Comparative Biochemistry and Physiology, Part A 284 (2023) 111473

Contents lists available at ScienceDirect

Comparative Biochemistry and Physiology, Part A

journal homepage: www.elsevier.com/locate/cbpa

# Physical performance during energy deficiency in humans: An evolutionary perspective

José L. Areta *

*Research Institute for Sport and Exercise Sciences, School of Sport and Exercise Sciences, Liverpool John Moores University, UK*

ARTICLE INFO

Edited by Michael Hedrick

*Keywords:*
Energy deficit
Human performance
Evolution
Low energy availability
Triad
REDs
Sports nutrition

ABSTRACT

Energy deficiency profoundly disrupts normal endocrinology, metabolism, and physiology, resulting in an orchestrated response for energy preservation. As such, despite energy deficit is typically thought as positive for weight-loss and treatment of cardiometabolic diseases during the current obesity pandemic, in the context of contemporary sports and exercise nutrition, chronic energy deficiency is associated to negative health and athletic performance consequences. However, the evidence of energy deficit negatively affecting physical capacity and sports performance is unclear. While severe energy deficiency can negatively affect physical capacity, humans can also improve aerobic fitness and strength while facing significant energy deficit. Many athletes, also, compete at an elite and world-class level despite showing clear signs of energy deficiency. Maintenance of high physical capacity despite the suppression of energetically demanding physiological traits seems paradoxical when an evolutionary viewpoint is not considered. Humans have evolved facing intermittent periods of food scarcity in their natural habitat and are able to thrive in it. In the current perspective it is argued that when facing limited energy availability, maintenance of locomotion and physical capacity are of high priority given that they are essential for food procurement for survival in the habitat where humans evolved. When energetic resources are limited, energy may be allocated to tasks essential for survival (e.g. locomotion) while minimising energy allocation to traits that are not (e.g. growth and reproduction). The current perspective provides a model of energy allocation during energy scarcity supported by observation of physiological and metabolic responses that are congruent with this paradigm.

## 1. Introduction

The prevailing view of energy deficit in the context of contemporary sports and exercise nutrition is that of an aetiological factor of conditions characterised by dysregulation of the endocrine milieu, normal physiological function, and that it directly results in impairment of health and athletic performance (De Souza et al., 2014; Mountjoy et al., 2018). While the influence of energy deficiency on some physiological and endocrine parameters, including bone metabolism and reproductive hormones, are well-characterised, evidence on the *direct* effect of energy deficiency on human physical capacity and athletic performance is scarce and limited (Melin et al., 2023). Available evidence suggests that even when facing energy deficit or showing signs of chronic energy deficiency, exercising individuals are able to maintain and increase physical capacity, or achieve levels of athletic performance compatible with international-level competition (Areta, 2020; Fudge et al., 2006; Garthe et al., 2011b; Garthe et al., 2011a; Hulmi et al., 2017; Langan-Evans et al., 2021; Stellingwerff, 2018; Tornberg et al., 2017; Zachwieja et al., 2001).

Given that a set of physiological responses are triggered by energy deficiency set to ensure energy preservation in humans (Areta et al., 2021; Aronne et al., 2021), it can expected that energetically demanding processes such as muscle contraction and high physical capacity, would be profoundly affected. However, this does not appear to necessarily be the case, and physical capacity may even improve while facing energy deficit. As an example, a randomized controlled trial study investigating the effect of ~40% energy reduction from energy balance in 40 males over 4 weeks with combined with intense exercise shows a clear contrast between endocrine and physiological effects of energy deficiency and changes in physical capacity (Longland et al., 2016). This intervention resulted in a reduction in body mass of ~5% in parallel with alteration of a broad range of hormones associated to energy preservation, including growth hormone, IGF-1, testosterone, insulin and cortisol (Longland et al., 2016). In contrast, however, lean body mass was either increased

* Corresponding author.
*E-mail address:* j.l.areta@ljmu.ac.uk.

https://doi.org/10.1016/j.cbpa.2023.111473
Received 7 March 2023; Received in revised form 29 June 2023; Accepted 30 June 2023
Available online 3 July 2023

or maintained, and physical capacity improved in almost all physical capacity and performance tests including leg press strength (~98% increase), bench press strength (~32% increase), push-up count (~32% increase), sit-up count (~32% increase), Wingate test mean power (~5% increase), Wingate test peak power (~12% increase), relative $VO_{2max}$ (~15% increase) and 250 kj cycling time-trial performance (~19% faster) (Longland et al., 2016). It may be argued that marked physical capacity and performance improvements in this population were possible because subjects were only recreationally active prior to the intensified training programme, and that these findings are irrelevant to other populations because individuals were overweight (BMI > 25 kg/m$^2$) (Longland et al., 2016). However, comparable findings have been reported in active and elite athlete population.

Improvements in physical capacity have been reported with concomitant energy deficit and weight-loss in active and trained individuals (Fogelholm et al., 1993; Louis et al., 2020; Zachwieja et al., 2001), and elite athlete populations (Garthe et al., 2011a; Langan-Evans et al., 2021). Energy deficiency concomitant with top-level competitive performances has been documented, for example, in elite long-distance runners prior to their main competitions (Fudge et al., 2006), in an Olympic middle-distance female (Stellingwerff, 2018), in an elite world-class female cyclist (Areta, 2020), and in race walkers (Burke et al., 2023). Moreover, menstrual dysfunction —also a proxy indicator of chronic energy deficiency— is prevalent among athletes that compete at an elite level (Torstveit, 2005). Though extreme energy deficiency clearly impairs physical capacity (Jenike, 1996; Keys, 1950), these reports suggest that achieving top-level athletic performance is possible in the face of a degree of energy deficiency (although it is unknown if being in energy deficiency can coexist with to top athletic performances for a given individual, see point 6, in section 6). This appears to be a biological contradiction: physiological responses for energy preservation are triggered but physical capacity —an energetically demanding trait— can be maintained or even improved.

This paradoxical response is difficult to make sense of, at least if the importance of physical capacity for survival is not considered in an evolutionary context. Intermittent energy scarcity is an important evolutionary pressure, and energy a unifying force in biology (Brown et al., 2004). As such, organisms have developed, through natural selection, mechanisms to cope with these selective pressures that span from cellular and sub-cellular level bioenergetics to behavioural adaptations (Efeyan et al., 2015; Niven and Laughlin, 2008). In this sense, modern humans are no exception given that in our origin we are hunter-gatherers and our biology has been shaped and adapted to this lifestyle (Pontzer and Wood, 2021). As part of this lifestyle food insecurity represented a stress factor through our evolutionary history (Berbesque et al., 2014; Prentice, 2007). Therefore, *Homo sapiens*, is possibly well-tooled to face periods of low energy availability without major injury risk while resulting in a mix of 'negative' and 'positive' outcomes. Indeed, caloric restriction has shown to decrease diseases onset and increase lifespan in a wide range of species, including our closely related primates, macaque monkeys (Colman et al., 2009), something that has been suggested to also happen in humans (Speakman, 2020). Nonetheless, given that in a natural hunter-gatherer habitat, locomotion and physical capacity are essential for food procurement, the machinery for physical activity may be maintained and likely spared from the same down-regulation that affects other traits that are non-essential for immediate survival such as growth, reproduction, and other somatic maintenance traits.

In this light, the aim of this perspective is to highlight that during energy deficit human physiology minimises non-essential energy expenditure at the expense of allocating limited energy available towards a trait that is essential for procuring itself of energy for the survival, namely physical capacity. It appears that physical capacity, despite being energetically expensive, is a high-priority trait for allocation of limited resources and unlikely to be affected by energy deficiency unless key energy stores (e.g. muscle glycogen) are critically low, or the deficit severe. With this hypothesis in mind, the current perspective piece provides a critical review of the literature supporting this framework.

To do this, and in line with the current special edition of this journal, the current piece will overlap fields that typically are not thought as synergistic: sports and exercise nutrition and evolution, with a focus on biological anthropology to use existing theories and frameworks to bring a different viewpoint to a topical area of investigation within sport and exercise science. To provide readers of different backgrounds with foundational knowledge, this piece will first provide a summary of our contemporary understanding of the effects of low energy availability in sports and exercise nutrition (section 2) followed by an outline of energy scarcity as a key selective pressure in evolution with a special reference to humans (section 3). Following this, I share a framework of physical capacity as a high-priority energy allocation task for humans (section 4), an idea which will then be supported by evidence of physiological responses to exercise in periods of energy deficiency (section 5). I will finally provide some points of reflection around the suitability of this conceptual framework for sports and exercise nutrition (section 6).

## 2. 'Low energy availability' in sports and exercise nutrition

'Energy availability' is a popular concept in sports and exercise nutrition, and it is currently operationally defined as dietary energy intake minus exercise energy expenditure, which represents the 'energy available' to sustain physiological processes outside exercise (Areta et al., 2021; Loucks, 2020). Defining what value 'low' energy availability (LEA) is represented by (in kcal/kg of fat-free mass/day) is difficult, particularly in field conditions (Heikura et al., 2021), and there may be no single threshold value for the population to define what is 'low'. However, LEA can be referred to as an amount of energy that triggers endocrine, metabolic and physiological responses coherent with energy preservation. LEA is referred to also as 'relative' energy deficiency, because the energy availability is reported —by definition— *relative* to exercise energy expenditure. Conceptually, LEA is somewhat different from the concept of energy deficit (Areta et al., 2021; Loucks et al., 2011) but for the sake of this review, energy deficit, LEA, energy deficiency, relative energy deficiency, energy restriction, and similar terms are used interchangeably. In all cases these will refer to insufficient energy for an organism to maintain normal homeostasis.

LEA is important because it is thought that many afflictions suffered by exercising and athletic populations are a consequence of underfuelling, and LEA is thought as a key etiological factor of negative health and performance consequence as outlined in the *Relative Energy Deficiency in Sport* (REDs) and the *male* and *female athlete triad* models (De Souza et al., 2014; Mountjoy et al., 2018; Nattiv et al., 2021; Thomas et al., 2016). In these models, LEA is thought to be the cause of impaired reproductive function and bone metabolism (increasing the likelihood of bone stress fractures), and several other dysregulations, including impaired athletic performance (De Souza et al., 2014; Mountjoy et al., 2018; Nattiv et al., 2021). A detailed description of the endocrine, metabolic and physiological effects of LEA is beyond the scope of this perspective piece and the reader is referred elsewhere for a detailed discussion (Areta et al., 2021; Loucks, 2020). It should briefly be summarised, however, that well-controlled laboratory-based studies have shown a causal effect between LEA and disruption of endocrine axes related to reproductive function (Loucks et al., 1998) and somatic maintenance (Loucks and Callister, 1993), bone metabolism (Ihle and Loucks, 2004; Papageorgiou et al., 2018) and other dysregulations (Koehler et al., 2016; Loucks et al., 1998). This literature shows that these perturbations are independent of the stress of exercise and possibly attributable to LEA as a causal factor, therefore providing a strong mechanistic support to epidemiological and cross-sectional observations of menstrual disorders in women, low bone mineral density and bone stress fractures in female (mainly) and male athletes.

Despite LEA has clear and remarkable effects on endocrine axes and

physiological systems which may result in negative health consequences such as stress bone fractures (Barrack et al., 2017; Barrack et al., 2014) that would ultimately affect performance, the **direct** effects on physical capacity before a *breaking point* is reached, are unclear. LEA is generally thought to rapidly trigger a negative state and even within-day energy deficits are suggested to be avoided (Torstveit et al., 2018). Instead of being thought of as key in the development of a disease-like affliction, the endocrine and physiological responses to LEA may be thought as a physiological adaptive and a teleological protective mechanism in a natural habitat (Jasienska, 2001): reproductive capacity —for species with heavy investment in offspring, at least— may be halted due to being an extremely expensive energetic process (Thurber et al., 2019), a fall in thyroid hormones may reduce resting metabolic rate, an increase in stress hormones mobilises endogenous energy stores, similar to the concomitant decrease in IGF-1 and increase in growth hormone: growth-related processes may be halted to increase the availability of endogenous alternative fuels (Chan and Mantzoros, 2005). These responses are consistent with the idea that in a state of limited energy, resources may be re-allocated based on a set of priorities from tasks that are not essential for immediate survival, to processes that are (Jasienska, 2001). Considering the hunter-gatherer origin of modern humans and its evolution through horticultural societies, foraging and food procurement may be considered essential for survival. Accordingly, locomotion and physical capacity would likely be protected against downregulation, unless the energetic stress is severe. Observations in an horticulturist population support the idea that activity levels are affected in males (but not in females), only when the degree of nutritional depletion is severe, and possibly not before (Jenike, 1996).

## 3. Energy scarcity as selective pressure for living organisms, including humans

Energy scarcity is a fundamental selective pressure in evolution, therefore, living organisms have developed through natural selection strategies to maximise the probability of survival when facing limited energy. Mechanisms to cope with energy scarcity and efficient use of energy have developed from single-celled to higher organisms (Brown et al., 2004; Niven and Laughlin, 2008; Wagner, 2005). Humans, as other mammalian and non-mammalian species, have historically faced seasonality in food availability with periods of food scarcity and famines during their evolutionary history (Anton et al., 2018; Prentice, 2007; Prentice et al., 2008; Speth, 1990), which means that on-demand, secure, constant food availability is a rarity evolutionarily speaking for our species when considering our hunter-gatherer lifestyle legacy. Hunting and gathering is characteristic since the origin of the genus *Homo* 2.4 million years ago, representing 99.6% of the time that have shaped the evolution of our species, given that agriculture arose ~12000/10000 years ago —when hunting-gathering, was drastically reduced as a mode of subsistence— (Cordain et al., 2000; Pontzer and Wood, 2021). This does not mean that with the advent of agriculture food scarcity and famines had been eliminated. In fact, periods of food scarcity are relatively common in hunter gatherers, but famines in agricultural societies are more common and also more severe (Berbesque et al., 2014; Prentice, 2007).

It has been argued that food scarcity in hunter-gatherers could be rather mild and the advent of agriculture (i.e. the neolithic), despite representing a briefer period in our hominin evolutionary history, have inflicted significant evolutionary pressure through severe famines resulting in positive selection of genes 'thrifty genes' that ensure survival in periods of scarcity —now linked to a prevalence of obesity in industrialised nations— (Chakravarthy and Booth, 2004; Neel, 1962; Prentice, 2005). Ongoing debate around the plausibility of genetic selection in this timeframe is unresolved (Prentice et al., 2008; Speakman, 2007). A relevant point of agreement in the debate, however, is that death by frank starvation during famines is remarkably low, with the majority of the deaths attributed to infectious diseases (Prentice et al., 2008; Speakman, 2007).

Therefore, traits that allow for survival in periods of food scarcity are likely highly effective and probably precede our most recent hominid evolutionary legacy. What is more relevant to consider in the context of this piece, however, is that populations that rely on hunter-gathering and subsistence farming appear to be highly active, at least when compared to the global population (Guthold et al., 2018). Hunter gatherers have been shown to spend over 130 min/day of moderate-to-vigorous physical activity (current recommendations in industrialised populations are 150 min per week) (Raichlen et al., 2017) and have been documented to cover on foot a daily distance of on average approx. 12 km in men (range ~ 6–18 km/day) and 6 km in women (~2–9 km/day) (Pontzer et al., 2015). Subsistence farmers also appear to be highly active (Levine et al., 2001) and physically fit (Sibson et al., 2021), possibly on par with hunter gatherers. Average physical activity levels (PALs; the ratio between total daily energy expenditure and resting metabolic rate) of general population are around 1.4–1.6 PALs, while for hunter gatherers is around 1.9 for men and 1.8 for women, and for subsistence farmers 2.1 for men and 1.9 for women (Lieberman, 2020).

There is no reason to believe that the necessity of foraging would be reduced in periods of food scarcity, as physical activity would be necessary to regain energy balance (Keys, 1950). In fact, frequency and gathering food activities has been documented to be higher in energy-stressed horticulturists (Jenike, 1996). The importance of locomotion for survival in hunter-gatherers becomes even more prominent when considering the importance of walking and the practices of *persistence hunting* and scavenging, posing the capacity to run long distances as key in the evolution of modern humans (Bramble and Lieberman, 2004; Liebenberg, 2006; Lieberman, 2020). Therefore, suppression of physical capacity during energy scarcity would reduce evolutionary fitness of humans. Consequently, in a state of low energy availability in a natural habitat, suppression of energetically demanding processes has been proposed to follow a hierarchy of needs whereby allocation of energy is prioritised to locomotion and physical capacity, above other energy allocation domains of lower priority, such as, for example, reproductive function or growth (Jasienska, 2001; Jenike, 1996; Wade and Schneider, 1992).

## 4. A hypothetical hierarchy of allocation of limited energy: locomotion and physical capacity as high-priority domains

Energy in an organism is a finite resource that is distributed among different competing organismal functions. Life history theory, a framework that explains how organisms are optimised to maximise reproductive success makes reference to *tradeoffs* of life history traits: the development of one trait may be at the expense of the development of another (Stearns, 2000). In an economic model of life history, energy —the common currency— that is utilised for one trait (such as maintenance, activity, growth or reproduction), cannot be used for another (Pontzer and McGrosky, 2022). Therefore, a life history perspective and an economic model of energy allocation, which are well-established concepts within the field of evolutionary anthropology, may be particularly relevant to interpret physiological responses to LEA in populations with high levels of physical activity or exercise (Pontzer and McGrosky, 2022; Shirley et al., 2022).

Endurance capacity is a fundamental characteristic of the genus *Homo*, which show a level of aerobic fitness and daily locomotion that far exceeds that of other non-extint primates. It is argued that walking and endurance running have been instrumental for food procurement in the evolution of humans, and are also essential for persistence hunting and/or scavenging (Bramble and Lieberman, 2004; Cordain et al., 1998; Liebenberg, 2006; Lieberman et al., 2020). Therefore, locomotion and physical capacity represent important tasks of energy allocation for survival in humans. Given that increasing physical activity represents an increase in the allocation of energy available to muscle contraction, something that needs to happen even in the face of reduced food

availability, it is logical to assume that to ensure survival physical capacity may have developed as a high-priority energy allocation task among different competing traits (Bronson, 1985; Ellison, 2001; Jasienska, 2003; Wade and Schneider, 1992). Importantly, locomotion (and physical capacity) is the only energy expenditure task that is directly linked to food/energy procurement in adults in a natural habitat (Fig. 1, A). Minimisation of the energy allocation to locomotion would therefore minimise the chance of food procurement in a natural habitat and therefore minimise evolutionary fitness. Here I refer specifically to *essential and voluntary* activity leading to procurement of food/energy and not to *non-essential and involuntary* activity, that can be reduced as a consequence of negative energy balance (Levine, 2004).

Accordingly, in this model of energy allocation, in the face of reduced energy availability in physically active population (Fig. 1, B and C), muscle, locomotion and physical capacity are of high-priority and energy is allocated to it both when energy is reduced due to reduced energy intake (Fig. 1, B) or increased physical activity/exercise energy expenditure (Fig. 1, C), as it has been suggested by others (Jasienska, 2001; Pontzer and McGrosky, 2022; Schneider et al., 2013; Sibly et al., 2013; Wade and Schneider, 1992). Note that other tasks within 'maintenance and survival' that may compete with locomotion, such as immune function, are not considered as part of the model due to being outside the scope of the current piece.

This model is based on indirect evidence and even though measuring energy allocation between different tasks and traits (that are mostly conceptual and virtual in nature) in humans may prove technically unfeasible, observations of physical capacity and physiological responses in the face of energy deficiency with concomitant physical activity can provide robust evidence to evaluate allocation of resources to test this model. Current evidence supports the idea that physiological systems that are not immediately relevant for survival such as reproduction and growth are down-regulated, while those that are linked to locomotion and physical capacity (e.g. muscle oxidative capacity, myofibrillar protein synthesis, strength and neuronal mitochondria), tend to be maintained or even improved when energy deficiency is overlayed on top of physical activity or exercise.

## 5. Evidence supporting the maintenance of metabolic and physiological capacity and machinery for locomotion and physical activity in the face of energy deficit, with concomitant physical activity and exercise

Relative to the research on endocrine consequences of energy deficit on endorcrine responses and potential heatlh impairments (Areta et al., 2021; De Souza et al., 2014; Loucks, 2020; Mountjoy et al., 2018), scientific studies on the effect energy deficit on muscle physiology, function and ahletic performance are comparatively small in number and this is a topic that is largely unexplored. Current research seems to suggest that when physical activity/exercise are undertaken in the face of energy deficit, physical capacity and skeletal muscle capacity can be maintained or even improved, possibly supported by a maintenance and/or optimisation of the machinery that supports this. To highlight this and provide evidence supporting the model outlined in section 4, this section presents evidence on physiological responses that are congruent with maintenance of locomotion and physical capacity when facing energy deficit, with a focus on skeletal muscle (summarised in Fig. 2).

Energy deficiency in the sedentary state can decrease skeletal muscle mass through blunting anabolic processes, but muscle contraction preserves lean mass losses and functional capacity. Even in the face of energy deficiency, scientific reports predominantly show strength maintenance or gains in a range of populations (Garthe et al., 2011a;

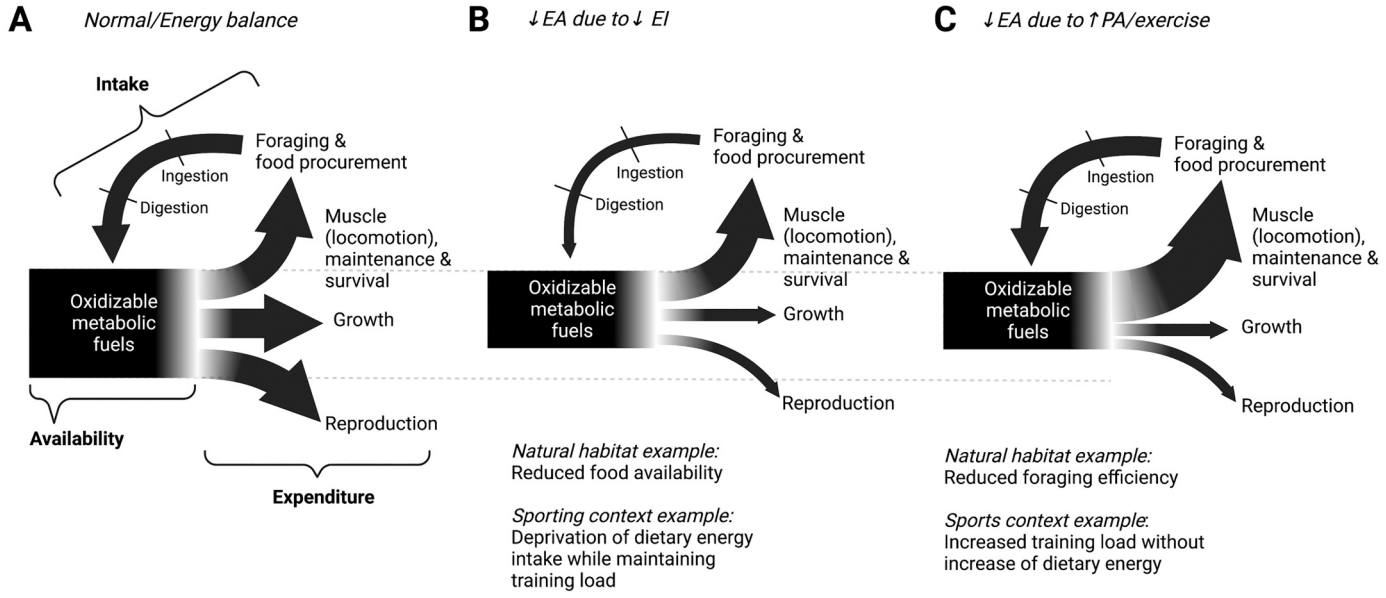


**Fig. 1.** Theoretical model of allocation of energy in situations of energy balance (A) or reduced energy availability (EA) due to a decrease in energy intake (B) or increase in physical activity (PA)/exercise energy expenditure (C). Arrows in each panel represent flow of energy from one compartment to another with the thickness of arrows representative of the magnitude of the flow of energy . Availability of energy is equal to the difference between intake and expenditure (intake line is not to scale relative to expenditure). In a state of energy balance, or *normal* energy availability (A), energy allocated between different compartments to match their requirements for normal function. Panel B, represents a hypothetical situation of reduced energy availability due to reduced energy intake with no changes in energy expenditure for maintenance and locomotion for food procurement, as it would be observed —for example— in a natural habitat through reduced food availability while maintaining the same foraging effort or, in a sporting context, through deprivation of energy intake while maintaining training load. Panel C, represents a hypothetical situation of increased energy expenditure while maintaining the same energy intake, as it would be observed —for example— in a natural habitat by reduced foraging efficiency leading to increase physical activity to achieve the same amount of energy intake as in (A) or, in a sporting context with increased training load without increase in a concomitant amount of dietary energy intake. In real world scenarios B and C would not necessarily happen in isolation. Inspired in similar models (Jasienska, 2001; Pontzer and McGrosky, 2022; Schneider et al., 2013; Sibly et al., 2013; Wade and Schneider, 1992). Figure was created with biorender.com.

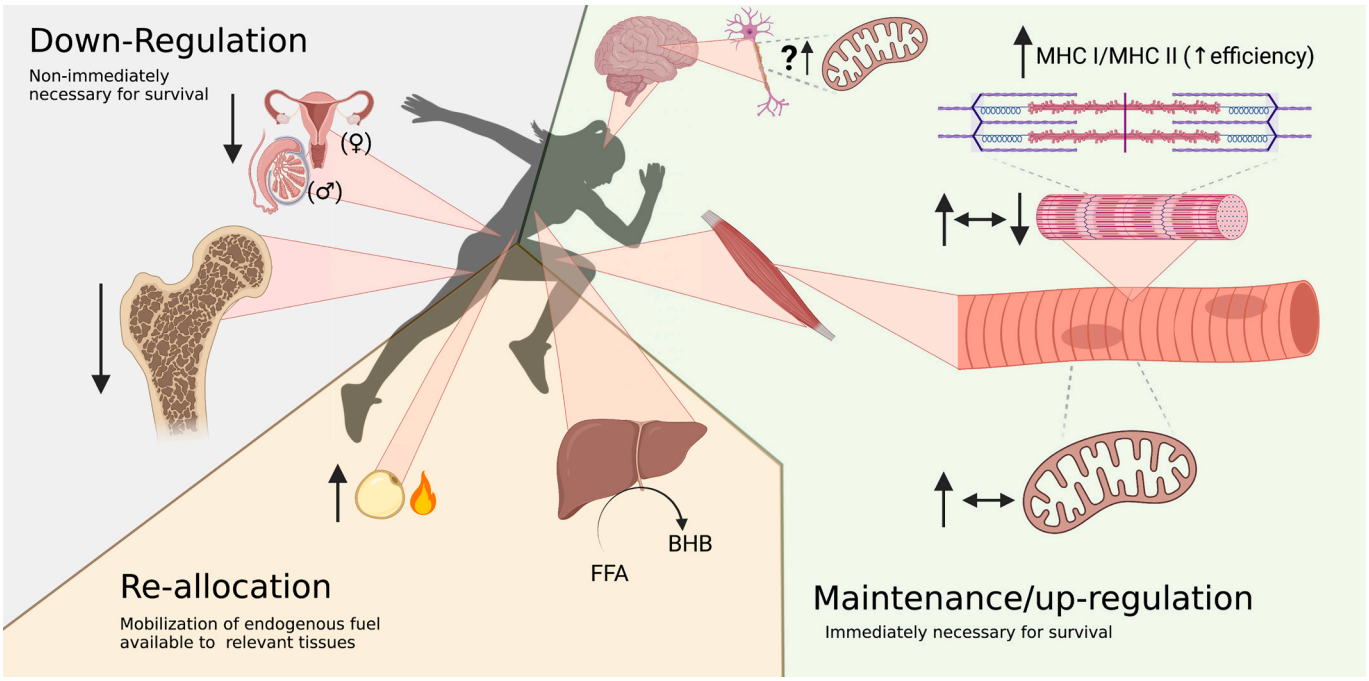


**Fig. 2.** Graphical representation of the physiological responses reflecting a priority of energetic resources allocation during energy deficiency. With reduced exogenous substrate availability metabolism switches to a mobilization and increase in use of endogenous energy reserves, prominently fatty acids and ketones. Concomitantly reproductive function and bone metabolism are down-regulated, while oxidative capacity and myofibrillar protein content in muscle may be maintained or enhanced while switching to a more energy-efficient phenotype. BHB, β-hydroxybutyrate; FFA, free fatty acids. Figure was created with biorender.com.

Hulmi et al., 2017; Langan-Evans et al., 2021; Longland et al., 2016; Rossow et al., 2013). The contractile force of a muscle is determined mainly by synchronised motor unit recruitment and the cross-sectional area of the muscle, which is determined by the size of a muscle which is, in turn, is determined by the size of the myofibril protein pool. Short-term energy deficiency has shown to decreases resting muscle protein synthesis (Areta et al., 2014; Pasiakos et al., 2010), but resistance exercise stimulus has shown to be able to rescue protein synthesis to energy balance baseline levels (Areta et al., 2014; Hector et al., 2018; Murphy et al., 2015). Similarly, loss of lean mass during a severe weight-loss intervention of short duration (4 days) has been observed to be exacerbated in the muscles that had not been exposed to contractile activity, compared to those that have (Calbet et al., 2017). Importantly, a meta-analysis evaluating the effect of energy deficit on lean mass with concomitant resistance exercise training, has shown that a degree of energy deficit is able to reduce gains in lean mass, without affecting gains in strength (Murphy and Koehler, 2021). Overall, these findings support the idea that muscle growth is downregulated by energy deficit, but upon muscle contraction protein synthesis can be maintained, as is the capacity to elicit force, at least up until certain level of energy deficit.

Aerobic fitness and muscle oxidative capacity can be maintained or potentially improved in the face of energy deficit. Aerobic capacity and performance that match the demands of competitive elite and world-class athletes seems to be achievable even in the face of acute and chronic energy deficiency (Areta, 2020; Burke et al., 2023; Fudge et al., 2006; Langan-Evans et al., 2021; Stellingwerff, 2018; Tornberg et al., 2017). Maintenance and improvements in maximal aerobic capacity and performance have been documented in different populations when exposed to significant energy deficit with concomitant training (Brady et al., 2021; Brennan et al., 2022; Burke et al., 2023; Langan-Evans et al., 2021; Longland et al., 2016; Zachwieja et al., 2001). For example, maintenance of maximal aerobic capacity has been documented in elite race-walkers after a short-term (9 day) 'low energy availability' intervention during a training camp (Burke et al., 2023), and in trained middle and long-distance runners following an 8-week time-restricted feeding protocol resulting in weight-loss (Brady et al., 2021). Improvement of maximal aerobic capacity has been documented in weight loss interventions in overweight and obese (Brennan et al., 2022; Longland et al., 2016), physically active population (Zachwieja et al., 2001), and an elite combat-sport athlete after a 9% body-mass loss during 7 weeks of 'making weight' for competition (Langan-Evans et al., 2021). There is possibly not enough evidence yet to indicate at what point a certain degree of energy deficiency may affect aerobic capacity, and if there is a negative effect, what may be the exact mechanisms behind, if those related the central nervous system, cardiovascular, skeletal muscle, or a combination of all of these.

An important component determining endurance capacity is the oxidative capacity of skeletal muscle which is supported by cellular processes of energy generation linked to mitochondrial metabolism. Research evaluating the effect of energy deficit on skeletal muscle mitochondrial pathways in humans is limited, but current evidence seems to be supportive of this model. For example, a mouse training model with alternate day fasting (ADF) resulting in reduced energy intake compared to an ad libitum group showed improvements in performance and skeletal muscle in the ADF group with concomitant up-regulation of pathways involved in mitochondrial biogenesis, metabolism and cellular plasticity (Marosi et al., 2018). Similar findings have been replicated in a similar rat model (Real-Hohn et al., 2018). In humans, the evidence of energy deficit upregulating skeletal muscle oxidative pathways appears to be limited to overweight and obese populations, but seems to support the idea that —if not improved— oxidative capacity or markers of mitochondrial content in skeletal muscle are at least maintained (Civitarese et al., 2007; Coen et al., 2015; Menshikova et al., 2007; Menshikova et al., 2005; Toledo et al., 2007; Toledo et al., 2006). Interestingly, a recent report has shown a short period (10 days) of 'low energy availability' reduced bulk myofibrillar and sarcoplasmic protein synthesis in exercising moderately trained young eumenorrheic women compared to an 'optimal energy availability' group, but provided no other analyses of skeletal muscle phenotype (Oxfeldt et al., 2023). Unpublished skeletal muscle proteomic

analyses from our research group suggest that when severe energy deficit is overlayed acutely on top of aerobic-type exercise in young, healthy young male population, could increase proteins of oxidative mitochondrial pathways in skeletal muscle (Taylor et al., 2023).

Despite energy deficit appears to have a modulatory role on the phenotype of skeletal muscle, one may need to be more specific when referring to 'energy deficit' in relation to skeletal muscle. There may be an effect of '*systemic*' energy deficit leading to changes of humoral factors such as circulating anabolic and catabolic hormones (e.g. testosterone, IGF-1, cortisol, etc) and metabolites (e.g. free fatty acids, ketones, etc.), and a '*local*' energy deficit represented by changes in endogenous fuel stores, of which glycogen is particularly relevant. Skeletal muscle glycogen is not only an important fuel source for muscle contraction, particularly for high intensity exercise (Areta and Hopkins, 2018), but also represents an energy storage metabolite that is tightly monitored by the cell (Hardie and Sakamoto, 2006; Philp et al., 2012). A decrease in skeletal muscle glycogen concentration triggers a cascade of intracellular signals that are associated with up-regulation of fatty acid metabolism and mitochondrial biogenesis in skeletal muscle, among other pathways (Hardie and Sakamoto, 2006; Philp et al., 2012; Pilegaard et al., 2002; Wojtaszewski et al., 2003). Training with low muscle glycogen has been attributed to improvements in skeletal muscle working of >2 fold capacity compared to training with normal muscle glycogen in humans after 10 weeks of training (Hansen et al., 2005).

This seminal research suggesting positive adaptive effects to training with low muscle glycogen (i.e. intracellular energy depletion), has led to a significant body of research investigating muscle molecular adaptations associated to enhanced adaptation to training, and some research directly assessing its performance effects. Completing specific training sessions with low muscle glycogen has shown a clear modulatory effect of intracellular molecular pathways, related to oxidative metabolism (Hawley and Morton, 2014; Hearris et al., 2018). However, this approach of *periodised* carbohydrate restriction whereby specific sessions are completed with low muscle glycogen, while allowing glycogen replenishment for other sessions, has ultimately shown no clear effect of improvement in performance (Gejl and Nybo, 2021). It is remarkable, however, that in these models when, repeatedly training with low muscle glycogen, performance *is not impaired* (though it likely is impaired with *chronic* carbohydrate deprivation of low-carbohydrate high-fat diets (Burke, 2020)). The independent effects of potential synergistic 'local' (glycogen) and 'systemic' energy deficits on skeletal muscle are an area of ongoing research. Short-term studies seem to suggest that reduced systemic energy does not necessarily affect skeletal muscle adaptation to training in (Areta et al., 2020; Gorski et al., 2023; Hammond et al., 2019), but more research is needed using intervention protocols that span more than a few hours.

Beyond the effect on the oxidative metabolism machinery, the phenotype shift in muscle with energy deficit appears to also minimise energy expenditure through improvement of efficiency and economy of movement. Research in overweight and obese individuals maintaining physical activity during a period of 6–7 months to achieve 10% of weight loss has shown that muscle contraction efficiency and walking economy are increased as a consequence (Foster et al., 1995; Goldsmith et al., 2010; Rosenbaum et al., 2003). This improvement in efficiency has been attributed to a shift of the ratio of myosin heavy chain (MHC) in skeletal muscle from less efficient MHC II to more efficient MHC I (Rosenbaum et al., 2018), something that appears to be modulated by the decrease in circulating triiodothyronine (Kim, 2008; Rosenbaum et al., 2018). To the best of my knowledge, it is unknown if a similar mechanism would be observed in normal sedentary or trained individuals exposed to energy deficit.

Finally, beyond the effect of energy deficit on skeletal muscle metabolism, the physiological effect on neurons may also be considered as relevant in the current context. The relevance of neuronal function for skeletal muscle and locomotion for foraging is twofold: first, muscle contraction is determined by the electro-chemical signal of neurons from the brain to the neuromuscular junction, and second, hunting and gathering are cognitively demanding (Liebenberg, 1990; Rosati, 2017). Consistent also with the model proposed in the previous section, energetic stress has also been shown to enhance neuronal mitochondrial biogenesis, synaptic plasticity, neurogenesis and cognition in rodent models (Mattson, 2012; Raefsky and Mattson, 2017), something that could have implications in cognitive capacity in relation to foraging cognition.

To conclude, when focusing on the metabolic and physiological responses associated to physical capacity and locomotion, it appears that these traits are maintained at the expense of traits that are not immediately necessary for survival in a natural habitat (i.e. growth and reproduction). A graphical summary of this section is shown in Fig. 2.

## 6. Implications and considerations of the current model for sports and exercise nutrition

To finish this perspective, I outline some implications and considerations of this paradigm for sports and exercise nutrition. It is important to highlight that this model outlines an orchestrated set of physiological responses that may have developed through human evolutionary history to enhance survival in the face of intermittent energy scarcity, and not to make a human fit to win any sort of sporting competition. Therefore, while it can provide a framework to interpret, understand the 'why' of and perhaps predict physiological responses in settings involving individuals with high levels of physical activity and relative energy deficiency, care should be taken of not over-interpreting this model. Calling for caution, I invite the reader to reflect on a non-exhaustive list of 6 key points that may allow to better blend the use of this model in real-world sports and exercise nutrition settings.

First, *hunter gatherers and subsistence farmers are not athletes*. While a typical hunter gatherer or subsistence farmer is more physically active than the average industrialised-world dweller, the belief that hunter-gatherers spontaneously follow a physical activity pattern like those of athletes in heavy training has been appropriately termed the 'fallacy of the athletic savage' (Lieberman et al., 2020). Physical activity resulting from a *necessity* to procure food for survival may impose very different physiological and metabolic demands from that of elite-athlete population *voluntarily* following a training programme to achieve sporting success. For example, in order to reach peak-performance, elite endurance athletes typically train 500–1000 h a year, following a structured programme of periodised training volume and intensities (Tønnessen et al., 2014). This training volume may be comparable to the time allocated to locomotive physical activity in hunter-gatherers (Pontzer et al., 2015), but the metabolic demands are likely very different, not only because of the patterns of high intensity training in athletes (e.g. high intensity interval training), but also because of the dissimilar energetic demands. For example, physical activity levels (PALs) of hunter-gatherers and subsistence farming populations have been reported to be ~1.8–2.3 (Pontzer et al., 2015; Pontzer et al., 2012), while PALs of top endurance athletes in multi-stage competitions lasting ~3 weeks (road-cycling grand tours) have been reported to be over twice as much, ranging between 3.9 and 5.3 (Plasqui et al., 2019; Van Hooren et al., 2022; Westerterp et al., 1986). As such, this may result in an 'evolutionary mismatch', whereby the demands of a new environment are different from the capacities of an organism which has adapted to an habitat with different demands (Lieberman, 2014), ultimately resulting in health complications. Therefore, due to unique energetic demands of athletes with high training load, absolute macronutrient and energetic needs of athletic populations with high training loads are likely very different from those of hunter gatherers and subsistence farmers.

Second, and following from the first point, *a physiological system evolved to increase the probability of food procurement for survival in a natural habitat, does not mean that evolved hard-wired physiological mechanisms are optimised for peak performance in a sporting setting.* Current sports nutrition interventions are designed according to a complex

set of guidelines that match nutritional recommendations to the specific requirements of individuals in a range of sports imposing different physiological and metabolic demands (Burke and Hawley, 2018). Typically, sports nutrition plans seek to anticipate the requirement of the individual based on a priori knowledge of the demands of the sport and the requirements of the individual to provide a wide array of carefully measured macronutrients and supplements, rather than relying mostly on internal physiological cues (e.g. hunger) and whatever foodstuff may be seasonally/circumstantially available. ***Nutrition for survival is, therefore, different in nature from nutrition for peak performance***. However, understanding how evolution may have shaped our physiology and metabolism could prove useful to optimise nutritional interventions in athletes. This seems particularly relevant in relation to energy deficiency, given that our physiology and metabolism may have adapted and optimised through natural selection to face periods of energy scarcity.

Third, energy deficit may —therefore— be thought as a natural 'stressor', which our (eukaryote/animal/chordate/mammalian/hominid) metabolism and physiology must have adapted to through millions of years natural selection, making us equipped with a degree of phenotypic plasticity to cope with it. Therefore, **energy deficiency may not be positive or negative *per se* in the context of sports nutrition: only the dose would determine that the effect is positive or negative**. Perhaps a small/moderate dose of energy deficiency may trigger adaptive mechanisms that could optimise the metabolic machinery and physiology, with prolonged and/or severe energy deficiency leading to negative health outcomes, ultimately impairing performance. In line with this paradigm, a degree of energy deficit may allow to maintain or even improve skeletal muscle phenotype for generating energy cellular energy while down-regulating some physiological processes not immediately essential for survival (see Fig. 2). Excessive energy deficiency and semi-starvation has shown to impair physical capacity (Keys, 1950; Rossow et al., 2013) and chronic energy deficiency can lead to health issues, some of them possibly irreversible, such as low bone mineral density (resulting in stress fractures) and others such as those documented and speculated in the athlete triad and relative energy deficiency in sport models (De Souza et al., 2014; Mountjoy et al., 2014; Nattiv et al., 2021). Care against these negative health outcome scenarios and anticipating them in exercising population is of utmost importance.

Fourth, that markers of energy deficiency (e.g. secondary hypothalamic amenorrhea & oligomenorrhea) can be present while athletes perform at a world-class level, does not mean that these are desirable or that better performances are not possible without energy deficiency. However, to date, there is no irrevocable evidence providing support that a measured of energy deficit can be better or worse for performance, and more research is needed.

Fifth, while in this perspective (and the literature in general) *energy deficiency* and its synonyms are unspecific terms that do not distinguish what the energy intake is composed of, it is possible that the macronutrient composition of the diet plays a major regulatory role in physiological adaptations and athletic performance. Specifically relevant to physical performance, **pronounced low carbohydrate availability would reduce the capacity for sports performance chronically and acutely and possibly impair adaptation to training** (Burke, 2020). Dietary carbohydrates are a key substrate to determine the concentrations of skeletal muscle glycogen, which, in turn, is key in determining work capacity and performance (Areta and Hopkins, 2018; Bergström et al., 1967; Vigh-Larsen et al., 2021). Therefore, studies that attribute impairment in athletic performance to energy deficit, should distinguish clearly between chronic 'energy deficit' and acute 'carbohydrate deficit', and carefully control carbohydrate intake to ensure that low levels of muscle glycogen are not a confounding factor in performance assessment.

Sixth, and as a corollary of the points above, if any syndrome or negative outcomes from chronic energy deficiency are to be avoided through detection of early 'signs and symptoms', then athletic performance is likely a poor marker. Given that the limited available energy during energy deprivation appears to be allocated to maintain physical capacity at the expense of other systems, then focusing on other markers of energy deficiency (e.g. endocrine and metabolic markers), may be a more promising option to detect chronic relative energy deficiency than performance.

## 7. Conclusions

In conclusion, in current sports nutrition chronic energy deficit is typically thought to have negative effects on health and performance, but the effects on performance are not clear. Evidence shows that it is possible to improve physical capacity and compete at an international level in sports even when facing energy deficit. Contrasting effects of energy deficit down-regulating energy-demanding physiological functions while seemingly maintaining physical capacity is an enigmatic response, given that physical activity is an energetically demanding task. Energy deficit is an important selective pressure for living organisms, including humans, and evolution seems to have tooled them with a degree of phenotypic plasticity to deal with energetic stress. Locomotion and physical capacity may have evolved as a high-priority energy allocation task, given it is the only energy outlet for an adult in a natural habitat that results in food/energy procurement. The effects of energy deficiency may not be 'all positive' or 'all negative': some energy deficit may trigger adaptive responses while excessive deficit may result in negative health consequences (e.g. low bone mineral density and stress fractures), which may ultimately affect performance. Evidence from physiological adaptations to energy deficit seems to support a model where some tissues machinery (e.g. skeletal muscle oxidative function) may be maintained or improved with a degree of energy deficit, while others down-regulated (e.g. reproductive function). The effect of energy deficit with concomitant exercise on physiology and physical capacity remains largely unexplored and to evaluate this model more quality scientific research is necessary. The model proposed herein may help interpreting and predicting physiological outcomes in periods of energy scarcity, but it needs to be tested scientifically to assess its robustness and usefulness in an applied context. Even though the physical activity patterns and energetic demands of elite athletes and hunter-gatherers are very different in nature, understanding responses through an evolutionary lens, may provide further insight into the 'why' of the physiological responses observed.

## Declaration of Competing Interest

I declare no conflict of interest.

## Data availability

No data was used for the research described in the article.

## Acknowledgments

The author would like to thank Dr. Eimear Dolan for extensive constructive feedback on this manuscript, and two anonymous reviewers for their excellent comments to improve this manuscript.

## References

Anton, S.D., Moehl, K., Donahoo, W.T., Marosi, K., Lee, S.A., Mainous, A.G., Leeuwenburgh, C., Mattson, M.P., 2018. Flipping the metabolic switch: understanding and applying the health benefits of fasting: flipping the metabolic switch. Obesity 26, 254–268. https://doi.org/10.1002/oby.22065.

Areta, J.L., 2020. Case study: resumption of Eumenorrhea in parallel with high training load after 4 years of menstrual dysfunction: a 5-year follow-up of an elite female cyclist. Int. J. Sport Nutr. Exerc. Metab. 30, 229–234. https://doi.org/10.1123/ijsnem.2019-0284.

Areta, J.L., Hopkins, W.G., 2018. Skeletal muscle glycogen content at rest and during endurance exercise in humans: a Meta-analysis. Sports Med. 48, 2091–2102. https://doi.org/10.1007/s40279-018-0941-1.

Areta, J.L., Burke, L.M., Camera, D.M., West, D.W.D., Crawshay, S., Moore, D.R., Stellingwerff, T., Phillips, S.M., Hawley, J.A., Coffey, V.G., 2014. Reduced resting skeletal muscle protein synthesis is rescued by resistance exercise and protein ingestion following short-term energy deficit. Am. J. Physiol.-Endocrinol. Metab. 306, E989–E997. https://doi.org/10.1152/ajpendo.00590.2013.

Areta, J.L., Iraki, J., Owens, D.J., Joanisse, S., Philp, A., Morton, J.P., Hallén, J., 2020. Achieving energy balance with a high-fat meal does not enhance skeletal muscle adaptation and impairs glycaemic response in a sleep-low training model. Exp. Physiol. 105, 1778–1791. https://doi.org/10.1113/EP088795.

Areta, J.L., Taylor, H.L., Koehler, K., 2021. Low energy availability: history, definition and evidence of its endocrine, metabolic and physiological effects in prospective studies in females and males. Eur. J. Appl. Physiol. 121, 1–21. https://doi.org/10.1007/s00421-020-04516-0.

Aronne, L.J., Hall, K.D., Jakicic, M., Leibel, R.L., Lowe, M.R., Rosenbaum, M., Klein, S., 2021. Describing the weight-reduced state: physiology, behavior, and interventions. Obesity 29. https://doi.org/10.1002/oby.23086.

Barrack, M.T., Gibbs, J.C., De Souza, M.J., Williams, N.I., Nichols, J.F., Rauh, M.J., Nattiv, A., 2014. Higher incidence of bone stress injuries with increasing female athlete triad–related risk factors: a prospective multisite study of exercising girls and women. Am. J. Sports Med. 42, 949–958. https://doi.org/10.1177/0363546513520295.

Barrack, M.T., Fredericson, M., Tenforde, A.S., Nattiv, A., 2017. Evidence of a cumulative effect for risk factors predicting low bone mass among male adolescent athletes. Br. J. Sports Med. 51, 200–205. https://doi.org/10.1136/bjsports-2016-096698.

Berbesque, J.C., Marlowe, F.W., Shaw, P., Thompson, P., 2014. Hunter–gatherers have less famine than agriculturalists. Biol. Lett. 10, 20130853. https://doi.org/10.1098/rsbl.2013.0853.

Bergström, J., Hermansen, L., Hultman, E., Saltin, B., 1967. Diet, muscle glycogen and physical performance. Acta Physiol. 71, 140–150.

Brady, A.J., Langton, H.M., Mulligan, M., Egan, B., 2021. Effects of 8 wk of 16:8 time-restricted eating in male middle- and long-distance runners. Med. Sci. Sports Exerc. 53, 633–642. https://doi.org/10.1249/MSS.0000000000002488.

Bramble, D.M., Lieberman, D.E., 2004. Endurance running and the evolution of Homo. Nature 432, 345–352. https://doi.org/10.1038/nature03052.

Brennan, A.M., Standley, R.A., Anthony, S.J., Grench, K.E., Helbling, N.L., DeLany, J.P., Cornnell, H.H., Yi, F., Stefanovic-Racic, M., Toledo, F.G.S., Coen, P.M., Carnero, E.A., Goodpaster, B.H., 2022. Weight loss and exercise differentially affect insulin sensitivity, body composition, cardiorespiratory fitness, and muscle strength in older adults with obesity: a randomized controlled trial. J. Gerontol. Ser. A 77, 1088–1097. https://doi.org/10.1093/gerona/glab240.

Bronson, F.H., 1985. Mammalian reproduction: an ecological perspective. Biol. Reprod. 32, 1–26. https://doi.org/10.1095/biolreprod32.1.1.

Brown, J.H., Gillooly, J.F., Allen, A.P., Savage, V.M., West, G.B., 2004. Toward a metabolic theory of ecology. Ecology 85, 1771–1789. https://doi.org/10.1890/03-9000.

Burke, L.M., 2020. Ketogenic low CHO, high fat diet: the future of elite endurance sport? J. Physiol. https://doi.org/10.1113/JP278928. JP278928.

Burke, L.M., Hawley, J.A., 2018. Swifter, higher, stronger: What's on the menu? Science 362, 781–787. https://doi.org/10.1126/science.aau2093.

Burke, L.M., Whitfield, J., Ross, M.L.R., Tee, N., Sharma, A.P., King, A.J., Heikura, I.A., Morabito, A., McKay, A.K.A., 2023. Short severe energy restriction with refueling reduces body mass without altering training-associated performance improvement. Med. Sci. Sports Exerc. https://doi.org/10.1249/MSS.0000000000003169. Publish Ahead of Print.

Calbet, J.A.L., Ponce-González, J.G., De Calle-Herrero, J.L., Perez-Suarez, I., Martin-Rincon, M., Santana, A., Morales-Alamo, D., Holmberg, H.-C., 2017. Exercise preserves lean mass and performance during severe energy deficit: the role of exercise volume and dietary protein content. Front. Physiol. 8 https://doi.org/10.3389/fphys.2017.00483.

Chakravarthy, M.V., Booth, F.W., 2004. Eating, exercise, and "thrifty" genotypes: connecting the dots toward an evolutionary understanding of modern chronic diseases. J. Appl. Physiol. 96, 3–10. https://doi.org/10.1152/japplphysiol.00757.2003.

Chan, J.L., Mantzoros, C.S., 2005. Role of leptin in energy-deprivation states: normal human physiology and clinical implications for hypothalamic amenorrhoea and anorexia nervosa. Lancet 366, 74–85. https://doi.org/10.1016/S0140-6736(05)66830-4.

Civitarese, A.E., Carling, S., Heilbronn, L.K., Hulver, M.H., Ukropcova, B., Deutsch, W.A., Smith, S.R., Ravussin, E., 2007. Calorie restriction increases muscle mitochondrial biogenesis in healthy humans. PLoS Med. 4, e76.

Coen, P.M., Menshikova, E.V., Distefano, G., Zheng, D., Tanner, C.J., Standley, R.A., Helbling, N.L., Dubis, G.S., Ritov, V.B., Xie, H., Desimone, M.E., Smith, S.R., Stefanovic-Racic, M., Toledo, F.G.S., Houmard, J.A., Goodpaster, B.H., 2015. Exercise and weight loss improve muscle mitochondrial respiration, lipid partitioning, and insulin sensitivity after gastric bypass surgery. Diabetes 64, 3737–3750. https://doi.org/10.2337/db15-0809.

Colman, R.J., Anderson, R.M., Johnson, S.C., Kastman, E.K., Kosmatka, K.J., Beasley, T. M., Allison, D.B., Cruzen, C., Simmons, H.A., Kemnitz, J.W., Weindruch, R., 2009. Caloric restriction delays disease onset and mortality in Rhesus monkeys. Science 325, 201–204. https://doi.org/10.1126/science.1173635.

Cordain, L., Gotshall, R., Eaton, S., Eaton, S., 1998. Physical activity, energy expenditure and fitness: an evolutionary perspective. Int. J. Sports Med. 19, 328–335. https://doi.org/10.1055/s-2007-971926.

Cordain, L., Miller, J.B., Eaton, S.B., Mann, N., Holt, S.H., Speth, J.D., 2000. Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. Am. J. Clin. Nutr. 71, 682–692. https://doi.org/10.1093/ajcn/71.3.682.

De Souza, M.J., Nattiv, A., Joy, E., Misra, M., Williams, N.I., Mallinson, R.J., Gibbs, J.C., Olmsted, M., Goolsby, M., Matheson, G., Expert Panel, 2014. 2014 female athlete triad coalition consensus statement on treatment and return to play of the female athlete triad: 1st international conference held in San Francisco, California, may 2012 and 2nd international conference held in Indianapolis, Indiana, may 2013. Br. J. Sports Med. 48, 289. https://doi.org/10.1136/bjsports-2013-093218.

Efeyan, A., Comb, W.C., Sabatini, D.M., 2015. Nutrient-sensing mechanisms and pathways. Nature 517, 302–310. https://doi.org/10.1038/nature14190.

Ellison, P.T. (Ed.), 2001. Reproductive Ecology and Human Evolution, 1st ed. Routledge.

Fogelholm, G.M., Koskinen, R., Laakso, J., Rankinen, T., Ruokonen, I., 1993. Gradual and rapid weight loss: effects on nutrition and performance in male athletes. Med. Sci. Sports Exerc. 25, 371–377.

Foster, G.D., Wadden, T.A., Kendrick, Z.V., Letizia, K.A., Lander, D.P., Conill, A.M., 1995. The energy cost of walking before and after significant weight loss. Med. Sci. Sports Exerc. 27, 888–894.

Fudge, B.W., Westerterp, K.R., Kiplamai, F.K., Onywera, V.O., Boit, M.K., Kayser, B., Pitsiladis, Y.P., 2006. Evidence of negative energy balance using doubly labelled water in elite Kenyan endurance runners prior to competition. Br. J. Nutr. 95, 59. https://doi.org/10.1079/BJN20051608.

Garthe, I., Raastad, T., Refsnes, P.E., Koivisto, A., Sundgot-Borgen, J., 2011a. Effect of two different weight-loss rates on body composition and strength and power-related performance in elite athletes. Int. J. Sport Nutr. Exerc. Metab. 21, 97–104.

Garthe, I., Raastad, T., Sundgot-Borgen, J., 2011b. Long-term effect of weight loss on body composition and performance in elite athletes. Int. J. Sport Nutr. Exerc. Metab. 21, 426–435.

Gejl, K.D., Nybo, L., 2021. Performance effects of periodized carbohydrate restriction in endurance trained athletes – a systematic review and meta-analysis. J. Int. Soc. Sports Nutr. 18, 37. https://doi.org/10.1186/s12970-021-00435-3.

Goldsmith, R., Joanisse, D.R., Gallagher, D., Pavlovich, K., Shamoon, E., Leibel, R.L., Rosenbaum, M., 2010. Effects of experimental weight perturbation on skeletal muscle work efficiency, fuel utilization, and biochemistry in human subjects. Am. J. Physiol.-Regul. Integr. Comp. Physiol. 298, R79–R88. https://doi.org/10.1152/ajpregu.00053.2009.

Gorski, P.P., Turner, D.C., Iraki, J., Morton, J.P., Sharples, A.P., Areta, J.L., 2023. Human skeletal muscle methylome after low carbohydrate energy balanced exercise (preprint). bioRxiv. https://doi.org/10.1101/2023.01.19.524676.

Guthold, R., Stevens, G.A., Riley, L.M., Bull, F.C., 2018. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1·9 million participants. Lancet Glob. Health 6, e1077–e1086. https://doi.org/10.1016/S2214-109X(18)30357-7.

Hammond, K.M., Sale, C., Fraser, W., Tang, J., Shepherd, S.O., Strauss, J.A., Close, G.L., Cocks, M., Louis, J., Pugh, J., Stewart, C., Sharples, A.P., Morton, J.P., 2019. Post-exercise carbohydrate and energy availability induce independent effects on skeletal muscle cell signalling and bone turnover: implications for training adaptation. J. Physiol. 597, 4779–4796. https://doi.org/10.1113/JP278209.

Hansen, A.K., Fischer, C.P., Plomgaard, P., Andersen, J.L., Saltin, B., Pedersen, B.K., 2005. Skeletal muscle adaptation: training twice every second day vs. training once daily. J. Appl. Physiol. 98, 93–99. https://doi.org/10.1152/japplphysiol.00163.2004.

Hardie, D.G., Sakamoto, K., 2006. AMPK: a key sensor of fuel and energy status in skeletal muscle. Physiology 21, 48–60. https://doi.org/10.1152/physiol.00044.2005.

Hawley, J.A., Morton, J.P., 2014. Ramping up the signal: promoting endurance training adaptation in skeletal muscle by nutritional manipulation. Clin. Exp. Pharmacol. Physiol. 41, 608–613.

Hearris, M., Hammond, K., Fell, J., Morton, J., 2018. Regulation of muscle glycogen metabolism during exercise: implications for endurance performance and training adaptations. Nutrients 10, 298. https://doi.org/10.3390/nu10030298.

Hector, A.J., McGlory, C., Damas, F., Mazara, N., Baker, S.K., Phillips, S.M., 2018. Pronounced energy restriction with elevated protein intake results in no change in proteolysis and reductions in skeletal muscle protein synthesis that are mitigated by resistance exercise. FASEB J. 32, 265–275. https://doi.org/10.1096/fj.201700158RR.

Heikura, I.A., Stellingwerff, T., Areta, J.L., 2021. Low energy availability in female athletes: from the lab to the field. Eur. J. Sport Sci. 1–18 https://doi.org/10.1080/17461391.2021.1915391.

Hulmi, J.J., Isola, V., Suonpää, M., Järvinen, N.J., Kokkonen, M., Wennerström, A., Nyman, K., Perola, M., Ahtiainen, J.P., Häkkinen, K., 2017. The effects of intensive weight reduction on body composition and serum hormones in female fitness competitors. Front. Physiol. 7 https://doi.org/10.3389/fphys.2016.00689.

Ihle, R., Loucks, A.B., 2004. Dose-response relationships between energy availability and bone turnover in young exercising women. J. Bone Miner. Res. 19, 1231–1240. https://doi.org/10.1359/JBMR.040410.

Jasienska, G., 2001. Why energy expenditure causes reproductive suppression in women - an evolutionary and bioenergetic perspective. In: Reproductive Ecology and Human Evolution. Routledge, p. 488.

Jasienska, G., 2003. Energy metabolism and the evolution of reproductive suppression in the human female. Acta Biotheor. 51, 1–18. https://doi.org/10.1023/A:1023035321162.

Jenike, M.R., 1996. Activity reduction as an adaptive response to seasonal hunger. Am. J. Hum. Biol. 8, 517–534. https://doi.org/10.1002/(SICI)1520-6300(1996)8:4<517::AID-AJHB12>3.0.CO;2-P.

Keys, A., 1950. The Biology of Human Starvation, volume 2. University of Minnesota Press, Minneapolis, Minn. London.
Kim, B., 2008. Thyroid hormone as a determinant of energy expenditure and the basal metabolic rate. Thyroid 18, 141–144. https://doi.org/10.1089/thy.2007.0266.
Koehler, K., Hoerner, N.R., Gibbs, J.C., Zinner, C., Braun, H., De Souza, M.J., Schaenzer, W., 2016. Low energy availability in exercising men is associated with reduced leptin and insulin but not with changes in other metabolic hormones. J. Sports Sci. 34, 1921–1929. https://doi.org/10.1080/02640414.2016.1142109.
Langan-Evans, C., Germaine, M., Artukovic, M., Oxborough, D.L., Areta, J.L., Close, G.L., Morton, J.P., 2021. The psychological and physiological consequences of low energy availability in a male combat sport athlete. Med. Sci. Sports Exerc. 53, 673–683. https://doi.org/10.1249/MSS.0000000000002519.
Levine, J.A., 2004. Nonexercise activity thermogenesis (NEAT): environment and biology. Am. J. Physiol.-Endocrinol. Metab. 286, E675–E685. https://doi.org/10.1152/ajpendo.00562.2003.
Levine, J.A., Weisell, R., Chevassus, S., Martinez, C.D., Burlingame, B., Coward, W.A., 2001. The work burden of women. Science 294, 812. https://doi.org/10.1126/science.1064627.
Liebenberg, L., 1990. The Art of Tracking: The Origin of Science. D. Philip, Claremont, South Africa.
Liebenberg, L., 2006. Persistence hunting by modern hunter-gatherers. Curr. Anthropol. 47, 1017–1026. https://doi.org/10.1086/508695.
Lieberman, D., 2014. The Story of the Human Body: Evolution, Health, and Disease. Vintage Books, A division of Random House LLC, New York.
Lieberman, D., 2020. Exercised: Why Something we Never Evolved to Do Is Healthy and Rewarding. Pantheon Books, New York.
Lieberman, D.E., Mahaffey, M., Cubesare Quimare, S., Holowka, N.B., Wallace, I.J., Baggish, A.L., 2020. Running in Tarahumara (Rarámuri) culture: persistence hunting, Footracing, dancing, work, and the fallacy of the athletic Savage. Curr. Anthropol. 61, 356–379. https://doi.org/10.1086/708810.
Longland, T.M., Oikawa, S.Y., Mitchell, C.J., Devries, M.C., Phillips, S.M., 2016. Higher compared with lower dietary protein during an energy deficit combined with intense exercise promotes greater lean mass gain and fat mass loss: a randomized trial. Am. J. Clin. Nutr. 103, 738–746. https://doi.org/10.3945/ajcn.115.119339.
Loucks, A.B., 2020. Exercise training in the normal female: effects of low energy availability on reproductive function. In: Hackney, A.C., Constantini, N.W. (Eds.), Endocrinology of Physical Activity and Sport, Contemporary Endocrinology. Springer International Publishing, Cham, pp. 171–191. https://doi.org/10.1007/978-3-030-33376-8_11.
Loucks, A.B., Callister, R., 1993. Induction and prevention of low-T3 syndrome in exercising women. Am. J. Physiol.-Regul. Integr. Comp. Physiol. 264, R924–R930. https://doi.org/10.1152/ajpregu.1993.264.5.R924.
Loucks, A.B., Verdun, M., Heath, E.M., With the Technical Assistance of T. Law, Sr. and J. R. Thuma, 1998. Low energy availability, not stress of exercise, alters LH pulsatility in exercising women. J. Appl. Physiol. 84, 37–46. https://doi.org/10.1152/jappl.1998.84.1.37.
Loucks, A.B., Kiens, B., Wright, H.H., 2011. Energy availability in athletes. J. Sports Sci. 29, S7–S15. https://doi.org/10.1080/02640414.2011.588958.
Louis, J., Tiollier, E., Lamb, A., Bontemps, B., Areta, J., Bernard, T., 2020. Retraining and nutritional strategy of an endurance master athlete following hip arthroplasty: a case study. Front. Sports Act. Living 2, 9. https://doi.org/10.3389/fspor.2020.00009.
Marosi, K., Moehl, K., Navas-Enamorado, I., Mitchell, S.J., Zhang, Y., Lehrmann, E., Aon, M.A., Cortassa, S., Becker, K.G., Mattson, M.P., 2018. Metabolic and molecular framework for the enhancement of endurance by intermittent food deprivation. FASEB J. fj.201701378RR https://doi.org/10.1096/fj.201701378RR.
Mattson, M.P., 2012. Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. Cell Metab. 16, 706–722. https://doi.org/10.1016/j.cmet.2012.08.012.
Melin, A.K., Areta, J.L., Heikura, I.A., Stellingwerff, T., Torstveit, M.K., Hackney, A.C., 2023. Direct and indirect impact of low energy availability on sports performance. Scand. J. Med. Sci. Sports sms.14327. https://doi.org/10.1111/sms.14327.
Menshikova, E.V., Ritov, V.B., Toledo, F.G.S., Ferrell, R.E., Goodpaster, B.H., Kelley, D. E., 2005. Effects of weight loss and physical activity on skeletal muscle mitochondrial function in obesity. Am. J. Physiol.-Endocrinol. Metab. 288, E818–E825. https://doi.org/10.1152/ajpendo.00322.2004.
Menshikova, E.V., Ritov, V.B., Ferrell, R.E., Azuma, K., Goodpaster, B.H., Kelley, D.E., 2007. Characteristics of skeletal muscle mitochondrial biogenesis induced by moderate-intensity exercise and weight loss in obesity. J. Appl. Physiol. 103, 21–27. https://doi.org/10.1152/japplphysiol.01228.2006.
Mountjoy, M., Sundgot-Borgen, J., Burke, L., Carter, S., Constantini, N., Lebrun, C., Meyer, N., Sherman, R., Steffen, K., Budgett, R., Ljungqvist, A., 2014. The IOC consensus statement: beyond the female athlete triad—relative energy deficiency in sport (RED-S). Br. J. Sports Med. 48, 491–497. https://doi.org/10.1136/bjsports-2014-093502.
Mountjoy, M., Sundgot-Borgen, J., Burke, L., Ackerman, K.E., Blauwet, C., Constantini, N., Lebrun, C., Lundy, B., Melin, A., Meyer, N., Sherman, R., Tenforde, A.S., Torstveit, M.K., Budgett, R., 2018. International Olympic committee (IOC) consensus statement on relative energy deficiency in sport (RED-S): 2018 update. Int. J. Sport Nutr. Exerc. Metab. 28, 316–331. https://doi.org/10.1123/ijsnem.2018-0136.
Murphy, C., Koehler, K., 2021. Energy deficiency impairs resistance training gains in lean mass but not strength: a meta-analysis and meta-regression. Scand. J. Med. Sci. Sports sms.14075. https://doi.org/10.1111/sms.14075.
Murphy, C.H., Churchward-Venne, T.A., Mitchell, C.J., Kolar, N.M., Kassis, A., Karagounis, L.G., Burke, L.M., Hawley, J.A., Phillips, S.M., 2015. Hypoenergetic diet-induced reductions in myofibrillar protein synthesis are restored with resistance training and balanced daily protein ingestion in older men. Am. J. Physiol.-Endocrinol. Metab. 308, E734–E743. https://doi.org/10.1152/ajpendo.00550.2014.
Nattiv, A., De Souza, M.J., Koltun, K.J., Misra, M., Kussman, A., Williams, N.I., Barrack, M.T., Kraus, E., Joy, E., Fredericson, M., 2021. The male athlete triad—a consensus statement from the female and male athlete triad coalition part 1: definition and scientific basis. Clin. J. Sport Med. 31, 335–348. https://doi.org/10.1097/JSM.0000000000000946.
Neel, J.V., 1962. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am. J. Hum. Genet. 14, 353–362.
Niven, J.E., Laughlin, S.B., 2008. Energy limitation as a selective pressure on the evolution of sensory systems. J. Exp. Biol. 211, 1792–1804. https://doi.org/10.1242/jeb.017574.
Oxfeldt, M., Phillips, S.M., Andersen, O.E., Johansen, F.T., Bangshaab, M., Risikesan, J., McKendry, J., Melin, A.K., Hansen, M., 2023. Low energy availability reduces myofibrillar and sarcoplasmic muscle protein synthesis in trained females. J. Physiol. JP284967 https://doi.org/10.1113/JP284967.
Papageorgiou, M., Martin, D., Colgan, H., Cooper, S., Greeves, J.P., Tang, J.C.Y., Fraser, W.D., Elliott-Sale, K.J., Sale, C., 2018. Bone metabolic responses to low energy availability achieved by diet or exercise in active eumenorrheic women. Bone 114, 181–188. https://doi.org/10.1016/j.bone.2018.06.016.
Pasiakos, S.M., Vislocky, L.M., Carbone, J.W., Altieri, N., Konopelski, K., Freake, H.C., Anderson, J.M., Ferrando, A.A., Wolfe, R.R., Rodriguez, N.R., 2010. Acute energy deprivation affects skeletal muscle protein synthesis and associated intracellular signaling proteins in physically active adults. J. Nutr. 140, 745–751. https://doi.org/10.3945/jn.109.118372.
Philp, A., Hargreaves, M., Baar, K., 2012. More than a store: regulatory roles for glycogen in skeletal muscle adaptation to exercise. AJP Endocrinol. Metab. 302, E1343–E1351. https://doi.org/10.1152/ajpendo.00004.2012.
Pilegaard, H., Keller, C., Steensberg, A., Wulff Helge, J., Klarlund Pedersen, B., Saltin, B., Neufer, P.D., 2002. Influence of pre-exercise muscle glycogen content on exercise-induced transcriptional regulation of metabolic genes. J. Physiol. 541, 261–271. https://doi.org/10.1113/jphysiol.2002.016832.
Plasqui, G., Rietjens, G., Lambriks, L., Wouters, L., Saris, W.H.M., 2019. Energy expenditure during extreme endurance exercise: the Giro d'Italia. Med. Sci. Sports Exerc. 51, 568–574. https://doi.org/10.1249/MSS.0000000000001814.
Pontzer, H., McGrosky, A., 2022. Balancing growth, reproduction, maintenance, and activity in evolved energy economies. Curr. Biol. 32, R709–R719. https://doi.org/10.1016/j.cub.2022.05.018.
Pontzer, H., Wood, B.M., 2021. Effects of evolution, ecology, and economy on human diet: insights from hunter-gatherers and other small-scale societies. Annu. Rev. Nutr. 41, 363–385. https://doi.org/10.1146/annurev-nutr-111120-105520.
Pontzer, H., Raichlen, D.A., Wood, B.M., Mabulla, A.Z.P., Racette, S.B., Marlowe, F.W., 2012. Hunter-gatherer Energetics and human obesity. PLoS One 7, e40503. https://doi.org/10.1371/journal.pone.0040503.
Pontzer, H., Raichlen, D.A., Wood, B.M., Emery Thompson, M., Racette, S.B., Mabulla, A. Z.P., Marlowe, F.W., 2015. Energy expenditure and activity among HADZA hunter-gatherers: HADZA ENERGETICS AND ACTIVITY. Am. J. Hum. Biol. 27, 628–637. https://doi.org/10.1002/ajhb.22711.
Prentice, A.M., 2005. Starvation in humans: evolutionary background and contemporary implications. Mech. Ageing Dev. 126, 976–981. https://doi.org/10.1016/j.mad.2005.03.018.
Prentice, A.M., 2007. Surviving famine. In: Survival: Survival of the Human Race. Cambridge University Press, Cambridge, pp. 146–177.
Prentice, A.M., Hennig, B.J., Fulford, A.J., 2008. Evolutionary origins of the obesity epidemic: natural selection of thrifty genes or genetic drift following predation release? Int. J. Obes. 32, 1607–1610. https://doi.org/10.1038/ijo.2008.147.
Raefsky, S.M., Mattson, M.P., 2017. Adaptive responses of neuronal mitochondria to bioenergetic challenges: roles in neuroplasticity and disease resistance. Free Radic. Biol. Med. 102, 203–216. https://doi.org/10.1016/j.freeradbiomed.2016.11.045.
Raichlen, D.A., Pontzer, H., Harris, J.A., Mabulla, A.Z.P., Marlowe, F.W., Josh Snodgrass, J., Eick, G., Colette Berbesque, J., Sancilio, A., Wood, B.M., 2017. Physical activity patterns and biomarkers of cardiovascular disease risk in hunter-gatherers. Am. J. Hum. Biol. 29 https://doi.org/10.1002/ajhb.22919.
Real-Hohn, A., Navegantes, C., Ramos, K., Ramos-Filho, D., Cahuê, F., Galina, A., Salerno, V.P., 2018. The synergism of high-intensity intermittent exercise and every-other-day intermittent fasting regimen on energy metabolism adaptations includes hexokinase activity and mitochondrial efficiency. PLoS One 13, e0202784. https://doi.org/10.1371/journal.pone.0202784.
Rosati, A.G., 2017. Foraging cognition: reviving the ecological intelligence hypothesis. Trends Cogn. Sci. 21, 691–702. https://doi.org/10.1016/j.tics.2017.05.011.
Rosenbaum, M., Vandenborne, K., Goldsmith, R., Simoneau, J.-A., Heymsfield, S., Joanisse, D.R., Hirsch, J., Murphy, E., Matthews, D., Segal, K.R., Leibel, R.L., 2003. Effects of experimental weight perturbation on skeletal muscle work efficiency in human subjects. Am. J. Physiol.-Regul. Integr. Comp. Physiol. 285, R183–R192. https://doi.org/10.1152/ajpregu.00474.2002.
Rosenbaum, M., Goldsmith, R.L., Haddad, F., Baldwin, K.M., Smiley, R., Gallagher, D., Leibel, R.L., 2018. Triiodothyronine and leptin repletion in humans similarly reverse weight-loss-induced changes in skeletal muscle. Am. J. Physiol.-Endocrinol. Metab. 315, E771–E779. https://doi.org/10.1152/ajpendo.00116.2018.
Rossow, L.M., Fukuda, D.H., Fahs, C.A., Loenneke, J.P., Stout, J.R., 2013. Natural bodybuilding competition preparation and recovery: a 12-month case study. Int. J. Sports Physiol. Perform. 8, 582–592. https://doi.org/10.1123/ijspp.8.5.582.
Schneider, J.E., Wise, J.D., Benton, N.A., Brozek, J.M., Keen-Rhinehart, E., 2013. When do we eat? Ingestive behavior, survival, and reproductive success. Horm. Behav. 64, 702–728. https://doi.org/10.1016/j.yhbeh.2013.07.005.

Shirley, M.K., Longman, D.P., Elliott-Sale, K.J., Hackney, A.C., Sale, C., Dolan, E., 2022. A life history perspective on athletes with low energy availability. Sports Med. 52, 1223–1234. https://doi.org/10.1007/s40279-022-01643-w.

Sibly, R.M., Grimm, V., Martin, B.T., Johnston, A.S.A., Kułakowska, K., Topping, C.J., Calow, P., Nabe-Nielsen, J., Thorbek, P., DeAngelis, D.L., 2013. Representing the acquisition and use of energy by individuals in agent-based models of animal populations. Methods Ecol. Evol. 4, 151–161. https://doi.org/10.1111/2041-210x.12002.

Sibson, B.E., Tobolsky, V.A., Kistner, T.M., Holowka, N.B., Jemutai, J., Sigei, T.K., Ojiambo, R., Okutoyi, P., Lieberman, D.E., 2021. Trunk muscle endurance, strength and flexibility in rural subsistence farmers and urban industrialized adults in western Kenya. Am. J. Hum. Biol. ajhb.23611 https://doi.org/10.1002/ajhb.23611.

Speakman, J.R., 2007. Genetics of obesity: Five fundamental problems with the famine hypothesis. In: Adipose Tissue and Adipokines in Health and Disease. Humana Press, pp. 221–236.

Speakman, J.R., 2020. Why does caloric restriction increase life and healthspan? The 'clean cupboards' hypothesis. Natl. Sci. Rev. 7, 1153–1156. https://doi.org/10.1093/nsr/nwaa078.

Speth, J.D., 1990. Seasonality, resource stress, and food sharing in so-called "egalitarian" foraging societies. J. Anthropol. Archaeol. 9, 148–188. https://doi.org/10.1016/0278-4165(90)90002-U.

Stearns, S.C., 2000. Life history evolution: successes, limitations, and prospects. Naturwissenschaften 87, 476–486. https://doi.org/10.1007/s001140050763.

Stellingwerff, T., 2018. Case study: body composition periodization in an Olympic-level female middle-distance runner over a 9-year career. Int. J. Sport Nutr. Exerc. Metab. 28, 428–433. https://doi.org/10.1123/ijsnem.2017-0312.

Taylor, H., Burniston, J.G., Nishimura, Y., Foo, W.L., Strauss, J.A., Cocks, M., Shepherd, S., Langan-Evans, C., Morton, J.P., Areta, J.L., 2023. Short-Term Low Energy Availability Down-Regulates Circulating Triiodothyronine and Bone Formation Markers in Males, Whilst Skeletal Muscle Protein Synthesis Is Preserved. Presented at the European Congress of Sport Science, Paris.

Thomas, D.T., Erdman, K.A., Burke, L.M., 2016. American college of sports medicine joint position statement. Nutrition and athletic performance. Med. Sci. Sports Exerc. 48, 543–568. https://doi.org/10.1249/MSS.0000000000000852.

Thurber, C., Dugas, L.R., Ocobock, C., Carlson, B., Speakman, J.R., Pontzer, H., 2019. Extreme events reveal an alimentary limit on sustained maximal human energy expenditure. Sci. Adv. 5, eaaw0341. https://doi.org/10.1126/sciadv.aaw0341.

Toledo, F.G.S., Watkins, S., Kelley, D.E., 2006. Changes induced by physical activity and weight loss in the morphology of intermyofibrillar mitochondria in obese men and women. J. Clin. Endocrinol. Metab. 91, 3224–3227. https://doi.org/10.1210/jc.2006-0002.

Toledo, F.G.S., Menshikova, E.V., Ritov, V.B., Azuma, K., Radikova, Z., DeLany, J., Kelley, D.E., 2007. Effects of physical activity and weight loss on skeletal muscle mitochondria and relationship with glucose control in type 2 diabetes. Diabetes 56, 2142–2147. https://doi.org/10.2337/db07-0141.

Tønnessen, E., Sylta, Ø., Haugen, T.A., Hem, E., Svendsen, I.S., Seiler, S., 2014. The road to gold: training and peaking characteristics in the year prior to a gold medal endurance performance. PLoS One 9, e101796. https://doi.org/10.1371/journal.pone.0101796.

Tornberg, Å.B., Melin, A., Koivula, F.M., Johansson, A., Skouby, S., Faber, J., Sjödin, A., 2017. Reduced neuromuscular performance in Amenorrheic elite endurance athletes. Med. Sci. Sports Exerc. 49, 2478–2485. https://doi.org/10.1249/MSS.0000000000001383.

Torstveit, M.K., 2005. Participation in leanness sports but not training volume is associated with menstrual dysfunction: a national survey of 1276 elite athletes and controls. Br. J. Sports Med. 39, 141–147. https://doi.org/10.1136/bjsm.2003.011338.

Torstveit, M.K., Fahrenholtz, I., Stenqvist, T.B., Sylta, Ø., Melin, A., 2018. Within-day energy deficiency and metabolic perturbation in male endurance athletes. Int. J. Sport Nutr. Exerc. Metab. 28, 419–427. https://doi.org/10.1123/ijsnem.2017-0337.

Van Hooren, B., Cox, M., Rietjens, G., Plasqui, G., 2022. Determination of energy expenditure in professional cyclists using power data: validation against doubly labeled water. Scand. J. Med. Sci. Sports sms.14271. https://doi.org/10.1111/sms.14271.

Vigh-Larsen, J.F., Ørtenblad, N., Spriet, L.L., Overgaard, K., Mohr, M., 2021. Muscle glycogen metabolism and high-intensity exercise performance: a narrative review. Sports Med. 51, 1855–1874. https://doi.org/10.1007/s40279-021-01475-0.

Wade, G.N., Schneider, J.E., 1992. Metabolic fuels and reproduction in female mammals. Neurosci. Biobehav. Rev. 16, 235–272. https://doi.org/10.1016/S0149-7634(05)80183-6.

Wagner, A., 2005. Energy constraints on the evolution of gene expression. Mol. Biol. Evol. 22, 1365–1374. https://doi.org/10.1093/molbev/msi126.

Westerterp, K.R., Saris, W.H., van Es, M., ten Hoor, F., 1986. Use of the doubly labeled water technique in humans during heavy sustained exercise. J. Appl. Physiol. 61, 2162–2167. https://doi.org/10.1152/jappl.1986.61.6.2162.

Wojtaszewski, J.F.P., MacDonald, C., Nielsen, J.N., Hellsten, Y., Hardie, D.G., Kemp, B.E., Kiens, B., Richter, E.A., 2003. Regulation of 5′AMP-activated protein kinase activity and substrate utilization in exercising human skeletal muscle. Am. J. Physiol. Endocrinol. Metab. 284, E813–E822. https://doi.org/10.1152/ajpendo.00436.2002.

Zachwieja, J.J., Ezell, D.M., Cline, A.D., Ricketts, J.C., Vicknair, P.C., Schorle, S.M., Ryan, D.H., 2001. Short-term dietary energy restriction reduces lean body mass but not performance in physically active men and women. Int. J. Sports Med. 22, 310–316. https://doi.org/10.1055/s-2001-13822.