

Energy Constraint as a Novel Mechanism Linking Exercise and Health

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Humans and other species adapt dynamically to changes in daily physical activity, maintaining total energy expenditure within a narrow range. Chronic exercise thus suppresses other physiological activity, including immunity, reproduction, and stress response. This exercise-induced downregulation improves health at moderate levels of physical activity but can be detrimental at extreme workloads.

Introduction

Exercise is essential for a healthy lifestyle. In clinical and observational studies, greater physical activity has been shown to decrease all-cause mortality (4, 9, 36, 42, 73) as well as the risk of cardiovascular disease (74), Type 2 diabetes (5), many cancers (14, 36), mental illness (76), and cognitive decline (66). Conversely, greater time spent inactive and sedentary is associated with increased cardiometabolic disease and shortened lifespan (11, 12, 37, 43).

Mechanisms underlying the health benefits of exercise have come increasingly into focus over the past few decades. For example, exercise is thought to promote cardiovascular health in large part by increasing cardiac output, which leads to myocardial strengthening and induces shear stresses in the vessels (74). This shear stress leads to increased nitric oxide production, which in turn promotes endothelial repair and vascular elasticity (74). Chronic exercise has been shown to blunt the responsiveness of the hypothalamus-pituitary-adrenal (HPA) axis, reducing stress hormone levels (namely cortisol) and improving mental health (76). The cognitive benefits of exercise appear to stem in large part from increased vascular supply to the brain and exercise-induced production of neurotrophins (66). Chronic exercise is also known to play a critical role in regulating energy intake (65), insulin sensitivity (44), and glucose trafficking (57).

It has long been assumed that increased physical activity leads to corresponding increases in total energy expenditure (TEE; kcal/day) and that increased expenditure was another protective benefit conferred by regular exercise. Certainly, in the immediate term, exercise can have profound effects on energy expenditure, with metabolic rate rising by an order of magnitude during strenuous exercise. Furthermore, if a person begins a regular exercise program or other lifestyle change that adds substantially to his or her typical workload,

TEE usually increases during the first weeks or months (see below). Nonetheless, results from doubly labeled water studies over the past two decades, measuring TEE during normal daily life, have come to challenge the view that high levels of habitual physical activity result in correspondingly high TEE. Human populations around the globe have similar TEE regardless of lifestyle (19). For example, Luke and colleagues demonstrated that women in a physically active farming community in Nigeria and a more sedentary urban community in the U.S. had similar TEE and activity energy expenditure (AEE; kcal/day), the portion of TEE not attributable to basal metabolic rate (BMR; kcal/day), or digestion costs (20). My colleagues and I have shown that TEE and AEE among physically active Hadza hunter-gatherers in northern Tanzania and Tsimane forager-farmers in Bolivia are similar to more sedentary populations in the U.S., Europe, and Asia (59, 61, 62, 64). In an analysis of 332 adults from the Modeling the Epidemiological Transition Study (METS), my colleagues and I found that daily physical activity measured by accelerometry was only weakly correlated with size-adjusted TEE, and above median levels of physical activity, we found no effect on TEE (58). Among non-human primates and other species, captive populations have similar TEE to their counterparts in the wild (60, 64).

The lack of correspondence between habitual physical activity and TEE is not limited to observational studies. In controlled exercise intervention studies, human subjects often exhibit a much smaller increase in TEE than expected from the induced exercise workload (28, 34, 38, 84). Similarly, weight loss in exercise interventions is often less than predicted from exercise workload, suggesting a smaller increase in TEE (and smaller energy imbalance) than expected (16, 26, 47, 70, 71, 79). In many controlled laboratory studies in rodents and birds, TEE does not respond to increased physical activity (41, 56, 63).

These observations have led me to propose a Constrained TEE model for energy compensation (63). The Constrained TEE model posits that humans and other animals share a set of evolved mechanisms to maintain TEE within a narrow range, dynamically compensating to changes in physical activity to keep daily expenditure in check (FIGURE 1). This compensation may take several weeks (or even months; see below); acute exercise bouts will still raise energy expenditure in the immediate term (exercise does not become “free” of energy cost), and lifestyle changes that affect daily activity workload may also affect TEE until compensation occurs. Nonetheless, in the long term, physical activity will have little, if any, measureable effect on TEE. Instead, an organism’s TEE will be a product of its evolutionary history and, potentially, its developmental milieu, and be matched to the availability of food energy in its environment (63). TEE may increase or decrease over evolutionary time, but habitual TEE does not correspond to habitual daily physical activity (59, 62–64).

A Constrained TEE model holds important implications for understanding the relationship between activity, metabolism, and health in humans and other species. In this review, I first examine the evidence for energy compensation from exercise intervention studies in humans to assess the effects of study duration and exercise workload. I then develop a model linking energy compensation and Constrained TEE to health.

Energy Compensation and Constrained TEE

Energy compensation, also called “metabolic adaptation” (58, 79), is a commonly observed phenomenon in which an organism responds behaviorally or physiologically to a change in activity or diet such that the impact of the change is blunted. For example, a person newly enrolled in an exercise regime that adds 200 kcal/day to their daily activity workload may be observed to show an increase in TEE of <200 kcal/day, indicating some form of compensation occurred that reduced the expected metabolic impact of the exercise program. Energy compensation to increased physical activity is a common phenomenon in exercise interventions, but the degree of compensation varies among subjects and studies (16, 26, 28, 34, 38, 46, 70, 71, 79, 84), leading to uncertainty in the size and regularity of the effect. Riou and colleagues (70) examined energy compensation data from 61 studies (928 subjects). They found that much of the variation in energy compensation was attributable to study duration and the age and body composition of the subjects (70). For interventions of <26 wk, energy compensation was highly variable and

generally lower than for interventions lasting ≥ 26 wk (FIGURE 2). For long-duration studies, energy compensation approached ~80%. For shorter studies (<26 wk), subjects with greater body fat percentage exhibited less compensation, and the

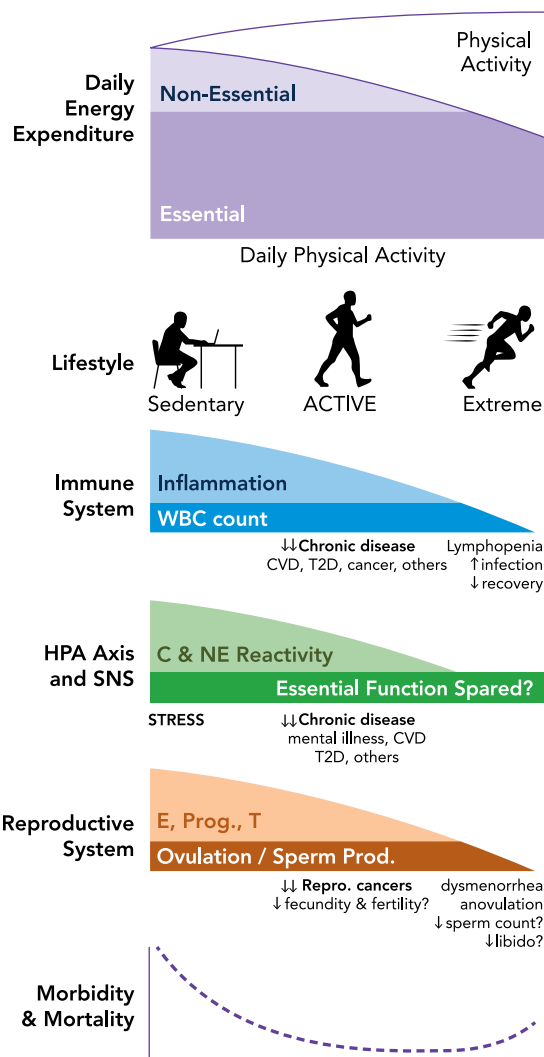


FIGURE 1. Constrained TEE, lifestyle, and health The Constrained TEE model posits that TEE is maintained within a narrow range (63). As daily physical activity increases, other components of daily energy expenditure are reduced to keep TEE in check. Non-essential expenditure is expected to decrease first; essential activity should be spared unless physical activity workload becomes too great. Moving from a sedentary to an active lifestyle leads to downregulation of non-essential expenditures including reduced inflammation (WBC, white blood cell), reduced HPA and SNS reactivity (C, cortisol; NE, norepinephrine), and reduced reproductive hormone levels (E, estrogen; Prog., progesterone; T, testosterone). These reductions lower the risk for a broad range of chronic diseases (CVD, cardiovascular disease; T2D, Type 2 diabetes). At extreme levels of physical activity (e.g., elite athletes), essential function is compromised, negatively affecting health. Consequently, all-cause morbidity and mortality may exhibit a U-shaped curve with physical activity, with increased chronic disease among sedentary people and increased infection and other maladies among the extremely active. ↓, small or moderate effect; ↓ ↓, large effect; ?, uncertain or inconsistent effect.

effect of body fat was strongest in young adults (70). The apparent effect of body fat on the timing or degree of metabolic compensation could reflect a kind of buffering: greater energy reserves (e.g., more fat) might blunt physiological signals of energy stress and thus diminish the speed or degree of metabolic response. Exercise workload (kcal/wk) had no effect on the degree of compensation (FIGURE 2).

The effect of duration on the degree of compensation is consistent with a high degree of metabolic compensation evident in ecological studies of TEE. TEE measured during normal daily life reflects years or even decades of habituation to some customary level of physical activity. It follows that physical activity is a poor predictor of TEE among populations (19, 20, 58–64). The duration effect should also inform future tests of the Constrained TEE model, since compensation to increased physical activity is inconsistent before ~6 mo (FIGURE 2). Notably, metabolic compensation appears to be much faster in rodents and birds, apparent in weeks rather than months (56, 63), suggesting that the rate of compensation might be related to body size or mass-specific metabolic rate. The factors affecting the timing and degree of compensation in humans and other species warrant further investigation.

One prediction of the Constrained TEE model is that energy compensation to exercise is proportional to the increase in physical activity expenditure. Data compiled by Riou and colleagues (70) support this view. In studies >26 wk in duration, energy compensation (kcal/wk) was strongly correlated with intervention exercise energy expenditure (FIGURE 2). This correlation is weaker, but still significant, when shorter studies (<26 wk) are included.

An important caveat in interpreting energy compensation data from exercise-based weight-loss interventions is that TEE was not typically measured in these studies. Changes in energy intake and TEE could both contribute to energy compensation, and their relative effects in these studies are typically unclear. However, in cases where TEE is measured (e.g., Refs. 28, 34, 38, 84), changes in TEE often account for all or most of the observed compensation. More direct measures of TEE are needed in exercise intervention studies.

Because energy intake was also not measured in these studies, the potential effects of caloric restriction on energy compensation are uncertain. Energy compensation and TEE constraint are apparent in subjects that are weight stable and thus in energy balance (58–64), indicating that caloric restriction to the point of energy imbalance and weight loss is not necessary to induce compensation. Nonetheless, some degree of food restriction could affect the timing and degree of compensation. For example, subjects in weight-loss studies might limit their intake even if not directed to do so. Similarly, in highly active, non-industrialized societies in which food availability might be limited, constraints on energy availability could affect metabolic compensation (63). The possible additive and interactive effects of physical activity and calorie restriction on metabolic compensation warrant future attention.

The relative contributions of behavioral and physiological changes to energy compensation in TEE also remain unclear (58, 63, 70). The evidence for behavioral compensation is mixed, with studies in humans suggesting that changes in non-exercise physical activity are insufficient to account for the observed degree of energy compensation (47, 48, 58). Instead, an emerging model of TEE suggests

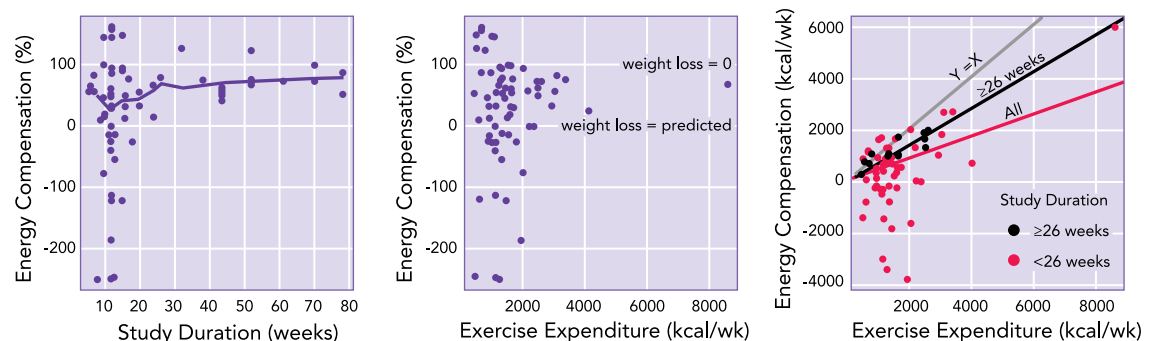


FIGURE 2. Energy compensation in exercise intervention studies

Data taken from a comprehensive review by Riou and colleagues (70), with additional data from more recent studies (26, 46) and used with permission. At 0% energy compensation, weight loss matches that predicted from imposed exercise expenditure; <0% indicates greater than expected weight loss. At 100% energy compensation, there is no weight loss; >100% indicates weight gain. A: for studies ≥26 wk in duration, compensation averaged ~80% (mean: 78%; SD: 23%; $n = 16$ cohorts). B: percent compensation was unrelated to the volume of imposed exercise expenditure. C: the absolute amount of compensation was strongly related to imposed exercise expenditure, particularly for studies ≥26 wk in duration (compensation = 0.70 ± 0.05 exercise expenditure; linear regression with intercept set at 0; adj. $r^2 = 0.95$; $P < 0.001$; $df = 12$; black dashed trend line).

changes in other non-musculoskeletal physiological activity contribute to energy compensation (47, 58, 63). Indeed, a large body of evidence shows that exercise has suppressive effects on physiological activity throughout the body, including the immune system, HPA axis, SNS, and reproductive system. Systemic exercise-induced downregulation has important implications for human ecology and may represent a previously unappreciated mechanism underlying the health effects of exercise.

Constrained TEE and Health

One of Darwin's (18) key insights was that the essential resources for growth, reproduction, and maintenance are limited; all species evolve under conditions of scarcity. For a given species, the allocation and prioritization of resources to various physiological tasks should reflect its evolved life history strategy. Heuristically, we can think of this prioritization as differentiating "non-essential" activities, which can be delayed or reduced without critical effects on evolutionary fitness (i.e., survival and reproduction), and "essential" activities, which cannot.

Such prioritization is most evident when resources are restricted. For example, in a graded caloric-restriction study, Speakman and colleagues showed that male mice reduce the size of the heart, kidneys, liver, and spleen in response to energy shortfall but maintain the size of the brain and testes (52). Maintenance of reproductive capacity (testes) at the expense of somatic maintenance and immune defense (spleen) is consistent with a life-history strategy that prioritizes fertility above longevity. Energy prioritization during periods of energy shortfall in humans is not well studied but likely differs from short-lived species such as mice (53). For example, in a recent study among Shuar children in rural Ecuador, Urlacher and colleagues found strong negative correlations between immune activity and linear growth (81), suggesting humans prioritize immune function over growth rate. During periods of resource abundance, we should expect energy allocation and cellular activity to increase in all parts of the organism, with highly prioritized functions leading the way.

Consider these changes in energy allocation in the context of a Constrained TEE model, in which TEE is limited and increased physical activity expenditure incurs corresponding reductions in other expenditures (FIGURE 1). We should expect most (perhaps all) species to exhibit an evolved energy compensation strategy that reduces non-essential expenditures first, sparing essential functions as physical activity increases (FIGURE 1). Once non-essential reductions are exhausted, further increases in physical activity would lead to

reductions in essential functions, compromising survival and reproduction (FIGURE 1).

Throughout the 2-million-year evolutionary history of our genus, high levels of physical activity would have been the norm, just as they are today in small-scale hunter-gatherer and horticulturalist societies (11–13, 59, 67). Consequently, our physiology evolved under conditions in which non-essential expenditures were usually held in check, and only fully engaged during limited and sporadic periods of energy abundance and low physical activity. By contrast, in modern industrialized societies, humans live in a perpetual state of energy abundance and low physical activity. Non-essential physiological function is chronically high, a condition unseen in our evolutionary past.

Reducing energy expenditure in non-essential functions may therefore be an important mechanism underlying the health benefits of exercise in industrialized populations today. This hypothesis predicts that physical activity should downregulate physiological activity elsewhere, throughout the body. Furthermore, these reductions should be associated with a continuum of health outcomes. At moderate levels of physical activity, the reduced non-essential expenditures should be associated with positive health outcomes. Extremely high levels of physical activity, in which essential function is compromised, should be associated with negative health outcomes.

Immune System

Immune system response to pathogens is essential for survival and involves a wide array of cell types, cytokines, and other factors. Innate (i.e., non-specific) immune response is thought to be particularly energetically costly (45, 88). Regulation of immune activity and reactivity, particularly of the innate response, should be expected to be sensitive to energetic cues. In a state of energy abundance, immune response would be greatest, with copious resources allocated to any insult. Under energy stress, immune response would be muted, with a higher threshold for response and fewer resources (cells, cytokines, and associated metabolic activity) directed toward a perceived challenge. The Constrained TEE model predicts that the energy-related regulation of immune function will be mediated by physical activity (FIGURE 1).

Inflammation, an important and pervasive component of the innate immune response, is known to respond to physical activity (27, 75, 76, 83). During exercise, inflammation increases in a dose-dependent manner with exercise intensity (27, 75, 76, 83). However, post-exercise, the body is in an anti-inflammatory state, and chronic exercise and physical fitness (an indicator of chronic exercise) are associated with lower levels of pro-inflammatory

cytokines, including C-reactive protein, in both cross-sectional and longitudinal (exercise intervention) studies (51, 76). In a large ($n = 3,638$) cross-sectional study of healthy U.S. adults, Abramson and Vaccarino (1) found that men and women reporting four or more bouts of physical activity in the previous month had lower plasma levels of C-reactive protein and fibrinogen, and lower white blood cell counts than those reporting three or fewer bouts of physical exercise.

The mechanisms underlying the anti-inflammatory effects of exercise are increasingly well-understood. Exercising muscle produces the pro-inflammatory cytokine interleukin (IL)-6. The transient (~1 h) elevation in IL-6 levels in turn stimulates the production of anti-inflammatory IL-10 and IL-1 receptor antagonist, IL-1A (27). Exercise also downregulates the number of pro-inflammatory monocytes and their expression of pro-inflammatory Toll-like receptors (TRL1, TRL2, and TRL4) (27). Cortisol and norepinephrine levels increase during exercise (see below), which also has anti-inflammatory effects (27, 76). Finally, exercise may reduce both the amount of visceral fat and macrophage infiltration into adipose tissue, thereby reducing the production of pro-inflammatory cytokines and adipokines (27).

Lower inflammation has been proposed as a mechanism underlying the health benefits of exercise for some time (27, 76, 83). A wide range of chronic diseases have been linked to chronic inflammation, including cardiovascular disease, metabolic disease, some cancers, and cognitive dysfunction (76, 89). Exercise can also help alleviate inflammation and symptoms associated with rheumatic autoimmune diseases, although the evidence for exercise as autoimmune therapy is mixed (7). High levels of physical activity might even contribute to the low prevalence of allergy and asthma in small-scale, non-industrialized populations, which has typically been attributed to childhood pathogen exposure (77, 90).

Immune suppressive effects of chronic exercise are not limited to innate immune response but can also affect acquired immune activity [e.g., T-cell and B-cell numbers and activity (75, 83)]. At high levels of physical activity, the downregulation of immune function can be severe enough to have negative consequences for health, diminishing the body's ability to fight infection (75, 83). Compromised immune function is a well-documented component of "overtraining syndrome" in elite athletes (30, 75, 87). Large workloads of high-intensity exercise are associated with reduced white blood cell count, including reduced neutrophils, monocytes, and lymphocytes (T cells) (6, 51, 75).

The contrast between the clear health benefits of moderate exercise and the increased incidence of

illness with high exercise workloads has been called the "elite athlete paradox" (27), but it follows directly from a Constrained TEE model (FIGURE 1). At moderate exercise workloads, physical activity expenditure leads to decreases in non-essential immune system activity (e.g., inflammation), with reduced reactivity and muted response to pathogens. At higher workloads, physical activity expenditure reduces essential function, compromising the immune response and increasing the likelihood and severity of infection.

HPA and SNS Reactivity

The HPA axis and SNS are the primary mediators of physiological readiness and response to physical and psychological stressors, increasing energy availability by catabolizing energy stores and raising heart rate and blood pressure (32, 76). Acute activation of the SNS and HPA axis (e.g., the fight-or-flight response) is an ancient and essential evolved mechanism to meet short-term challenges and promote survival. However, chronic activation of the SNS and HPA axis is associated with a range of negative health outcomes including poor cardiovascular health, obesity, and mental illness (32, 76).

HPA and SNS activity require energy to catabolize energy stores and maintain increased heart rate and blood pressure. Thus a Constrained TEE model predicts HPA and SNS activity and reactivity to be sensitive to physical activity and energy availability (FIGURE 1). As with inflammation, cortisol (HPA) and norepinephrine (SNS) levels rise in a dose-dependent manner during exercise (76, 82), but chronic exercise and greater physical fitness are associated with reduced reactivity and baseline levels of HPA and SNS activity.

In an early meta-analysis, Crews and Land (17) demonstrated that the stress response was reduced among physically fit subjects. In a recent and comprehensive review, Silverman and Deuster (76) discuss the body of evidence consistently showing that individuals with greater physical fitness (i.e., with greater long-term levels of daily physical activity) exhibit less HPA and SNS reactivity to acute stressors. For example, Rimmele and colleagues (69) reported that trained, physically fit men showed a smaller increase in cortisol and heart rate (a measure of SNS activity) in response to a psychological stressor (Trier Social Stress Test) than untrained, less fit counterparts. Notably, trained and untrained men had similar baseline cortisol levels and heart rates (69). Intense physical training can also blunt the cortisol response to sub-maximal exercise (82). Studies are mixed as to whether chronic exercise also blunts the cortisol awakening response (CAR); the effect may only be evident with large exercise workloads (2). A recent

within-subjects study design in recreational runners found a decrease in cortisol awakening response with greater exercise workload (3).

Blunted SNS and HPA reactivity are associated with better cardiovascular, metabolic, and mental health (76). An exercise intervention study by Nabkasorn and colleagues (55) of $n = 49$ women with mild to moderate depression nicely demonstrates the connections between exercise, energy compensation, neuroendocrine response, and health. Using a randomized crossover design, they assessed the effects of an 8-wk exercise intervention (30 min of group jogging, 5 days/wk) on depression symptoms and neuroendocrine measures. The exercise intervention had no effect on body weight, indicating ~100% energy compensation. Daily cortisol and norepinephrine secretion (mg/day) both decreased by ~30% with exercise, and depression symptoms as assessed by the Centre for Epidemiologic Studies Depression scale were significantly improved (55).

It is unclear whether extreme exercise workloads can compromise essential HPA or SNS function. Reduced cortisol and norepinephrine levels and reactivity are evident in some cases of overtraining syndrome but not all (15). Furthermore, it is unclear whether the HPA or SNS dysregulation apparent in some cases of overtraining is associated with negative health outcomes. It is possible that non-essential HPA and SNS activity responds to changes in physical activity expenditure but that essential HPA and SNS activity is protected (FIGURE 1).

Reproductive Function

Reproduction is an energetically costly activity that is known to be responsive to energy balance cues in humans and other species (25). Reproductive costs include not only those of pregnancy and lactation, but also the costs of maintaining reproductive readiness and/or access to mates. In female primates, including humans, ovarian and menstrual cycles require energy investment for tissue growth and turnover (25). In male primates, the costs of reproductive readiness and mating access include sperm production as well as maintenance of muscle mass and the costs of male-male competition. A Constrained TEE model predicts that energy allocation to reproductive readiness is mediated by physical activity expenditure (FIGURE 1).

Ellison et al. (22–24) showed that human ovarian function and cycle quality occur along a graded continuum (amenorrhea, irregular/anovulatory cycling, regular ovulatory cycling) that is highly sensitive to physical activity and energy balance. Even moderate exercise interventions that do not lead to energy imbalance and weight loss can decrease estrogen levels and reduce ovarian activity

in healthy women (23, 24). In physically active, rural Nepalese farmers, seasonal increases in physical activity workload were associated with diminished ovarian function (22). Women in more rural, less economically developed (and presumably more physically active) populations have lower luteal phase progesterone levels (35). In female athletes, large exercise workloads are associated with irregular cycling and amenorrhea, even when these athletes are in energy balance (40, 49). Indeed, Lagowska and colleagues (40), in a study of 31 weight-stable female athletes with menstrual irregularity, found no effect of 3 mo of dietary energy supplementation on menstrual cyclicity or on ovarian hormone levels (estrogen and progesterone), indicating that ovarian suppression was driven by exercise workload rather than by food availability or energy imbalance.

Men also show an inverse relationship between reproductive investment and physical activity. As with inflammation and HPA activity, testosterone levels rise during exercise, but endurance athletes exhibit lower baseline levels and a blunted exercise-induced rise (29, 31, 72). Morning salivary testosterone is also lower among men in physically active non-industrial populations compared with those in less active, industrialized countries (21). For example, among the Hadza, a hunter-gatherer population in northern Tanzania, men accumulate nearly 2 h of moderate and vigorous physical activity per day (59, 67), several times more than men in the U.S., and have morning salivary testosterone concentrations roughly 50% lower than those of U.S. men (54). In male endurance athletes, exercise-induced depression of basal testosterone is associated with lower libido as well as decreased sperm density, motility, and in vitro penetration, but not all studies find these effects (31).

Given their anabolic and proliferative effects, the downregulation of reproductive hormone levels may contribute to the well-documented reduction in cancer risk with chronic exercise (14, 36). Jasieńska and colleagues (35) showed that women in less economically developed populations have lower luteal progesterone levels and a correspondingly reduced risk of breast cancer. Chronic exercise is associated in a dose-dependent manner with reduced risk for a wide range of cancers, including those involving the reproductive system (14). Regular physical activity reduces the risk of breast cancer by ~20–30%, prostate cancer by ~10%, endometrial cancer by ~23–29%, and ovarian cancer by ~19% (14). Thus the effects of exercise expenditure on reproductive function are consistent with a Constrained TEE model in which moderate levels of physical activity are associated with decreased non-essential activity (e.g., subclinical reductions in estrogen or testosterone) and

improved health outcomes (e.g., reduced cancer risk), whereas high exercise workloads impinge on essential function, leading to clinical suppression of the reproductive system associated with over-training syndrome.

Although moderate physical activity and its effects on the reproductive system may be beneficial for health, it is worth noting that activity-induced downregulation of the reproductive system likely has costs in terms of fecundity and fertility (FIGURE 1). Physical activity is associated with later age at menarche in many studies (8, 50, 80, 85) but not all (e.g., Ref. 78). In adults, reduced ovarian hormone levels and cycle quality may lower the probability of ovulation and conception (24). And for mothers with nursing children, physical activity may delay the resumption of cycling. For example, among the physically active Hadza hunter-gatherer population (a non-contracepting population), nursing mothers appear to resume cycling ~1–2 yr postpartum, based on observed birth spacing of 2–4 yr (10). By comparison, in relatively sedentary industrialized populations, mothers practicing intensive breastfeeding and relying on lactational amenorrhea for contraception typically resume cycling, and occasionally conceive, within 1 yr postpartum (39).

Constrained TEE and the Health Effects of Exercise

Constrained TEE provides a unifying explanatory framework for the widespread suppressive effects of chronic exercise on physiological activity throughout the body and provides a novel mechanism underlying the health benefits of physical activity. Rather than separate phenomena, the downregulation of immune activity, HPA and SNS activity and reactivity, and reproductive function with chronic exercise may reflect an integrated, evolved response, reducing non-essential physiological activity as physical activity expenditure increases within a constrained energy budget. A Constrained TEE model can also explain why chronic exercise has positive health effects at moderate levels but negative effects at high volumes, the so-called “elite athlete paradox” (27). Activity-induced reductions in non-essential physiological function (reduced inflammation, HPA and SNS reactivity, and reproductive hormone levels) improve health, but the large exercise workloads of elite athletes impinge on essential function and increase health risks. Constrained TEE thus provides an explanation for the U-shaped relationship between exercise intensity and all-cause mortality reported in some studies (Refs. 9, 42, 73; FIGURE 1).

The suppressive effects of exercise are often attributed to “energy stress” or inadequate intake (24, 27, 35, 49, 72, 76). But with the superabundance of food energy in modern industrialized populations, it is unclear why increased physical activity should result in energy stress, unless TEE is constrained. Indeed, the suppressive effects of exercise are generally evident in weight-stable subjects who are in energy balance with adequate energy intake, and can even persist when intake is supplemented (40). Thus traditional Additive TEE models, in which TEE increases with physical activity without suppressing other expenditures (63, 64), are inconsistent with the suppressive effects of exercise and the shift from positive to negative health effects at high exercise intensities.

It is notable that the systemic suppressive effects of exercise outlined in this study are similar in many ways to those observed with caloric restriction (53, 68). Although responses to caloric restriction and chronic exercise might involve different mechanisms, both likely reflect evolved physiological strategies to match TEE to energy availability (59). And, like chronic exercise, moderate caloric restriction might be beneficial (68), whereas extreme restriction (e.g., starvation) has obvious negative effects. Work on Constrained TEE and its health effects might benefit by drawing on insights from studies of caloric restriction.

Challenges and Future Directions

Constrained TEE is a promising and powerful model for understanding the relationships between lifestyle, energy expenditure, and health, but more work is needed. One important direction for future research is to explore the signaling mechanisms that link chronic exercise to the physiological regulation of other systems. Exercise produces numerous signaling molecules (86), and the pathways linking exercise to downregulation in some areas (e.g., inflammation) are known. Still, other pathways are unresolved, and it remains unclear whether myokines from exercising muscle, secondary signals of reduced energy availability, or some combination, drive exercise-induced downregulation in other systems. Exercise is also known to affect glucose trafficking and insulin sensitivity (44, 57), which may affect physiological activity in multiple systems. Chronic exercise also affects gene expression and is associated with hypomethylation of some genes, and may even have transgenerational epigenetic effects (33). The question for future study, then, is not whether chronic exercise can signal other systems throughout the body but rather which signals and pathways provide the primary mechanisms by which physical activity mediates other metabolic activity.

Energy compensation is highly variable among individuals and studies, particularly over the short term (FIGURE 2), and the causes of this variability are poorly known. Some studies, and cohorts within studies, show relatively little compensation (34). My colleagues and I have suggested that individuals who are extremely sedentary or have greater body fat percentage at baseline might compensate less, and show a greater increase in TEE with chronic exercise, due to their greater energy reserves (58, 63); with greater energy reserve, the energy stress of adding daily physical activity might be minimal, and the energy compensation response blunted. There is some support for this prediction. Individuals with greater body fat percentage compensate less (at least initially) (70), and exhibit marginally greater size-adjusted TEE (58). Wang and colleagues (84) found the greatest energy compensation to an exercise program in elderly women with the highest daily physical activity at baseline. In contrast, Herrmann and colleagues (34) report no anthropometric differences at baseline between adults whose TEE increased in a dose-dependent manner with exercise vs. those who exhibited energy compensation and TEE constraint. More work is needed to determine which factors, either internal or environmental, affect the energy compensation response to changes in chronic exercise.

Finally, the limits of energy compensation and TEE constraint are unclear. If energy compensation is an evolved response to variation in daily physical activity (63), it is likely that the range of daily activity over which humans can compensate effectively is bounded by the range of activity typically encountered in our evolutionary past. Indeed, the negative health outcomes evident with both extreme sedentism and extreme physical activity probably indicate the boundaries of our species' evolved range of daily physical activity. Maintaining an evolutionary perspective on diet and exercise should help in establishing effective public health strategies (59). Abandoning traditional metabolic models and exploring the dynamic and interdependent nature of energy regulation should advance our understanding of human physiology and ecology and improve our approaches to metabolic health. ■

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References

1. Abramson JL, Vaccarino V. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. *Arch Intern Med* 162: 1286–1292, 2002. doi:10.1001/archinte.162.11.1286.
2. Anderson T, Wideman L. Exercise and the cortisol awakening response: a systematic review. *Sports Med Open* 3: 37, 2017. doi:10.1186/s40798-017-0102-3.
3. Anderson T, Lane AR, Hackney AC. The cortisol awakening response is associated with training load in endurance runners. *Int J Sports Physiol Perform* 27: 1–21, 2018. doi:10.1123/ijspp.2017-0740.
4. Arem H, Moore SC, Patel A, Hartge P, Berrington de Gonzalez A, Viswanathan K, Campbell PT, Freedman M, Weiderpass E, Adami HO, Linet MS, Lee IM, Matthews CE. Leisure time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. *JAMA Intern Med* 175: 959–967, 2015. doi:10.1001/jamainternmed.2015.0533.
5. Aune D, Norat T, Leitzmann M, Tonstad S, Vatten LJ. Physical activity and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis. *Eur J Epidemiol* 30: 529–542, 2015. doi:10.1007/s10654-015-0056-z.
6. Bachero-Mena B, Pareja-Blanco F, González-Badillo JJ. Enhanced strength and sprint levels, and changes in blood parameters during a complete athletics season in 800 m high-level athletes. *Front Physiol* 8: 637, 2017. doi:10.3389/fphys.2017.00637.
7. Benatti FB, Pedersen BK. Exercise as an anti-inflammatory therapy for rheumatic diseases-myokine regulation. *Nat Rev Rheumatol* 11: 86–97, 2015. doi:10.1038/nrrheum.2014.193.
8. Bernstein L, Ross RK, Lobo RA, Hanisch R, Krailo MD, Henderson BE. The effects of moderate physical activity on menstrual cycle patterns in adolescence: implications for breast cancer prevention. *Br J Cancer* 55: 681–685, 1987. doi:10.1038/bjc.1987.139.
9. Blair SN, Cheng Y, Holder JS. Is physical activity or physical fitness more important in defining health benefits? *Med Sci Sports Exerc* 33, Suppl: S379–S399, 2001. doi:10.1097/00005768-200106001-00007.
10. Blurton Jones N. *Demography and Evolutionary Ecology of Hadza Hunter-Gatherers*. Cambridge, UK: Cambridge Univ. Press, 2016. doi:10.1017/CBO9781107707030.
11. Booth FW, Lees SJ. Fundamental questions about genes, inactivity, and chronic diseases. *Physiol Genomics* 28: 146–157, 2007. doi:10.1152/physiolgenomics.00174.2006.
12. Booth FW, Roberts CK, Thyfault JP, Rueggsegger GN, Toedebusch RG. Role of inactivity in chronic diseases: evolutionary insight and pathophysiological mechanisms. *Physiol Rev* 97: 1351–1402, 2017. doi:10.1152/physrev.00019.2016.
13. Bramble DM, Lieberman DE. Endurance running and the evolution of Homo. *Nature* 432: 345–352, 2004. doi:10.1038/nature03052.
14. Brown JC, Winters-Stone K, Lee A, Schmitz KH. Cancer, physical activity, and exercise. *Compr Physiol* 2: 2775–2809, 2012. doi:10.1002/cphy.c120005.
15. Cadegiani FA, Kater CE. Hormonal aspects of overtraining syndrome: a systematic review. *BMC Sports Sci Med Rehabil* 9: 14, 2017. doi:10.1186/s13102-017-0079-8.
16. Church TS, Martin CK, Thompson AM, Earnest CP, Mikus CR, Blair SN. Changes in weight, waist circumference and compensatory responses with different doses of exercise among sedentary, overweight postmenopausal women. *PLoS One* 4: e4515, 2009. doi:10.1371/journal.pone.0004515.
17. Crews DJ, Landers DM. A meta-analytic review of aerobic fitness and reactivity to psychosocial stressors. *Med Sci Sports Exerc* 19, Suppl: S114–S120, 1987. doi:10.1249/00005768-198710001-00004.
18. Darwin C. *On The Origin of Species by Means of Natural Selection, or Preservation of Favoured Races in the Struggle for Life*. London: John Murray, 1859.

19. Dugas LR, Harders R, Merrill S, Ebersole K, Shoham DA, Rush EC, Assah FK, Forrester T, Durazo-Arvizu RA, Luke A. Energy expenditure in adults living in developing compared with industrialized countries: a meta-analysis of doubly labeled water studies. *Am J Clin Nutr* 93: 427–441, 2011. doi:10.3945/ajcn.110.007278.
20. Ebersole KE, Dugas LR, Durazo-Arvizu RA, Adeyemo AA, Tayo BO, Omatode OO, Brieger WR, Schoeller DA, Cooper RS, Luke AH. Energy expenditure and adiposity in Nigerian and African-American women. *Obesity (Silver Spring)* 16: 2148–2154, 2008. doi:10.1038/oby.2008.330.
21. Ellison PT, Bribiescas RG, Bentley GR, Campbell BC, Lipson SF, Panter-Brick C, Hill K. Population variation in age-related decline in male salivary testosterone. *Hum Reprod* 17: 3251–3253, 2002. doi:10.1093/humrep/17.12.3251.
22. Ellison PT, Panter-Brick C, Lipson SF, O'Rourke MT. The ecological context of human ovarian function. *Hum Reprod* 8: 2248–2258, 1993. doi:10.1093/oxfordjournals.humrep.a138015.
23. Ellison PT. Energetics, reproductive ecology, and human evolution. *PaleoAnthropology* 2008: 172–200, 2008.
24. Ellison PT. Human ovarian function and reproductive ecology: new hypotheses. *Am Anthropol* 92: 933–952, 1990. doi:10.1525/aa.1990.92.4.02a00050.
25. Emery Thompson M. Comparative reproductive energetics of human and nonhuman primates. *Annu Rev Anthropol* 42: 287–304, 2013. doi:10.1146/annurev-anthro-092412-155330.
26. Flack KD, Uffholz KE, Johnson LK, Fitzgerald JS, Roemmich JN. Energy compensation in response to aerobic exercise training in overweight adults. *Am J Physiol Regul Integr Comp Physiol*. In press. doi:10.1152/ajpregu.00071.2018.
27. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol* 11: 607–615, 2011. doi:10.1038/nri3041.
28. Goran MI, Poehlman ET. Endurance training does not enhance total energy expenditure in healthy elderly persons. *Am J Physiol Endocrinol Metab* 263: E950–E957, 1992.
29. Hackney AC, Aggon E. Chronic low testosterone levels in endurance trained men: the exercise-hypogonadal male condition. *J Biochem Physiol* 1: 103, 2018.
30. Hackney AC. Clinical management of immunosuppression in athletes associated with exercise training: sports medicine considerations. *Acta Med Iran* 51: 751–756, 2013.
31. Hackney AC. Effects of endurance exercise on the reproductive system of men: the “exercise-hypogonadal male condition”. *J Endocrinol Invest* 31: 932–938, 2008. doi:10.1007/BF03346444.
32. Handa RJ, Weiser MJ. Gonadal steroid hormones and the hypothalamo-pituitary-adrenal axis. *Front Neuroendocrinol* 35: 197–220, 2014. doi:10.1016/j.yfrne.2013.11.001.
33. Hargreaves M. Gene expression and exercise. *Prog Mol Biol Transl Sci* 135: 457–469, 2015. doi:10.1016/bs.pmbts.2015.07.006.
34. Herrmann SD, Willis EA, Honas JJ, Lee J, Washburn RA, Donnelly JE. Energy intake, nonexercise physical activity, and weight loss in responders and nonresponders: The Midwest Exercise Trial 2. *Obesity (Silver Spring)* 23: 1539–1549, 2015. doi:10.1002/oby.21073.
35. Jasieńska G, Thune I. Lifestyle, hormones, and risk of breast cancer. *BMJ* 322: 586–587, 2001. doi:10.1136/bmj.322.7286.586.
36. Jee Y, Kim Y, Jee SH, Ryu M. Exercise and cancer mortality in Korean men and women: a prospective cohort study. *BMC Public Health* 18: 761, 2018. doi:10.1186/s12889-018-5669-1.
37. Katzmarzyk PT, Lee IM. Sedentary behaviour and life expectancy in the USA: a cause-deleted life table analysis. *BMJ Open* 2: e000828, 2012. doi:10.1136/bmjopen-2012-000828.
38. Keytel LR, Lambert MI, Johnson J, Noakes TD, Lambert EV. Free living energy expenditure in postmenopausal women before and after exercise training. *Int J Sport Nutr Exerc Metab* 11: 226–237, 2001. doi:10.1123/ijnsn.11.2.226.
39. Labbok MH, Hight-Laukan V, Peterson AE, Fletcher V, von Hertzen H, Van Look PFA. Multi-center study of the Lactational Amenorrhea Method (LAM): I. Efficacy, duration, and implications for clinical application. *Contraception* 55: 327–336, 1997. doi:10.1016/S0010-7824(97)00040-1.
40. Lagowska K, Kapczuk K, Friebe Z, Bajerska J. Effects of dietary intervention in young female athletes with menstrual disorders. *J Int Soc Sports Nutr* 11: 21, 2014. doi:10.1186/1550-2783-11-21.
41. Lark DS, Kwan JR, McClatchey PM, James MN, James FD, Lighton JRB, Lantier L, Wasserman DH. Reduced nonexercise activity attenuates negative energy balance in mice engaged in voluntary exercise. *Diabetes* 67: 831–840, 2018. doi:10.2337/db17-1293.
42. Lee DC, Pate RR, Lavie CJ, Sui X, Church TS, Blair SN. Leisure-time running reduces all-cause and cardiovascular mortality risk. *J Am Coll Cardiol* 64: 472–481, 2014. doi:10.1016/j.jacc.2014.04.058. A correction for this article was published in *J Am Coll Cardiol* 64: 1537, 2014. doi:10.1016/j.jacc.2014.08.004.
43. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT; Lancet Physical Activity Series Working Group. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* 380: 219–229, 2012. doi:10.1016/S0140-6736(12)61031-9.
44. Mayer-Davis EJ, D'Agostino R Jr, Karter AJ, Haffner SM, Rewers MJ, Saad M, Bergman RN. Intensity and amount of physical activity in relation to insulin sensitivity: the Insulin Resistance Atherosclerosis Study. *JAMA* 279: 669–674, 1998. doi:10.1001/jama.279.9.669.
45. McDade TW, Georgiev AV, Kuzawa CW. Trade-offs between acquired and innate immune defenses in humans. *Evol Med Public Health* 2016: 1–16, 2016. doi:10.1093/emph/eov033.
46. McNeil J, Brenner DR, Courneya KS, Friedenreich CM. Dose-response effects of aerobic exercise on energy compensation in postmenopausal women: combined results from two randomized controlled trials. *Int J Obes* 41: 1196–1202, 2017. doi:10.1038/ijo.2017.87.
47. Melanson EL, Keadle SK, Donnelly JE, Braun B, King NA. Resistance to exercise-induced weight loss: compensatory behavioral adaptations. *Med Sci Sports Exerc* 45: 1600–1609, 2013. doi:10.1249/MSS.0b013e31828ba942.
48. Melanson EL. The effect of exercise on non-exercise physical activity and sedentary behavior in adults. *Obes Rev* 18, Suppl 1: 40–49, 2017. doi:10.1111/obr.12507.
49. Melin A, Tornberg ÅB, Skouby S, Møller SS, Sundgot-Borgen J, Faber J, Sidelmann JJ, Aziz M, Sjödin A. Energy availability and the female athlete triad in elite endurance athletes. *Scand J Med Sci Sports* 25: 610–622, 2015. doi:10.1111/sms.12261.
50. Merzenich H, Boeing H, Wahrendorf J. Dietary fat and sports activity as determinants for age at menarche. *Am J Epidemiol* 138: 217–224, 1993. doi:10.1093/oxfordjournals.aje.a116850.
51. Michishita R, Shono N, Inoue T, Tsuruta T, Node K. Effect of exercise therapy on monocyte and neutrophil counts in overweight women. *Am J Med Sci* 339: 152–156, 2010. doi:10.1097/MAJ.0b013e3181c6a980.
52. Mitchell SE, Tang Z, Kerbois C, Delville C, Konstantopoulos P, Bruel A, Deros D, Green C, Aspden RM, Goodyear SR, Chen L, Han JJ, Wang Y, Promislow DE, Lusseau D, Douglas A, Speakman JR. The effects of graded levels of calorie restriction: I. impact of short term calorie and protein restriction on body composition in the C57BL/6 mouse. *Oncotarget* 6: 15902–15930, 2015. doi:10.18632/oncotarget.4142.
53. Müller MJ, Enderle J, Pourhassan M, Braun W, Eggeling B, Lagerpusch M, Glüer CC, Kehayias JJ, Kiosz D, Bosy-Westphal A. Metabolic adaptation to caloric restriction and subsequent refeeding: the Minnesota Starvation Experiment revisited. *Am J Clin Nutr* 102: 807–819, 2015. doi:10.3945/ajcn.115.109173.
54. Muller MN, Marlowe FW, Bugumba R, Ellison PT. Testosterone and paternal care in East African foragers and pastoralists. *Proc Biol Sci* 276: 347–354, 2009. doi:10.1098/rspb.2008.1028.
55. Nabkasorn C, Miyai N, Sootmongkol A, Junprasert S, Yamamoto H, Arita M, Miyashita K. Effects of physical exercise on depression, neuroendocrine stress hormones and physiological fitness in adolescent females with depressive symptoms. *Eur J Public Health* 16: 179–184, 2006. doi:10.1093/eurpub/cki159.
56. O'Neal TJ, Friend DM, Guo J, Hall KD, Kravitz AV. Increases in physical activity result in diminishing increments in daily energy expenditure in mice. *Curr Biol* 27: 423–430, 2017. doi:10.1016/j.cub.2016.12.009.
57. Padilla J, Olver TD, Thyfault JP, Fadel PJ. Role of habitual physical activity in modulating vascular actions of insulin. *Exp Physiol* 100: 759–771, 2015. doi:10.1113/EP085107.
58. Pontzer H, Durazo-Arvizu R, Dugas LR, Plange-Rhule J, Bovet P, Forrester TE, Lambert EV, Cooper RS, Schoeller DA, Luke A. Constrained total energy expenditure and metabolic adaptation to physical activity in adult humans. *Curr Biol* 26: 410–417, 2016. doi:10.1016/j.cub.2015.12.046.
59. Pontzer H, Raichlen DA, Wood B. Hunter-gatherers as models in public health. *Obesity (Silver Spring)*. In press.
60. Pontzer H, Raichlen DA, Gordon AD, Schroepfer-Walker KK, Hare B, O'Neill MC, Muldoon KM, Dunsworth HM, Wood BM, Isler K, Burkart J, Irwin M, Shumaker RW, Lonsdorf EV, Ross SR. Primate energy expenditure and life history. *Proc Natl Acad Sci USA* 111: 1433–1437, 2014. doi:10.1073/pnas.1316940111.
61. Pontzer H, Raichlen DA, Wood BM, Emery Thompson M, Racette SB, Mabulla AZ, Marlowe FW. Energy expenditure and activity among Hadza hunter-gatherers. *Am J Hum Biol* 27: 628–637, 2015. doi:10.1002/ajhb.22711.
62. Pontzer H, Raichlen DA, Wood BM, Mabulla AZ, Racette SB, Marlowe FW. Hunter-gatherer energetics and human obesity. *PLoS One* 7: e40503, 2012. doi:10.1371/journal.pone.0040503.
63. Pontzer H. Constrained total energy expenditure and the evolutionary biology of energy balance. *Exerc Sport Sci Rev* 43: 110–116, 2015. doi:10.1249/JES.0000000000000048.
64. Pontzer H. The crown jewels: energetics, ecology, and evolution in humans and other primates. *Evol Anthropol* 26: 12–24, 2017. doi:10.1002/evan.21513.
65. Prentice A, Jebb S. Energy intake/physical activity interactions in the homeostasis of body weight regulation. *Nutr Rev* 62: S98–S104, 2004. doi:10.1111/j.1753-4887.2004.tb00095.x.

66. Raichlen DA, Alexander GE. Adaptive capacity: an evolutionary neuroscience model linking exercise, cognition, and brain health. *Trends Neurosci* 40: 408–421, 2017. doi:[10.1016/j.tins.2017.05.001](https://doi.org/10.1016/j.tins.2017.05.001).
67. Raichlen DA, Pontzer H, Harris JA, Mabulla AZ, Marlowe FW, Josh Snodgrass J, Eick G, Colette Berbesque J, Sancio A, Wood BM. Physical activity patterns and biomarkers of cardiovascular disease risk in hunter-gatherers. *Am J Hum Biol* 29: e22919, 2017. doi:[10.1002/ajhb.22919](https://doi.org/10.1002/ajhb.22919).
68. Redman LM, Smith SR, Burton JH, Martin CK, Il'yasova D, Ravussin E. Metabolic Slowing and reduced oxidative damage with sustained caloric restriction support the rate of living and oxidative damage theories of aging. *Cell Metab* 27: 805–815.e4, 2018. doi:[10.1016/j.cmet.2018.02.019](https://doi.org/10.1016/j.cmet.2018.02.019).
69. Rimele U, Zellweger BC, Marti B, Seiler R, Mohiyeddini C, Ehlert U, Heinrichs M. Trained men show lower cortisol, heart rate and psychological responses to psychosocial stress compared with untrained men. *Psychoneuroendocrinology* 32: 627–635, 2007. doi:[10.1016/j.psyneuen.2007.04.005](https://doi.org/10.1016/j.psyneuen.2007.04.005).
70. Riou MÈ, Jomphe-Tremblay S, Lamothe G, Stacey D, Szczotka A, Doucet É. Predictors of energy compensation during exercise interventions: a systematic review. *Nutrients* 7: 3677–3704, 2015. doi:[10.3390/nu7053677](https://doi.org/10.3390/nu7053677).
71. Ross R, Janssen I. Physical activity, total and regional obesity: dose-response considerations. *Med Sci Sports Exerc* 33, Suppl: S521–S527, 2001. doi:[10.1097/00005768-200106001-00023](https://doi.org/10.1097/00005768-200106001-00023).
72. Sato K, Iemitsu M, Katayama K, Ishida K, Kanao Y, Saito M. Responses of sex steroid hormones to different intensities of exercise in endurance athletes. *Exp Physiol* 101: 168–175, 2016. doi:[10.1113/EP085361](https://doi.org/10.1113/EP085361).
73. Schnohr P, O'Keefe JH, Marott JL, Lange P, Jensen GB. Dose of jogging and long-term mortality: the Copenhagen City Heart Study. *J Am Coll Cardiol* 65: 411–419, 2015. doi:[10.1016/j.jacc.2014.11.023](https://doi.org/10.1016/j.jacc.2014.11.023).
74. Schuler G, Adams V, Goto Y. Role of exercise in the prevention of cardiovascular disease: results, mechanisms, and new perspectives. *Eur Heart J* 34: 1790–1799, 2013. doi:[10.1093/eurheartj/ehh111](https://doi.org/10.1093/eurheartj/ehh111).
75. Shaw DM, Merien F, Braakhuis A, Dulson D. T-cells and their cytokine production: The anti-inflammatory and immunosuppressive effects of strenuous exercise. *Cytokine* 104: 136–142, 2018. doi:[10.1016/j.cyto.2017.10.001](https://doi.org/10.1016/j.cyto.2017.10.001).
76. Silverman MN, Deuster PA. Biological mechanisms underlying the role of physical fitness in health and resilience. *Interface Focus* 4: 20140040, 2014. doi:[10.1098/rsfs.2014.0040](https://doi.org/10.1098/rsfs.2014.0040).
77. Strachan DP. Hay fever, hygiene, and household size. *BMJ* 299: 1259–1260, 1989. doi:[10.1136/bmj.299.6710.1259](https://doi.org/10.1136/bmj.299.6710.1259).
78. Ramezani Tehrani F, Mirmiran P, Gholami R, Moslehi N, Azizi F. Factors influencing menarcheal age: results from the cohort of tehran lipid and glucose study. *Int J Endocrinol Metab* 12: e16130, 2014. doi:[10.5812/ijem.16130](https://doi.org/10.5812/ijem.16130).
79. Thomas DM, Bouchard C, Church T, Slentz C, Kraus WE, Redman LM, Martin CK, Silva AM, Vossen M, Westerterp K, Heymsfield SB. Why do individuals not lose more weight from an exercise intervention at a defined dose? An energy balance analysis. *Obes Rev* 13: 835–847, 2012. doi:[10.1111/j.1467-789X.2012.01012.x](https://doi.org/10.1111/j.1467-789X.2012.01012.x).
80. Trentham-Dietz A, Nichols HB, Remington PL, Yanke L, Hampton JM, Newcomb PA, Love RR. Correlates of age at menarche among sixth grade students in Wisconsin. *WMJ* 104: 65–69, 2005.
81. Urlacher SS, Ellison PT, Sugiyama LS, Pontzer H, Eick G, Liebert MA, Cepon-Robins TJ, Gildner TE, Snodgrass JJ. Tradeoffs between immune function and childhood growth among Amazonian forager-horticulturalists. *Proc Natl Acad Sci USA* 115: E3914–E3921, 2018. doi:[10.1073/pnas.1717522115](https://doi.org/10.1073/pnas.1717522115).
82. Uusitalo AL, Huttunen P, Hanin Y, Uusitalo AJ, Rusko HK. Hormonal responses to endurance training and overtraining in female athletes. *Clin J Sport Med* 8: 178–186, 1998. doi:[10.1097/00042752-199807000-00004](https://doi.org/10.1097/00042752-199807000-00004).
83. Walsh NP, Gleeson M, Shephard RJ, Gleeson M, Woods JA, Bishop NC, Fleshner M, Green C, Pedersen BK, Hoffman-Goetz L, Rogers CJ, Northoff H, Abbasi A, Simon P. Position statement. Part one: Immune function and exercise. *Exerc Immunol Rev* 17: 6–63, 2011.
84. Wang X, Bowyer KP, Porter RR, Breneman CB, Custer SS. Energy expenditure responses to exercise training in older women. *Physiol Rep* 5: e13360, 2017. doi:[10.14814/phy2.13360](https://doi.org/10.14814/phy2.13360).
85. Warren MP. The effects of exercise on pubertal progression and reproductive function in girls. *J Clin Endocrinol Metab* 51: 1150–1157, 1980. doi:[10.1210/jcem-51-5-1150](https://doi.org/10.1210/jcem-51-5-1150).
86. Whitham M, Parker BL, Friedrichsen M, Hingst JR, Hjorth M, Hughes WE, Egan CL, Cron L, Watt KI, Kuchel RP, Jayasooriah N, Estevez E, Petzold T, Suter CM, Gregorevic P, Kiens B, Richter EA, James DE, Wojtaszewski JFP, Febbraio MA. Extracellular vesicles provide a means for tissue crosstalk during exercise. *Cell Metab* 27: 237–251.e4, 2018. doi:[10.1016/j.cmet.2017.12.001](https://doi.org/10.1016/j.cmet.2017.12.001).
87. Winsley R, Matos N. Overtraining and elite young athletes. *Med Sport Sci* 56: 97–105, 2011. doi:[10.1159/000320636](https://doi.org/10.1159/000320636).
88. Wolowczuk I, Verwaerde C, Viltart O, Delanoye A, Delacre M, Pot B, Grangette C. Feeding our immune system: impact on metabolism. *Clin Dev Immunol* 2008: 639803, 2008. doi:[10.1155/2008/639803](https://doi.org/10.1155/2008/639803).
89. Wu Y, Antony S, Meitzler JL, Doroshov JH. Molecular mechanisms underlying chronic inflammation-associated cancers. *Cancer Lett* 345: 164–173, 2014. doi:[10.1016/j.canlet.2013.08.014](https://doi.org/10.1016/j.canlet.2013.08.014).
90. Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. *Science* 296: 490–494, 2002. doi:[10.1126/science.296.5567.490](https://doi.org/10.1126/science.296.5567.490).