gradients, heartbeat, and basic brain function, among others) that are prioritized for immediate survival.

Warburg effect: aerobic glycolysis (lactate production despite oxygen) supporting rapid ATP synthesis and anabolic biosynthesis in tumors and activated immune cells.



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Figure 1. The human energy budget: basis and limits. (A) Energy supply and transformation systems contribute to setting the total human energy budget, set here to 100 units for illustrative purposes. A constraint on the rate of converting food substrates into adenosine triphosphate (ATP) as the physiologically usable form of energy constitutes the rate-limiting step that establishes the finite budget, even under conditions of caloric surplus. (B) Empirically measured limits to human energy expenditure from endurance performance events, including events ranging from 10 s (left) to 9 months (right), establish the limit of what is energetically possible for humans. The factors determining this species-level limit are discussed in the text. (C) Over short time scales, the limit on the human energy budget can be temporarily exceeded by several fold during exercise or severe stressors. In studies examining individuals maintaining excess energy expenditure over several weeks, a variable magnitude of energy compensation is observed, implying a reduction in basal energy costs driven by increased efficiency or by other mechanisms. (B) is adapted from [66]. EE: energy expenditure.

consequences, even increasing mortality in critically ill adults and children [70,71]. Thus, for reasons that remain unclear, increasing food consumption does not increase the total human energy budget.

Excess energy spent now requires resting later with a blunted increase in total energy expenditure. Over short time scales, the energy budget temporarily expands up to 20-fold in endurance-trained athletes performing at their maximum for several minutes [72], and multiday events raise the metabolic rate by several fold [66]. Over minutes to hours, whole-body energy expenditure also can temporarily decrease—by 20–30% during sleep [73] and by up to 40% during deep meditation [74]. Hibernating animals in torpor decrease their **total energy expenditure (TEE)** by 80–95% [75], a state during which the molecular changes associated with biological aging halt [76].

However, integrated over months to years (the scale at which most chronic illnesses develop), the whole-body energy budget of animals is relatively stable. It follows periods of elevated energy expenditure that are compensated for with periods of lower energy expenditure. This

compensation helps explain why, over the long term, exercise training does not increase TEE by the amount of energy expended during the exercise. For example, the heart beats faster during exercise (and shortly after as resources are replenished), but training adaptations decrease resting and sleep heart rate [77,78], increase blood volume and cardiac output, allowing the system to operate at a greater overall efficiency. The origin of efficiency gains remains incompletely resolved [27] but could involve various psychobiological processes similar to heart rate reduction [68], including reduced inflammation and stress reactivity. In turn, this would account for the metabolic compensation apparent when integrating energy expenditure over several weeks.

The existence of metabolic compensation means that some other nonactivity-related process has become less costly, or that some processes are suppressed during the nonactive period (Figure 1C). These patterns are consistent with use-dependent resource allocation: recurrent demand steers **growth, maintenance, and repair (GMR)** investment toward the used system (capacity and efficiency gains), while disuse permits cost-saving divestment.

Not all systems can be fully active at the same time. Trade-offs in physiological function are a natural consequence of a fixed energy budget. For example, postprandial fatigue or ‘food coma’ [79], fighting serious infection [80], and overtraining [81] all decrease other functions such as mental focus and endocrine and reproductive systems. At the tissue level, this principle also limits skeletal muscle adaptation to exercise training, where the **interference effect** [82] highlights trade-offs between competing, energetically demanding resistance (e.g., hypertrophy and myosin heavy chain class switching) and endurance adaptation (e.g., mitochondrial biogenesis and angiogenesis) programs.

Most of the organism’s supply of energy precursors (e.g., oxygen, lipids, and carbohydrates) is distributed via blood flow. Therefore, organisms deliberately reallocate energetic resources to different organs by redirecting blood flow. This occurs through a combination of local and brain-based regulatory processes that control tissue perfusion, driving whole-body physiological energy trade-offs [23]. For example, during strenuous exercise, blood flow is diverted away from the gonads, skin, and digestive system toward the active muscles, brain, cardiorespiratory system, and metabolic systems [83].

In the context of infections, immune activation quickly consumes considerable energy [84], consistent with the increased blood flow at sites of injury or inflammation. To survive the bacterial or viral threat, energy must be actively mobilized by hormones (glucocorticoids) and cytokines, including interleukins and growth differentiation factor 15 (GDF15) [85]. Simultaneously, other energetic costs required for locomotion, cognitive functions, and even digestion are actively suppressed—an energy conservation response termed **sickness behavior** [86] and torpor in animals [87]. Thus, both active suppression and passive restriction likely contribute to energetic trade-offs and their functional consequences.

Limited energy flux drives the rate of development and aging. As defined in allometric scaling relations linking basal metabolic rates and lifespan, a limited energy budget explains the ~20-fold change in developmental rates and lifespans [31,32,54] across many, although not all, species. During embryogenesis, developmental rates are driven by species- and cell-specific metabolic rates [88]. In fact, perturbing mitochondrial OxPhos accelerates or decelerates development in the expected direction—accelerating the metabolism of human embryos makes them more ‘mouse-like’, whereas slowing down mouse embryo metabolism makes it more ‘human-like’ in terms of developmental pacing [89,90]. These findings highlight the instructive role of energy (rather than a purely permissive one) in development.

Daily energy budgets are the critical aspect in understanding cross-species physiology and functions, but the mechanisms they reveal are equally applicable to within-species shifts and health-related processes. During child development, EC forces trade-offs between growth and other functions. Individuals with limited access to food exhibit stunted growth [91,92], leaving physiological traces consistent with the developmental phase when energy became limited [93]. Even in the presence of sufficient calories, growth can be limited by internally generated energy trade-offs [91], including chronic immune activation in childhood [94,95] and chronic life stress [96,97].

Thus, the four classes of phenomena above highlight the apparent limited total human energy budget. We note that, in addition to the ‘budgetary’ framework applied here (limits to how fast energy can flow per unit time), some evidence is also consistent with constraints to energy dissipation limits (how quickly metabolism-related heat can be dissipated) (e.g., [53]). Subsuming these two perspectives, we have also proposed that living systems operate as biological ‘energetic circuits’ that are limited by the amount of energy resistance they can tolerate over time [2]. Here, continuing with our energy budgeting framework, we next explore a biologically informed approach to partitioning the energetic costs underlying whole-body energy expenditure.

What do we spend energy on?

Differing perspectives on energy allocation

The human EC model draws from rich literatures ranging from cellular metabolism to ecological/evolutionary theory. To apply energetic thinking to human health-related questions, this exercise forces us to think about multiple levels of organization and to reconceptualize key aspects of traditional models, as we discuss here.

Basic cellular metabolism recognizes (i) catabolic reactions required to power stress responses and (ii) anabolic reactions required for growth. These two broad categories compete for metabolites and regulatory priority and serve distinct functional goals. While catabolic flux is required to fuel anabolic synthesis, and both processes therefore occur simultaneously, cells often exhibit a dominant metabolic bias toward either catabolism or anabolism depending on functional state (e.g., cellular work/maintenance vs. proliferation) [98,99].

Human energetics typically partition energy use between (i) TEE, (ii) **basal energy expenditure (BEE)**, (iii) **active energy expenditure (AEE)**, and (iv) **thermic effect of food (TEF)** [100]. These categories are useful for organizing empirically measurable components of the total budget, particularly those related to physical activity.

Evolutionary theory and **life history theory** generally distinguish between growth and reproduction (both of which involve biomass accumulation) and maintenance (background activities required for survival, such as the beating heart, immune function, neural activity, and metabolic processes supporting the organs) as the major categories of energy costs. This energy allocation framework has proven useful in understanding patterns of growth, fertility, and senescence across species, as well as physiological responses to energetic challenges within species [27].

All three theoretical systems are useful in specific contexts but obscure some core notions. The catabolic/anabolic distinctions are biochemically critical, but we can arrive at a satisfactory model of energy distribution without micromanaging this level of biochemistry. The human energetics TEE/BEE/AEE/TEF and evolutionary/life history frameworks are useful for broadly mapping

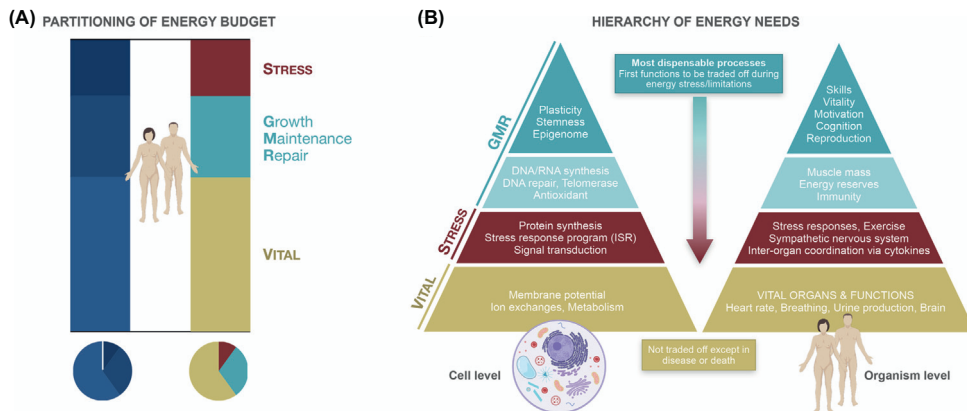
human behaviors but lack resolution and detailed connections to (sub)cellular processes we know to be relevant at both short and long timescales.

An integrated, health-centric, three-part hierarchy of energy costs

The EC model pursues three objectives: (i) simplicity and conceptual alignment with key biomedical concepts related to human health, (ii) alignment with mostly nonreproductive (adult-related) energy partitioning in humans, and (iii) amenability to developing measurable constructs in the final model. Therefore, we subdivide energy costs into three main classes of processes that must flexibly share the organism's finite energy resources (Figure 2A).

First are the **vital costs**. Life-sustaining costs essential to prevent acute systemic failure and entropic decay on short timescales (minutes to days). These include the continuous operation of core physiological functions, including maintaining cellular electrochemical gradients, sustaining circulation at rest, maintaining basic organ function, and supporting waking consciousness. Vital costs refer to the minimum energy required for immediate survival, with its distribution changing dynamically across physiological contexts. Thus, vital costs do not imply a fixed set of constant organ activity levels, but reflect context-dependent reallocation within a constrained energy budget, where energy is transiently diverted among systems to maintain organismic function. Vital thereby denotes a functional category of energy allocation. This is in contrast to measurement conditions such as basal metabolic rate (BMR), which provide a standardized estimate of these costs (plus unaccounted stress costs, e.g., driven by anxiety), captured at rest over a relatively short interval. In the EC model, vital costs are constrained by species- and organism-specific features, setting a lower bound on energy expenditure required to avoid system collapse.

Second are **stress costs**. We define stress as any stimulus that incurs an additional energy cost. Stressors perturb the homeostasis of the system [101], causing adaptive changes at any level, all



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Figure 2. Partitioning of the energy budget and prioritization along the hierarchy of energy needs. (A) The EC model proposes a division of energetic costs into three categories: vital, stress, and GMR. Note that the same biological process, such as gene expression, can contribute to any of the three categories based on whether genes are expressed and required for immediate survival to sustain basal protein abundance (vital), whether they are directly induced by stress and fuel the stress response (stress), or whether they fuel adaptation, recovery, or resilience building (GMR). (B) Adaptation of Maslow's pyramid of needs to cellular (left) and organismal (right) energy needs. The most vital and prioritized functions are near the bottom of the pyramid. In times when stress-related energy costs are high, the energy budget is consumed by the bottom portion of the pyramid, so the top portion cannot be actualized, selectively affecting the most acutely dispensable functions and structures. EC: energy constraint; GMR: growth, maintenance, and repair.

of which necessarily consume energy [102]. This includes (i) physical activity and exercise, (ii) low-grade, long-term exposures to stressors, such as an environmental toxin, endemic parasite, or persistent psychosocial stressors, and (iii) 'emergency' programs that support classical stress response programs. The latter includes anticipatory allostatic processes that ready the organism for future potential threats [103,104]. Stress responses can include intracellular signaling cascades, cell–cell connection remodeling, synthesis of endocrine hormones (e.g., adrenocorticotrophic hormone, cortisol, and neuro-modulators), ion pumps supporting action potentials, and gene expression shifts. At the organ and organism level, they include increased muscle tone, increased heart rate, sweating, and piloerection, as well as activation of neural threat and salience networks. Thus, resting heart rate contributes to vital costs, whereas additional heart rate contributes to stress costs.

Third are **GMR costs**. GMR costs include acutely dispensable processes not required on short timescales but necessary to sustain the organism over long timescales. (i) 'Growth'—growing tissues and organs either during development or as adaptive responses to stimuli. This includes brain development, ontogeny, growth of a fetus, muscle hypertrophy, and regeneration. (ii) 'Maintenance'—replacing or replenishing dysfunctional or impaired components such as telomere elongation, stem cell divisions, and memory consolidation. (iii) 'Repair'—removing accumulated damage such as DNA mutations, cell apoptosis, and angiogenesis following ischemic events. GMR costs occur at all levels, from organelle to organism, and often require a prior stimulus to justify the expenditure (e.g., stress of exercise stimulating adaptive responses). The central nervous system can mobilize GMR processes via the parasympathetic 'rest-and-digest' arm of the autonomic nervous system, along with GMR-promoting behaviors, including feeding and sleep [105].

Hierarchy of energy needs

Interrupting each class of processes has vastly different consequences on health-related outcomes. Insufficient energy to preserve vital processes can lead to severe dysfunction and death (e.g., multiorgan failure in intensive care unit (ICU) sepsis with hypermetabolism), while insufficient energy allocation to GMR may only lead to gradual damage accumulation and accelerated biological aging [106]. If there is insufficient energy to enable stress processes, the organism cannot mobilize the appropriate behavioral, physiological, or biological responses to cope with environmental demands, leading to frailty or 'low resilience' phenotypes. This rarely happens independently of severe pathological states, as 'stress' processes are prioritized over GMR processes.

As in Maslow's pyramid reflecting a hierarchy of human needs [107,108], biological and physiological processes exist along a priority continuum. The evolutionarily established prioritization of biological and physiological processes ensures that, in the event of an energy shortage, the most essential processes are preserved 'at all costs', while dispensable expenses are temporarily deprioritized through the dynamic reallocation of limited resources (Figure 2B, left).

The hierarchy of energy needs has been well defined in cells. Cells with limited energy availability first power plasma membrane ion pumps to maintain vital electrochemical gradients. Given sufficient resources, the ribosomes synthesize proteins. Only next in the hierarchy, or up in the pyramid, are RNA and DNA synthesis [109], which can span categories depending on their functional role. Beyond minimal transcriptional and translational activity required to maintain existing cellular structures and vital function, these processes are often acutely dispensable GMR processes. A cell with membrane potential and sufficient proteins will survive days or weeks without DNA or RNA synthesis; cells survive and behave normally for multiple days without a nucleus [110]. This explains why, under scarce energy situations, cells do not enter the cell cycle [111], avoiding the energetic cost of DNA replication and minimizing behavioral complexity, likely to conserve energy and remain alive. In actively dividing cells, energy-consuming processes are both

temporally (e.g., across phases of the cell cycle) and spatially (e.g., in organelles) compartmentalized [112], avoiding competition between the costs of cell migration versus DNA replication [113], for example.

These same principles apply across the scales of the organism. Organ systems share finite energetic resources and similarly operate along a hierarchy of energy needs (Figure 2B, right). To sustain life, the heart, lungs, and autonomic nervous system functions are preserved at all costs. For example, under hypothermic environmental conditions, the organism sacrifices extremal tissues through frostbite by inducing peripheral vasoconstriction, striving to conserve energy and heat centrally, where the vital organs operate. In dynamically changing environments, energy is preferentially invested in systems that face recurrent demand (stress costs), expanding GMR programs (repair, biogenesis, and remodeling) in those tissues, while resources are withdrawn from underutilized systems. Energy management over the lifespan aligns with older ideas such as the disposable soma theory [108] and the efficiency arguments made earlier [28–34]. As energetic resources dwindle, including at the end of life, the organs and functions absolutely necessary for survival are prioritized over other ones and are the last to go.

Thus, vital, stress, and GMR categories of processes coexist and constantly trade off at multiple levels of organization.

Hypermetabolism—why is energy overspending unsustainable?

As discussed earlier (Figure 1C), the state of **hypermetabolism**—excess energy expenditure above what is typical for the cellular or physiological hardware of an organism—is unsustainable over long time periods. Excess energy metabolism relative to cellular demands has also been proposed to contribute to psychiatric disorders, including manic phases in bipolar disorder [114].

The unsustainability of hypermetabolism is apparent in isolated human cells, in clinical studies of energy expenditure and lifespan, and in ecosystems [115]. As one cellular example, cultured human fibroblasts exposed to mitochondrial OxPhos perturbations [38] or glucocorticoid signaling [104] activate stress response programs that elevate energy expenditure by 60–100%, revealing that endocrine or mitochondrial stressors can nearly double the energetic cost of life. In these and other hypermetabolic experimental conditions (where energy supply is not limited and where heat dissipation should not be limited either), DNA methylation clocks, telomere length, and senescence markers reveal an accelerated rate of aging that scales proportionally with the degree of hypermetabolism [116]. On the other hand, **hypometabolism** (a reduction in energy expenditure) achieved through lowered body temperature or calorie restriction decreases the rate of aging and prolongs lifespan [53,116,117].

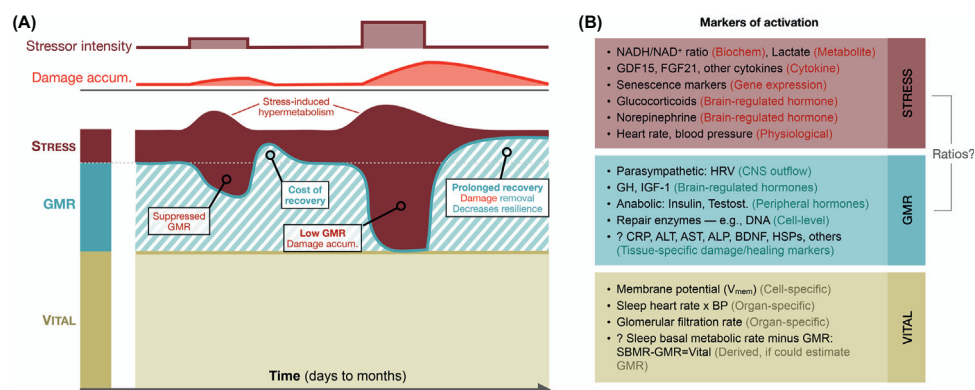
Potential mechanisms of unsustainability

Hypermetabolism is unsustainable and shortens lifespan for two mutually compatible reasons. The first has to do with entropy. Power output in biological systems requires irreversible mechanisms for energy transduction that come with entropy production [2]. In many thermodynamic regimes, the rate of dissipation is closely related with, and sometimes proportional to, the rate of entropy production [118]. For example, chemical reactions produce heat, which, in turn, may cause protein or other macromolecular damage that disrupts normal functions [119]. Increased temperature also modulates all biological rates [120], including lifespan [53,117]. So, in the absence of substantial compensatory investments in GMR, hypermetabolism should accelerate damage accumulation. Supporting evidence for this phenomenon includes the finding that lifespans are inversely proportional to the metabolic rate of a unit of tissue, or a single cell, across diverse species [29,31,54,57], including humans [121,122]. Animals with faster metabolic rates

also accumulate mutations and erode their telomeres faster [123,124], supporting the imperfect ‘rate of living’ theory of aging [31].

The second reason is that in an energetically constrained system, to support hypermetabolism, specific processes must be deactivated. For example, immediately after strenuous exhaustive exercise [125] and chronically with overtraining syndrome [officially called **relative energy deficiency in sport (RED-S)**] [126], deficits in the anabolic hormone growth hormone (GH) and gonadal hormones are associated with lean mass loss and sustained anabolic hormone deficits. Similarly, for cells growing in a dish, the energetic cost of secreting large amounts of proteins is linked to division arrest and the state of senescence, which is reversible by inhibiting protein synthesis [38,127]. These and other examples show how energy overconsumption by one process deactivates or compresses cell- and organism-level GMR, reflecting trade-offs with elevated stress costs. If this is the case, the reduced lifespan of various cellular and *in vivo* models in response to stressors could largely be driven by energetically constrained GMR processes.

The EC model integrates these two possibilities. In the EC model, stress-induced hypermetabolism is illustrated as the expansion of the stress component (Figure 3A). Because the vital component is relatively fixed and cannot be compromised, GMR must shrink to accommodate stress costs. As stated earlier, temporary suppression of GMR may not be damaging—given that it can expand and ‘repair’ compromised components in a recovery phase. However, chronically pausing GMR processes without periodic expansions (rest and sleep) to repair damage and produce adaptive recalibrations is expected to cause damage accumulation, suppress normal functions, accelerate aging, and increase disease risk. Energy management over the lifespan



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Figure 3. The energy constraint (EC) model of human health. (A) Stressors of varying intensities increase stress-related energy costs, actively or passively suppressing GMR processes. Once the stressor resolves, GMR costs can expand, contributing to recovery. In some cases, GMR processes trigger positive remodeling, increasing resilience to future stressors. The vital costs required to sustain life on a minute-by-minute basis are assumed to be stable but, under certain conditions discussed in the subsequent sections, can increase. Damage accumulation occurs when GMR is strongly suppressed for extended time periods, followed by (partial) removal during recovery. (B) Initial proposal for the operationalization of stress, GMR, and vital components of the human energy budget highlighting measurable biomarkers that are most directly, but not necessarily uniquely, associated with each of the three categories of energetic costs. Ratios of GMR and stress indices may provide the greatest sensitivity to dynamically assess trade-offs. Some situations could also involve the upregulation of both stress and GMR. Question marks indicate speculative suggestions. accum.: accumulation; ALT: alanine aminotransferase (liver derived); AST: aspartate aminotransferase (multiple tissues); ALP: alkaline phosphatase (multiple tissues); BDNF: brain-derived neurotrophic factor; BP: blood pressure; CNS: central nervous system; CRP: C-reactive protein; FGF21: fibroblast growth factor 21; GDF15: growth differentiation factor 15; GH: growth hormone; GMR: growth, maintenance, and repair; HRV: heart rate variability; HSPs: heat shock proteins; IGF-1: insulin-like growth factor 1; SBMR: sleep basal metabolic rate; Testost: testosterone.

aligns with older ideas such as the disposable soma theory [108] and the efficiency arguments made earlier [28–34]. Indeed, the chronic suppression of GMR, as in animals with deficient DNA repair systems, has long-term consequences that shorten lifespan [128,129].

Testing this proposal and its explanatory potential for health and aging requires that all three components of the EC model are quantified over time—either directly or indirectly. Figure 3B lists potential commonly used clinical and molecular markers that may reflect vital, stress, and GMR processes. Box 2 outlines a measurement framework and its current limitations.

Consequences of energy trade-offs across time and size scales

In this final section, we highlight how constrained energy can account for acute fluctuations in the energy budget over short time scales (Figure 4A) and how factors that increase (Figure 5A) or decrease (Figure 5B) disease risk operate by forcing trade-offs between vital, stress, and GMR processes.

Factors that increase disease risk and accelerate aging

Immune activation and inflammation. The activation, proliferation, and sustained activity of immune cells entail substantial energy costs [132,133]. For example, even nonfebrile (without elevation in body temperature) upper respiratory tract infections can increase resting metabolic rates by up to 14% in young males [134]. In children with higher pathogen burden, immune activation stunts growth [94,95], and animals infected with bacterial and viral challenges naturally adopt energy-conserving sickness behaviors [98,135]. In adult humans, stressful (i.e., energetically

Box 2. Key challenges to measuring vital, stress, and GMR costs

Testing and validating the EC model of human health under different contexts requires measurement of its individual components: vital, stress, and GMR-related costs.

While this feature review article outlines the general framework, a full measurement program will require diverse research groups working across health-related challenges. We highlight some guiding considerations, challenges, and opportunities to develop a quantitative EC framework in biomedicine and for preclinical research. Putative biochemical, metabolic, hormonal, bioelectric, and functional biomarkers are listed in Figure 3B. Five major considerations to developing valid markers of vital, stress, and GMR processes are as follows:

- (i) **Direct versus indirect markers.** The energetic cost of several processes cannot be directly measured because they are either distributed across multiple anatomical structures (e.g., digestion) or occur in parallel with other system changes (e.g., sympathetic deactivation).
- (ii) **Timescales.** Because baseline activity varies widely, dynamic measurement over time will be most sensitive and relevant. This comes with technical challenges and the need to establish the appropriate temporal resolution. Infrequent sampling may miss meaningful variation, while frequent sampling can perturb the system.
- (iii) **Multilevel drivers of energy costs.** The energetic cost of a given function is driven by processes at the organellar, cellular, organ, or system level. For example, the cost of cardiac contraction can be influenced by mitochondrial bioenergetic efficiency, cellular contractility, cardiac fibrosis, and/or peripheral vascular resistance—all of which modulate the vital cost of sustaining blood flow.
- (iv) **Delocalized, distributed effects.** The integrated bioenergetic efficiency of organismal functions relies not only on specific, localized functions within cells and organs, but also on their interactions and coordination. Organisms are cell collectives that must cooperate to sustain life. Poor coordination can require sustained hormonal/metabolic/cytokine signaling, promoting multisystem dysregulation and likely increasing vital costs; optimal coordination (supported by exercise and sleep) may improve efficiency.
- (v) **Composite indices.** Because each category includes multiple activities, no single measure of each is likely to capture meaningful recalibration across contexts. Because each of the vital, stress, and GMR categories subsumes several specific activities, no single measure of each is likely to satisfactorily capture meaningful recalibrations across contexts. Thus, the most powerful indicators will likely be multimodal indices (e.g., proteomics for organ-specific signals) combined with continuous physiology (heart/respiratory rate, glucose/lactate/ketones, and blood pressure) and behavior (activity, sleep, and posture). Such assessments should consider temporal lags (e.g., cortisol follows the adrenocorticotropic hormone with delay).

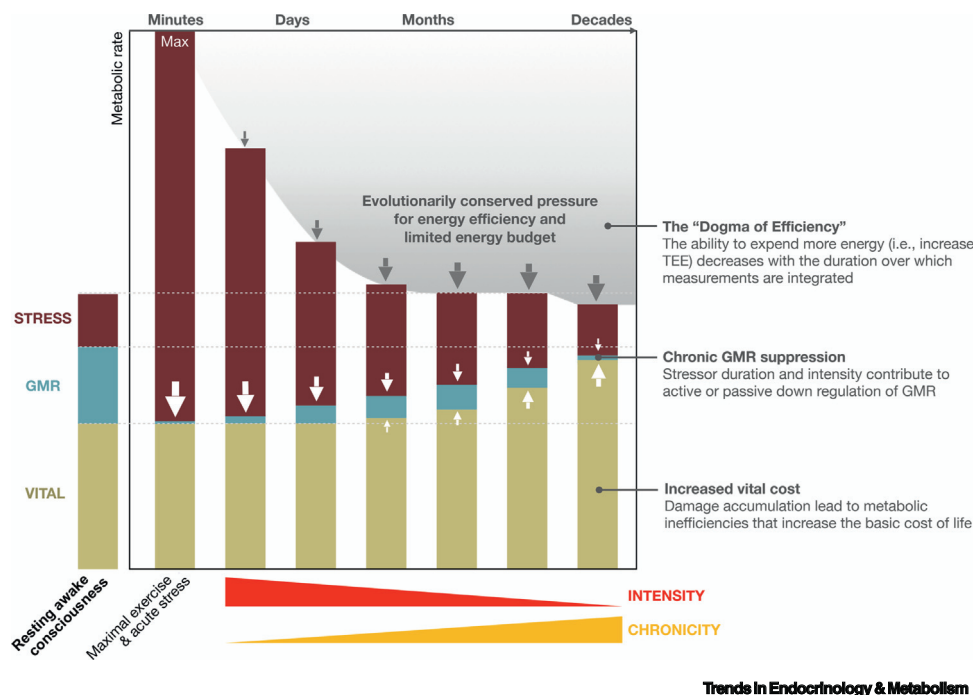
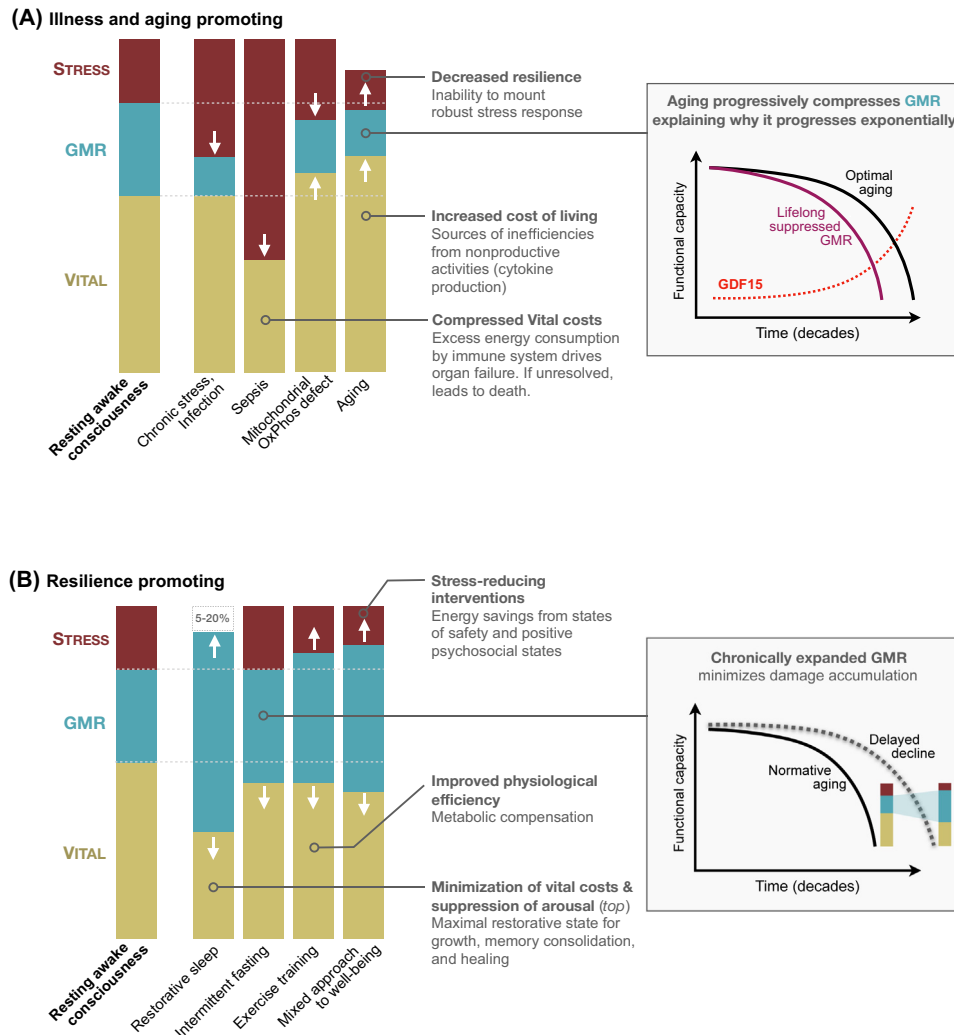


Figure 4. Influence of health-related behaviors, exposures, and interventions on energy constraint model components. The EC model assumes different energetic strategies when dealing with stressors of different durations. On time frames of minutes to days, there is a large (temporary) reserve where physiological limits appear to stretch, allowing for a transient state of stress-induced hypermetabolism. With increasing timescale, phylogenetically established constraints acting to optimize efficiency limit or ‘cap’ the energy budget—an axiom we coin the ‘dogma of efficiency’. Exposure to unrelenting, chronic stressors over longer timescales (e.g., chronic stress and adversity, and unresolved illness or infection) results in chronic compression of GMR processes. Over time, damage accumulation can increase the vital cost of life. EC: energy constraint, GMR: growth, maintenance, and repair.

demanding) challenges accelerate biological aging [106], while adequate energy supply can enable sick mice to be rescued from death [136].

Obesity. Carrying excess adipose tissue may have health-damaging consequences because it (i) increases the energetic cost associated with moving a greater body mass around, contributing to stress costs [137]; (ii) causes chronic inflammation associated with white adipose tissue macrophage infiltration [138] and cytokine signaling [131], which incur energetic costs; (iii) leads to unrestrained hepatic gluconeogenesis with insulin resistance, which can consume up to 22–39% of BMR [139]; (iv) results in elevated insulin concentrations (as with cytokines) that drive elevated costs in the pancreas [140] and in target cells [141]; and (v) the psychosocial burden associated with the stigma around obesity also activates psychosocial, energy-consuming stress pathways [142].

Chronic psychosocial stress. The major ‘stress response’ axes, such as the hypothalamic–pituitary–adrenal and sympathetic–adrenal–medullary, are, in fact, metabolic axes that mobilize energy [143] but also consume energy [144]. Mental stress alone increases heart rate, sweating, and muscle tension (all of which cost energy), while chronic stress is linked to the accumulation of markers of reduced GMR, including accelerated telomere shortening [145], oxidative stress [146], epigenetic aging [147], endocrine dysregulation [148], and elevated cytokine levels (sterile inflammation) [149]. Chronic mental stress also predisposes individuals to psychiatric disorders associated with molecular signatures of reduced GMR processes, including oxidative stress



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Figure 5. Health-damaging and resilience-promoting exposures or interventions. (A) Examples illustrating how energy trade-offs actively promote disease and accelerate aging. Stronger stimuli cause more severe GMR suppression. Symptoms emerge when vital costs are overridden by ‘stress’ costs, as in sepsis where immune costs override vital organ costs (i.e., multiorgan failure). Primary mitochondrial disorders causing persistent hypermetabolism [38,130] or damage accumulation in aging driving hypermetabolism in senescent cells [131] can increase vital costs, compressing GMR. Chronically compressed GMR accelerates aging, explaining why aging progresses exponentially. When stress-related costs are constrained by obligatory vital and GMR costs (advanced aging), this leads to decreased resilience and frailty. (B) EC model-based visualization addressing the health-promoting effects of relaxation, sleep, and exercise as stimuli that promote either (i) suppression of stress-related expenditures, enabling the passive expansion of GMR, and/or (ii) active energy investment into GMR processes. The EC model predicts that regular expansions of GMR contribute to recovery and longevity through minimizing the accumulation of damage and improving the physiological efficiency of vital processes [105]. EC: energy constraint; GMR: growth, maintenance, and repair.

[150–152], accelerated telomere shortening [153], and epigenetic aging [154]. These manifestations may dynamically appear in phasic and episodic fluctuations of symptoms in psychiatric disorders, marked by ups and downs in brain and immune bioenergetic profiles [155,156]. Energy limitations may also force trade-offs between brain networks [157,158], thereby altering mood and cognition.

Factors that promote resilience and extend lifespan

Sleep. The EC model proposes that sleep allows GMR costs to expand by shrinking stress costs. Sleep is also associated with reduced body temperature and hypometabolism [73,159], achieved in part by reducing stress-related sympathetic activation across multiple organ systems. Experimentally enhancing slow wave sleep improves left ventricular function in humans both during and after the sleep period [160]. Several hours of energy conservation during sleep likely compensate for the high energetic costs of arousal and wakeful consciousness [161] (Figure 5A). In flies, accumulation of reductive stress (NADH/NAD⁺, a marker of stress processes and energy resistance) drives the pressure to sleep [162]. As the model predicts, sleep relieves and decreases NADH/NAD⁺ [162]. In humans, sleep is associated with a decrease in stress-related hormones such as cortisol [163], and the elevation of GMR markers, including GH [164] and testosterone [165], substantiating sleep as a period that favors the investment of energetic resources and the expansion of GMR processes.

Stress-reducing and relaxation interventions. Active stress reduction, guided relaxation, and psychotherapy that stimulate the parasympathetic arm of the autonomic nervous system downregulate stress-related processes [105]. This generally reduces heart rate, resting blood pressure, circulating cytokines (i.e., inflammation), and likely other difficult-to-quantify physiological processes that otherwise consume energy. Meditation can reduce whole-body energy expenditure by 30–40% [74,166], suggesting that stress-reducing and relaxation strategies may potentially free up and reallocate energetic resources toward GMR to promote resilience and longevity (e.g., enhanced DNA repair [152]). This area requires more research combining time-resolved trajectories spanning both high- and low-arousal psychobiological states.

Sociality. All of the longest-lived mammals are social, and living in social groups affords clear fitness and lifespan advantages [167]. Energetically, animals exposed to stressors expend the most energy when they are isolated, whereas the (calming) presence of a conspecific lowers TEE [168]. In humans, sociality decreases the risk of dying in older adults and improves mental and physical health [167,169]. This may stem from reduced **allostatic load**—the anticipatory preparation for potential threats [170]. For these reasons, urbanization over the last 3 decades could have contributed to the apparent slowing of human metabolic rates—through decreasing basal metabolic rates [171], thereby freeing up resources to support GMR and longer, healthier lives [172]. A prediction of our model is that social isolation or perceived loneliness in social humans is linked to the activation of stress costs. This is supported by multiple lines of evidence, including the upregulation of the cytokines GDF15 [173,174] and fibroblast growth factor 21 (FGF21) [175] with psychosocial stress.

The seemingly paradoxical effects of exercise and calorie restriction

Exercise acutely increases stress costs, yet when repeated interspersed with sufficient recovery periods, it improves general health outcomes and acts as an effective treatment for several chronic illnesses [176]. Similarly, calorie restriction limits the energy budget yet extends lifespan and improves metabolic health [177,178]. How can interventions that expand stress costs and exacerbate EC ultimately promote health and longevity? Resolving this apparent paradox requires careful consideration of dose-, timing-, and context-dependent integration within a hierarchy of competing needs.

The central idea is that although exercise elevates energy expenditure and energy resistance acutely, the immediate costs of exercise are outweighed by the adaptations and recalibrations that occur in the post-exercise period. The energy cost of activity necessitates the deprioritization

of dispensable processes such as inflammatory signaling [179,180] and neuroendocrine stress reactivity [181]. At the same time, specific GMR processes in the muscle, cardiorespiratory system, and brain [182] are actively prioritized [68]. The resulting mitochondrial biogenesis, contractile and vascular protein synthesis, capillary network expansion, and increased stroke volume reduce the relative cost of future physical activity, while increasing resting metabolic efficiency, bioenergetic capacity, and physiological resilience [68,183,184].

The benefits of exercise also depend on dose [176]. The therapeutic window of physical activity reflects an evolved strategy of use-dependent resource allocation, whereby systems facing recurrent demand receive investment, while underutilized systems are stripped of resources. Below minimum activity thresholds, sedentariness triggers divestment from movement-supporting infrastructure: mitochondrial networks contract, vascular beds regress, and insulin sensitivity deteriorates [185–187]. On the other hand, excessive doses of activity impose sufficiently high stress costs that GMR processes are suppressed and compressed, leading to RED-S—a condition marked by lean tissue loss, hormonal deficits, compromised immunity, and accelerated damage accumulation [126,188]. The optimal amount of physical activity is likely shaped by our evolutionary history of hunting and gathering [189]. Species evolving under different pressures are likely calibrated to different amounts of activity.

Caloric restriction similarly exhibits a therapeutic window bounded by evolved physiological tolerances. Our ancestors faced prolonged food scarcity, creating selection pressure for robust physiological plasticity to survive temporary energy deficits. Accordingly, modest caloric restriction activates conserved dormancy programs [98]. Biological dormancy programs decrease entropy while also downregulating stress-related energy expenditure [137] and upregulating autophagy [190], mitochondrial biogenesis [191], and DNA repair [178], thereby effectively expanding GMR's proportional share of a reduced budget. However, when calorie restriction is excessive or coincides with high energy demands, GMR is squeezed out of the energy budget, producing the pathological tissue catabolism, endocrine dysfunction, and immune deficits characteristic of RED-S [188] and catabolic illness [192]. Thus, the effect of the supply-side constraint imposed by calorie restriction depends on the demand-side context (and vice versa).

The timing-, dose-, and context-dependent effects of exercise and calorie restriction reveal that optimal health emerges not from avoiding all stressors and supply constraints but from recapitulating the variations in energy supply and demand conditions under which human physiology evolved—transiently compressing GMR processes with stress costs, and subsequently resting to let GMR processes bounce back, enhancing the system's efficiency through mechanisms that remain to be fully defined. The sedentarism and food abundance that characterize contemporary human societies represent significant deviations from our evolved norm that compromise energetic capacity and efficiency. In this context, we understand that properly dosed exercise and calorie restriction can trigger adaptive trade-offs that suppress nonurgent costs while expanding GMR investments, yielding compounding gains in efficiency, robustness, and resilience across the lifespan.

Concluding remarks

We have presented a simply partitioned account of the energetic cost of cellular, physiological, and behavioral regulation in humans. The EC model's subdivision into vital, stress, and GMR costs outlines the plurality of energetic processes involved in sustaining health (not just surviving), and their competition within the context of a limited energy budget. However, we cannot simply eat more and invest the resulting surplus energy toward damage-mitigating, longevity-

Outstanding questions

Is the increase in human lifespan over the last decades driven by a reduction in basal energy expenditure resulting from reduced stress or vital processes, thereby leaving more resources to be invested in GMR?

Is the exponential nature of the aging process driven by the natural accumulation of damage, leading to a gradual elevation in the vital energy costs, thus gradually constraining GMR, resulting in feedforward propagating dynamics?

Is the phenomenon of multimorbidity driven by diseases acting as energy sinks, diverting energy from other systems and from GMR, thereby increasing the risk of other diseases?

Can we quantify direct elevations in GMR markers in response to stress-reduction approaches, interventions, and behaviors that mitigate biological aging and have restorative effects on the mind and body?

How can we empirically isolate and measure the energetic costs of disease processes or compensatory mechanisms?

Can we isolate and measure the metabolic rates of specific organs and tissues? How do these energy expenditure rates change in response to specific stressors?

What sets the hierarchy of energy needs across the body–mind system when energy is reallocated during exercise, illness, or other stressors?

Over what time frame do energy compensation and constraints act? How quickly are specific cellular and physiological processes downregulated or upregulated?

What is the role of specific signaling mechanisms (such as cytokines, hormones, and metabolites) in sensing and mobilizing the appropriate responses to energy stress?

How much energy does it cost to heal physical wounds and to metabolize traumatic psychological experiences?

promoting GMR processes. Human health is energetically constrained for reasons we have yet to fully resolve.

The energetic perspective of human health outlined here leads to several open questions (see [Outstanding questions](#)). The central principle of this model is that the chronic activation of prioritized stress systems overrides and suppresses GMR, hindering innate healing mechanisms required to support adaptation and a long, healthy life. As athletes know, if you train hard, you need to rest hard—for the health benefits come from the post-exercise expansion of GMR processes (not the stress processes that occur during exercise itself). Like exercise-related energy costs, the daily life demands of chronic stressors, including professional and social circumstances ranging from purpose, affordances, social isolation, and discrimination, interacting with both inherited and acquired energetic resources, all converge on the organism's integrated energetic circuitry. How much energy do different processes cost? And how do they compete with each other in relation to health-related processes?

As mitochondrial diseases have taught us, energy transformation defects alone are sufficient to cause diseases and shorten lifespan [130]. Likewise, robust evidence reviewed earlier and elsewhere shows that the (dis)allocation of energy resources can affect long-term health. Changes in energy availability and energy allocation thus emerge, in parallel with traditional molecular disease features [193], as potential drivers in the onset and/or progression of acute and chronic illnesses. We discuss a general approach to measurement and timescales, including GDF15, in [Box 3](#).

In terms of implications for biomedicine, resolving the role of EC on body–mind processes can provide new light to guide us toward the development of resilience-promoting approaches. The goal here would be to optimize allocation of energy across the lifespan—from hypermetabolic

Box 3. Measurement and temporal considerations

The EC model invites a shift in perspective—from molecular to energetic—by emphasizing that energy constrains all biological and physiological processes. This turns the spotlight away from characterizing isolated trade-offs, conditions, or molecular pathways at the interspecies level, to instead investigating the energetic transitions that define health, disease, and aging at the intraspecies and intra-individual level. Thinking about the energetic dimension of life in terms of dynamic competition for energetic resources may resolve some long-standing biomedical conundrums.

One question is why exposure to chemicals, pollutants, and chronic psychosocial stress increases the risk not of specific diseases, but of broad groups of disorders [194]? Likewise, why does having one disease predispose individuals to developing other diseases—the phenomenon of multimorbidity [195]? We propose a simple possible reason connecting these two questions: diseases and the energy-consuming clearance processes triggered by exogenous chemicals are ‘energy sinks’ that deplete a finite pool of organismal resources. Thus, regardless of the molecular underpinnings of their responses, the energetic liability of such persistent exposures is predicted to lead to an underlying, cross-diagnostic disease vulnerability.

With an energetic perspective on biology, researchers might rethink the origin and purpose of ‘inflammation’ beyond the immune system. Cellular stress responses involve the release and sensing of molecules called cytokines by immune and nonimmune cells [196]. Both secretion by source cells and sensing by target tissues cost energy [131,133]. If we could mitigate costly cellular stress responses and prevent the associated cytokine release, might we be able to allocate a greater fraction of the limited energy budget to longevity-promoting GMR processes [103]? Might this be why dampening cytokine release, or simply diluting the plasma in old animals, improves markers of health and rejuvenation (reviewed in [131])? Sustaining health through restorative ‘healing’ mechanisms requires the periodic allocation of energetic resources to GMR processes, which must—along with all other expenditures—fit within the limited energy budget.

Moreover, as energetic resources dwindle with aging, the EC model implies that investments in stress responses and GMR are progressively constrained to preserve vital functions for immediate survival. Thus, functional aging syndromes, such as frailty [131], could be understood as an energy-conservation strategy driven by the convergence of a shrinking energy budget (due to limitations in supply and transformation) with rising vital costs, each driven by accumulated damage due to prior underinvestment in GMR.

children to hypometabolic elderly [131,197]—necessary to empower each person to flourish and sustainably fulfill their full health potential.

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