

Physical activity and metabolic rates in humans

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ABSTRACT

All animals perform physical activity, but humans engage in a special kind of physical activity – exercise, defined as discretionary physical activity for health and fitness. However, the effects of physical activity on whole-organism metabolism and health are unresolved, partly because it is difficult to measure the three major components of metabolism: active energy expenditure (AEE), resting energy expenditure (REE) and dietary induced thermogenesis (DIT), which together equal total energy expenditure (TEE). Three competing models make different predictions about the effects of AEE on REE and TEE. Whereas the traditional ‘additive’ model of energy balance predicts that AEE is independent of REE, the ‘stress’ model hypothesizes that AEE temporarily increases REE partly because of transient effects of excess post-exercise oxygen consumption (EPOC). In contrast, the ‘constrained energy’ model predicts that increases in AEE cause compensatory decreases in REE to maintain a constant TEE. Here, we discuss how different analytical models, measurements, experimental designs and statistical methods affect tests of these three models’ hypotheses. After accounting for spurious correlations, we find that longitudinal and cross-sectional data provide most support for the additive model. However, more and better data are needed to test these hypotheses rigorously. To conclude, we also review the evidence, mostly from humans, that increased levels of physical activity slow aging and reduce vulnerability to disease by diverting energy away from processes that improve reproductive success at the expense of long-term health and by increasing energy allocation to repair, maintenance and capacity-building.

Keywords: Physical activity, exercise, metabolism, excess post-exercise oxygen consumption, lifespan, health

SUMMARY STATEMENT

This Review evaluates different models of the effects of physical activity on metabolism, and how exercise alters organisms' energy allocation to processes that potentially slow aging and reduce disease vulnerability.

Introduction

All adult animals, even sloths, must engage in physical activity to survive and reproduce, but some species are more physically active than others. Humans are evidently one of those species, especially compared to other primates (Pontzer et al., 2016b; Lieberman et al., 2024). In addition, some humans engage in a special kind of activity – exercise, defined as discretionary, voluntary physical activity undertaken for the sake of health or fitness (Lieberman, 2020). Exercise, however, is not a human universal. Only one-quarter of adult Americans meet minimal physical activity recommendations (Elgaddal et al., 2020), and until recently most humans rarely, if ever, exercised because of tradeoffs explained by life-history theory. A basic tenet of this theory is that organisms allocate limited energy to just five different functions: growth, maintenance, energy storage, reproduction and physical activity (Stearns, 1992). Because energy is a limited resource for most organisms, and natural selection favors tradeoffs that increase reproductive success, life-history theory predicts that organisms are selected to avoid unnecessary, discretionary physical activity – that is, exercise – so they can allocate that precious energy to functions that increase reproductive success. Humans are no exception. Although children in all societies play to develop skills and physiological capacities, and adults everywhere sometimes engage in rewarding activities like dancing or sports, almost no one in small-scale non-industrial societies goes for a morning jog to stay fit or lifts weights to build or maintain strength as they age. Instead, foragers and subsistence farmers work hard and otherwise rest, spending as much time per day sitting as average westerners (Raichlen et al., 2020).

Human physical activity, including exercise, is special compared to that of other primates, particularly our closest relatives, the great apes, from whom the human lineage diverged about 7–9 million years ago. The fact that all great apes are comparatively physically inactive is strong evidence that the last common ancestor of apes and humans must also have been relatively sedentary. Orangutans and gorillas travel <2 km per day, and chimpanzees travel ~2–4 km/day, typically about 5000 steps/day (Raichlen and Lieberman, 2022). In contrast, at

some point during human evolution, hominins were selected to considerably increase their levels of daily activity. Average hunter-gatherers in tropical habitats walk 9–15 km/day, taking about 15–20,000 daily steps, and engage in ~2 hours per day of moderate physical activity (50–70% of maximum heart rate) and 20 minutes per day of vigorous activity (>70% maximum heart rate) (Marlowe, 2005; Raichlen et al., 2019; Raichlen and Lieberman, 2022). Subsistence farmers who labor without the assistance of machines typically work even harder (Dufour and Piperata, 2008; Harris et al., 2025).

Although the human lineage underwent selection to be more physically active than other apes, our activity levels are changing radically, with concerning consequences. Over the last few generations, technological innovations have enabled some humans, mostly in industrial environments, to be as inactive as apes. The worldwide average for daily step counts (measured with cell phones) has plunged to slightly less than 5000 (Althoff et al., 2017), and the average adult American engages in <20 minutes per day of moderate-to-vigorous physical activity (Troiano et al., 2008). Although these ape-like levels of activity are apparently not harmful for apes, they are an evolutionary mismatch (see Glossary) for humans. Abundant evidence confirms that insufficient activity in humans fails to slow processes that cause aging, and it increases vulnerability to dozens of common diseases (Pedersen and Saltin, 2015). In terms of lifespan, there is a dose-response relationship between physical activity and mortality, with just 150 minutes per week of moderate-to-vigorous activity associated with a 30% reduction in age-adjusted rates of all-cause mortality; higher doses are associated with greater reductions that eventually level off (Arem et al., 2015; Wasfy and Lee, 2022). In terms of healthspan, moderate levels of physical activity decrease the incidence of a wide range of illnesses, including cardiovascular disease, many cancers, type 2 diabetes, Alzheimer's and depression (for reviews, see Pedersen and Saltin, 2015; Lieberman, 2021). Because of these manifold benefits, exercise helps humans in industrialized societies to increase healthspans and lifespans.

Everyone knows that exercise is beneficial, but how and why does physical activity affect how organisms – humans particularly – allocate metabolic energy towards processes that reduce vulnerability to disease and slow aging? More specifically, is activity healthy because it allocates more or less energy towards metabolic processes that influence how bodies get sick and age? This Review therefore evaluates alternative models of how physical activity (including exercise) influences whole-organism metabolic rates with potential effects on health and aging. (Note this

Review does not evaluate other, -non-metabolic forms compensation to exercise, notably lower levels of non-exercise physical activity and increased energy intake.) Because testing these hypotheses depends largely on how one defines and measures metabolic rates, we first review different measures of metabolism and assess the assumptions and errors they entail. After outlining alternative models for the effects of activity on metabolism and the hypotheses they raise, we then review and critique relevant evidence from longitudinal and cross-sectional studies that use different kinds of data. We conclude by considering briefly how different models of the effects of physical activity on metabolism inform our understanding of the health benefits of exercise, and whether these benefits are amplified in humans compared to other primates.

Measuring metabolism

Metabolic energy can be quantified at many different levels, from specific reactions within organelles and cells to total energy use by a whole organism. This Review focuses solely on the major organism-level categories of energy use summarized by the widely used energy balance model:

$$TEE = REE + AEE + DIT$$

in which total energy expenditure (TEE) is the sum of the organism's energy use over 24 hours; resting energy expenditure (REE) is the energy the body expends daily at rest in a non-prandial state; active energy expenditure (AEE) is the cost per day of all physical activities, including locomotion, chewing and gesticulating; and diet-induced thermogenesis (DIT, also termed the thermic effect of food) is the post-prandial increase in metabolism that includes the cost of digestion. Please refer to the Glossary for a list of terms and their synonyms.

To use this model to evaluate energy allocation, we first consider how each of these variables involves assumptions and measurement errors, how and when these variables are estimated rather than measured, and how these variables differ from other closely related metabolic variables.

Resting energy expenditure

How to define and measure resting metabolism can be confusing. Many studies use basal metabolic rate (BMR; see Glossary), basal energy expenditure or sleeping metabolic rate – all of which measure an individual's metabolism in a fasted, thermoneutral state following at least 24 hours of inactivity. However, it is hard to measure metabolism during sleep outside very controlled lab settings, and it is unnatural for organisms to be physically inactive for 24 or more hours. Therefore, many researchers measure REE, the sum of all energy an organism expends at rest in a non-prandial state over 24 hours (Heymsfield et al., 2021). REE thus potentially includes the cost of thermogenesis as well as short-term residual effects on metabolic rate from physical activity (see below). REE can also include the metabolic costs of growth (in non-adult organisms), immune function and reproduction. Although REE is best measured using respirometry, some studies estimate REE with reasonable accuracy using anthropometric variables such as height, weight, age and sex (Heymsfield, 2019). Note that REE, like body temperature, fluctuates throughout the day with a circadian variation of ~55 kcal (Zitting et al., 2008).

Total energy expenditure

TEE (sometimes termed daily energy expenditure, DEE), is also difficult to measure accurately, independently and without assumptions. Until recently, TEE could be measured only under highly restricted conditions in metabolic chambers, but the doubly labeled water (DLW) method now enables TEE measurements in free-ranging organisms. Despite sometimes being labeled as the 'gold standard' method for quantifying TEE, the DLW method measures only metabolizable energy (the energy remaining after correcting for digestive, skin and urinary losses); it also measures aerobic metabolism indirectly by quantifying CO₂ loss, which then permits estimation of O₂ consumption either by measuring or estimating an organism's respiratory quotient (RQ), the ratio of CO₂ production to O₂ consumption. RQs, however, vary over time and between individuals depending on many factors, including diet and circadian rhythms (Zitting et al. 2018). A 5% error in estimating RQ (e.g. 0.86 versus 0.90) will lead to a 5% error in TEE.

Active energy expenditure

How much energy organisms spend being physically active over the course of 24 hours is difficult to measure without error and assumptions. The most accurate short-term method of measuring AEE is respirometry, but this is impossible to achieve in free-living organisms over long time periods, and also requires subtracting estimates or measures of REE. Sensor-based methods of measuring AEE, such as accelerometry and heart rate monitors, have the advantage of independently quantifying movement or effort, but do not measure energy use directly and thus require regression models to estimate energy costs, potentially introducing error. Further, no sensor measures all types of physical activity. For this reason, many studies calculate AEE by subtracting REE and DIT from TEE, but this potentially leads to problems of non-independence of AEE from REE or TEE (see below).

Diet-induced thermogenesis

Because it takes hours to digest food, measuring DIT requires a long period of laboratory-based respirometry under controlled conditions. Consequently, DIT is almost always assumed to be 10% of TEE in humans and many mammals, thus introducing unknown error. DIT is highly variable across species (Secor, 2009), and in humans typically ranges from 5–15% of TEE depending on the individual, the nutrients being digested and other perhaps factors such as the microbiome (Westerterp, 2004).

Covariates of metabolism

A final methodological concern when evaluating metabolic measurements is to correct for body size and other variables that affect metabolic rates independently of physical activity when comparing individuals, populations and species. Because bigger bodies have more cells that engage in more chemical reactions, and because adipose tissue is relatively inert, fat-free body mass (FFM) explains $\geq 70\%$ of the variation in REE or BMR (Heymsfield et al., 2019). Nearly a century of research has shown that BMR, REE and, to a lesser extent, TEE scale with body mass, M , according to the power law aM^b , where a is a mass coefficient and b is a scaling exponent. Although b is ~ 0.75 across vertebrates, both a and b need to be determined empirically depending on the individuals or species being analyzed (Glazier, 2022). Because of this nonlinear scaling, simple ratios of TEE or REE to FFM (e.g. REE/kg) are an incorrect way to

compare metabolic rates among different-sized organisms. In addition, although REE scales primarily with FFM, AEE is a function of whole-body inertia and thus should scale with M . For this reason, TEE as the sum of REE and AEE should scale with a combination of M and FFM (Yegian et al., 2024).

Body mass effects introduce an additional potential complication for longitudinal studies on the effects of changing activity levels because exercise interventions can cause significant changes in FFM or percent body fat. In one extreme example (discussed further below), Thurber et al. (2019) measured metabolic rates in six individuals who ran approximately a marathon a day across the USA. Over the course of 20 weeks, the runners' BMR increased on average 4%, while FFM and percent body fat decreased 2% and 11%, respectively. Another complication is that FFM refers to everything present in the human body except fat, and thus does not account for between-individual differences in FFM composition (for example, the amount of muscle) related to sex, age, activity level and other factors that could affect REE.

Another potentially significant factor that affects REE is environmental temperature. REE is higher in animals from colder environments largely because of the cost of maintaining thermal homeostasis (Speakman and Król, 2010). On average, mammals living at $-10\text{ }^{\circ}\text{C}$ have ~40% higher REEs than similar-sized mammals in $25\text{ }^{\circ}\text{C}$ habitats (Clark et al., 2010). REE can also be affected by additional factors such as energy spent on growth, the cost of immune activity to fight an infection, and reproductive processes such as gestation and lactation. Because of the challenges of measuring these costs, studies of the effects of physical activity on metabolism often exclude individuals who are immature, reproducing or sick.

A final, rarely considered covariate of metabolism is mitochondrial efficiency. It is well established that physical activity upregulates genes that promote, repair and replace mitochondria and increase their volume, increasing the efficiency of the electron transport chain in mitochondria. Trained individuals can thus produce significantly more ATP for a given amount of O_2 (Salin et al., 2019; Koch et al., 2021). A potential effect of increased mitochondrial efficiency is that studies may often underestimate how much energy fitter individuals allocate to AEE, including studies that analyze increased activity levels over long periods of time.

Models of whole-organism metabolism

Notwithstanding the errors and assumptions that underlie measures of metabolic rates, the three general models illustrated in Figure 1 make significantly contrasting predictions regarding the effects of AEE on TEE and REE, as discussed below.

Additive model

The additive or null hypothesis model (Fig. 1A), sometimes termed the ‘factorial’ model, considers an organism’s TEE simply as the sum of AEE, REE and DIT. If this model is correct, then organisms neither trade off how much energy they allocate to these different metabolic categories, nor does physical activity influence energy allocation to REE. For example, if an organism increases its AEE by 200 kcals per day, its TEE increases by 200 kcals without any change in REE (after adjusting for changes in body mass and composition). For decades, most studies of whole-organism metabolism have employed this model either explicitly or implicitly.

Stress model

The stress model (Fig. 1B) considers AEE and REE (adjusted for body mass and composition) to be positively correlated over the short term through the effects of EPOC (excess post-exercise oxygen consumption; see Glossary), a transient increase in REE induced by physical activity. Originally termed ‘oxygen debt’ (and colloquially referred to as ‘afterburn’), EPOC can be divided into the two phases shown in Figure 2. The rapid phase, EPOC-R, which declines exponentially (rarely lasting 30 minutes) following a bout of activity, is thought to primarily reflect the cost of resynthesizing used energy stores such as ATP, creatine phosphate and glycogen, plus other immediate homeostatic functions, such as clearing lactate (Gaesser and Brooks, 1985; Børsheim and Bahr, 2003; LaForgia et al., 2006). In contrast, the prolonged phase (EPOC-P) typically lasts <3–4 hours but can potentially last for 24–48 hours, depending on the intensity, duration and type of activity. EPOC-P tends to increase linearly with duration and exponentially with intensity of aerobic activities; resistance activities tend to cause higher values of EPOC-P. Although incompletely understood, EPOC-P presumably reflects the cost of repairing and maintaining muscle tissue plus other functions necessary to restore damage caused by physical activity (homeostasis) or increase capacity (allostasis). Among the many responses to activity-induced stress that potentially contribute to EPOC are muscle hypertrophy, angiogenesis,

mitochondrial biogenesis, erythropoiesis, immune upregulation (e.g. production of natural killer and CD8⁺ cells), antioxidant synthesis and autophagy (for review see Lieberman et al., 2021). Although EPOC is unlikely to have a meaningful effect on weight loss (LaForgia et al., 2006), it potentially adds up to significant amounts of energy over months and years. Using experimental data from Gore and Withers (1990), Lieberman et al. (2021) estimated that a 70 kg individual who engages in 20 minutes per day of vigorous and 115 minutes of moderate activity (typical of hunter-gatherers) will expend 282,800 more kcals on EPOC over 20 years than an average sedentary individual who engages in 20 minutes per day of moderate activity.

Because it is a time-limited phenomenon, EPOC causes only short-term increases in REE but, by definition, not BMR. Because most animals, humans included, evolved to engage in regular, substantial daily amounts of physical activity, measurements of REE among regularly active individuals (as indicated in Figure 1B) potentially sometimes include some component of EPOC, depending on the intensity, duration and type of activities undertaken prior to measurement. Most experiments find that EPOC elevates REE for <3–4 hours (Børsheim and Bahr, 2003), but one study that asked ten healthy male subjects to walk briskly for 3 hours found that average REE was increased by 4.7% after 18 hours (Bielinski et al. 1985). In addition, and as noted above, increased levels of activity over time can increase FFM and decrease percent body fat, also leading to increased mass-specific REEs. Therefore, to test the hypothesis that AEE can alter REE by influencing energy allocation to repair, maintenance and capacity-building processes, it is necessary to correct not just for body mass but also FFM (for review see Speakman and Selman, 2003).

Constrained energy model

The constrained energy model proposes that an organism's TEE relative to body mass (usually FFM) is approximately invariant (Pontzer et al., 2016a). If so, then an individual in energy balance who allocates 500 additional kcals to AEE will experience either no change in their TEE or an increase of <500 kcals, with the difference offset by reductions in mass-adjusted REE. This model, illustrated in Fig. 1C, can be expressed as:

$$\text{TEE} = \text{DIT} + \text{REE} + \text{AEE} - c \cdot \text{AEE}$$

in which *c* is the percentage of metabolic compensation caused by AEE that lowers REE. This model was inspired by DLW studies that reported that TEE relative to FFM is not significantly

different between highly physically active hunter-gatherers from Tanzania and more-sedentary Americans (Pontzer et al., 2012), as well as individuals from industrial and non-industrial environments whose activity levels are substantially different (Dugas et al., 2011; Pontzer et al., 2018). Similar inferences have been made from claims that size-adjusted TEEs of wild animals are similar to those of zoo animals that are presumably less active (see Halsey, 2021). If DIT is 10% of TEE regardless of activity levels, then it is logical to infer that maintaining a constant TEE relative to FFM under conditions of higher AEE requires some degree of metabolic compensation involving decreased energy allocation to processes measured by REE that are unrelated to increased levels of activity, such as growth, reproduction or homeostatic repair and maintenance of organs and tissues.

Note that many studies underlying the hypothesis that mass-specific TEE is constrained regardless of AEE are cross-sectional comparisons of human populations that primarily measure TEE without also measuring both AEE and REE. The strongest support for the hypothesis derives from regressions of samples that find a significantly negative slope between AEE and REE (Careau et al., 2021). Although that is a cross-sectional analysis, as Fig. 1C highlights, the constrained energy model is fundamentally a longitudinal prediction about how individuals' metabolisms change over time in response to changes in AEE. In particular, the constrained energy model predicts that over some unspecified long-term period, individuals in energy balance who spend more energy on AEE (exercise and non-exercise activity) will have no change in mass-specific TEE but their mass-specific REE will decrease (Pontzer, 2025). By the same logic, if an individual's AEE decreases without any change in their body mass or composition, their REE should increase.

The constrained energy model raises several questions. First, given the well-documented but short-term phenomenon of EPOC, over what time scale does the metabolic compensation proposed to decrease mass-specific REE occur? According to Pontzer (2025), it takes days, weeks or possibly longer for the metabolic compensation hypothesized by the constrained energy model to increase or decrease REE in response to changes in AEE, but how long and by what mechanisms this proposed time lag occurs are unspecified and untested. In addition, because EPOC can elevate REE, whereas BMR needs to be measured in individuals who have not been physically active for at least 24 hours, should one test the constrained energy model using measurements of REE instead of BMR? Additionally, what physiological processes contribute to

the proposed decreased levels of REE in response to increased levels of AEE? If additional energy spent on AEE downregulates instead of upregulating energy allocation to tissues, possibilities include decreased production of anabolic hormones such as steroids, decreased activation of the sympathetic nervous system and reduced energy allocation to the immune system (Pontzer, 2018).

An important caveat is that the constrained energy model is not the same as the well-studied phenomenon of energy compensation. Sometimes when humans spend more energy on exercise, they compensate by spending less energy on other physical activities such as non-exercise activity thermogenesis, NEAT; see Glossary), or by increasing food intake (Careau, 2017; Halsey and Perna 2019). This Review does not evaluate these non-metabolic forms of compensation, but they can confound efforts to test the constrained energy hypothesis in the absence of high-quality data on total active energy expenditure and energy intake (Halsey, 2021).

The three models outlined above make useful, contrasting, testable predictions. These predictions and the data used to test them, however, are not the same for longitudinal and cross-sectional studies, which we next evaluate separately.

Testing the models I: Longitudinal studies

As Figure 1 illustrates, models of the effects of physical activity on metabolism are intrinsically longitudinal predictions in which an individual's AEE, REE and TEE are plotted relative to time on the x-axis. Time, however, is not the independent variable upon which these variables are dependent, because time is not hypothesized to change their values. Even so, the additive model predicts that as an individual's AEE changes over time, there will be no corresponding change in mass-adjusted REE. The stress model predicts that increases in an individual's AEE will be associated with short-term increases in REE, hence also TEE. The constrained energy model predicts that, over time, increases in AEE should decrease mass-adjusted REE in order to maintain a constant TEE. Note also that the additive and stress models predict how changes in AEE influence REE and thus indirectly affect TEE. In contrast, the constrained energy model either implies or posits that TEE itself is constrained.

Longitudinal experiments to test these models have several advantages. One is that they can be tested using within-subjects, repeated-measures experimental designs in which each participant serves as their own control, thus increasing statistical power by avoiding the

confounding effects of covariates that vary among individuals (e.g. body mass, percent body fat, age, fitness and sex). Drawbacks of longitudinal studies, however, are that they often do not include diverse samples of participants, and they are potentially biased by confounding effects caused by the order of treatments or time between treatments (i.e. carry-over effects; see Glossary). It has also been proposed that it takes days, weeks or possibly longer for the metabolic compensation hypothesized by the constrained energy model to increase or decrease REE in response to changes in AEE (Pontzer, 2025). Yet if AEE primarily influences REE by causing changes in FFM and percent body fat, then it is reasonable to hypothesize that controlling for FFM and percent body fat should reveal changes in REE over the same timescale. In addition, it has been hypothesized that increases in AEE lower REE by damping activity of the sympathetic nervous system, reducing levels of reproductive hormones and depressing immune function (Pontzer, 2018). However, these hypothesized effects on REE should be relatively rapid, on the order of hours or possibly days. Although these hypotheses require testing, a conservative approach favors longitudinal studies over long time periods, with washout periods between treatments to avoid carry-over effects, and which control for body size and composition.

Despite questions about timescale, numerous studies have measured the short-term effects of AEE on EPOC (for reviews, see Børsheim and Bahr, 2003; Gore and Withers, 1990; LaForgia et al., 2006). Because EPOC is the total additional oxygen consumed over several hours following physical activity, it is not a measure of long-term REE. Mackenzie-Shalders et al. (2020) conducted a meta-analysis of 22 randomized controlled studies (totaling 822 participants) that evaluated the effects of aerobic and resistance exercise interventions on longer-term REE. Contrary to predictions of the constrained energy model, of the 18 studies that could be analyzed quantitatively, aerobic exercise had only a small and not significantly positive effect on REE (81.7 kcal/day, $p=0.25$), and resistance exercise significantly increased REE by 96.2 kcal/day ($p<0.0002$).

To our knowledge, only two long-term longitudinal studies of the effects of AEE on REE have been used to support the constrained energy model in humans. The most cited of these studies collected metabolic data on 32 normal-weight adults (16 men, 16 women) who trained for a half marathon over 44 weeks, leading to average decreases in fat mass of 3.8 kg and 2.0 kg in men and women, respectively, but respective increases in FFM of 1.6 kg and 1.2 kg, and an average decline in BMR of ~112 kcals/day (Westerterp et al., 1992). A reanalysis of these data

found a negative correlation between TEE and REE within individuals (but not across individuals), but this study did not measure AEE versus REE, and the data suggest that much of the observed energy compensation is accounted for by a reduction in non-exercise physical activity (Careau, 2017; Halsey and Perna, 2019). Another possibility is that the BMR decreases reported in this experiment resulted from negative energy balance, which lowers resting metabolism even after accounting for changes in body mass and body composition (Martin et al., 2007; Schwartz and Doucet, 2010).

The other longitudinal study cited as support for the constrained energy model followed six individuals who ran across the United States, completing approximately a marathon every day, six days a week (Thurber et al., 2019). As expected, these runners had high TEEs of nearly 3000 kcals/day and lost ~4 kg over the first 18 weeks of the race. However, although the runners' average TEE declined by ~600 kcals/day during the race, their average BMR increased slightly, thus supporting the additive or stress models. Unless the runners (all experienced ultramarathoners) significantly increased their running economy during the race, it is therefore likely that the marathoners' lower TEEs resulted from reductions in NEAT, which was not measured (Halsey, 2021).

In short, most longitudinal evidence from humans indicates that individuals who increase their AEE levels either maintain or increase REE levels, thus supporting the additive model more than the stress model, and not the constrained energy model. However, we need high-quality, long-term longitudinal studies that more comprehensively and directly test the effects of AEE on REE and TEE by measuring both exercise and non-exercise contributions to AEE, as well as measuring REE and TEE, and accounting for changes in body composition as well as factors such as mitochondrial efficiency.

Testing the models II: Cross-sectional studies

Despite the advantages of longitudinal studies, more data are available to test the predictions of the additive, stress and constrained energy models using cross-sectional comparisons of individuals, groups or populations with different levels of AEE. In such studies, AEE or some other measure of physical activity is the appropriate independent variable, with REE and TEE as dependent variables. As Figure 3 illustrates, the additive model predicts that – all things being equal – AEE is independent of REE but not TEE; the stress model predicts that AEE is positively

associated with REE, hence also TEE; and the constrained energy model predicts that AEE is negatively associated with REE and independent of TEE.

Cross-sectional studies have many practical advantages: they potentially sample more variance in AEE, and existing large data sets permit them to be accomplished rapidly. Their major drawback is the challenge of controlling for covariates that affect REE and TEE independently or differently from their effects on AEE. Some of these covariates are well known, especially those related to body size, body composition and environmental temperature (Heymsfield et al., 2019; Glazier, 2022). Other potential covariates are less well studied, including age, sex and level of fitness. In addition, some potential covariates are unknown or untested. For example, just as genetic variation can influence how an individual's maximum oxygen consumption adapts to similar levels of physical activity (Bouchard et al., 2011), genetic differences between individuals or populations potentially affect how REE responds to changes in AEE. Another untested source of variation is the microbiome, which has been shown to change in response to physical activity in ways that affect metabolism (Scheiman et al., 2020).

A final important concern with cross-sectional studies is how they test the different predictions of the three models. Potential misinterpretations can arise because of faulty model assumptions, different methods of estimating metabolic rates, sources of error, and the metrics used to quantify metabolic rates. We therefore consider separately four general types of cross-sectional studies that have tested the effects of physical activity on REE or TEE.

The physical activity level index versus REE or TEE

An index called the 'physical activity level' (PAL), defined as TEE/BMR (and sometimes calculated as TEE/REE) was devised in the aftermath of World War II, and has since been used to estimate mass-specific levels of physical activity. By convention, values of PAL below ~ 1.6 indicate light levels of activity, values of $\sim 1.6-1.8$ are considered moderate levels, and values >1.8 are generally considered heavy levels of activity (James and Schofield, 1990). Because PAL indexes a person's TEE relative to their BMR, and BMR scales to body mass, PAL indirectly estimates a person's mass-specific level of activity. PALs are also simple to calculate. For these reasons, numerous studies have used PALs to assess inferences about the effects of activity on TEE and REE. As examples, Luke et al. (2009) reported similar PALs in rural Nigerian and urban African American women despite strikingly different environments and occupations, and

Dugas et al. (2011) found no significant association between PALs and an index of life-expectancy, per-capita income and education levels among individuals from high- and low-income countries after controlling for age and weight.

Although PALs are widely used, they are problematic measures of physical activity. Most obviously, because PALs are the ratio of TEE to BMR they do not measure activity directly. Thus, two individuals of the same size with similar levels of activity but different resting metabolic rates will falsely appear to have different levels of physical activity. In addition, because BMR and TEE scale differently to body mass, PALs do not scale isometrically with increased AEE, complicating their interpretation. For example, a PAL of 1.8 is 12.5% higher than a PAL of 1.6, but reflects a 25% increase in AEE for two individuals with the same TEE of 2600 kcal. Furthermore, few studies accurately measure BMR, so in practice most PALs are TEE/REE (rather than TEE/BMR), and thus can potentially include some component of EPOC. Harris et al. (2025) found that PALs inaccurately measured different levels of physical activity among Rwandan farmers and office workers compared to other metrics including metabolic quotients (described below).

PALs pose yet other problems for testing the additive, stress and constrained energy models described above. Although PALs are often equated with AEE and thus sometimes used as the independent variable in a regression against BMR, REE or TEE, this is a statistical error. Because PALs are calculated as TEE/BMR or TEE/REE, they are mathematically coupled to the dependent variable in these regressions, thus leading to potentially spurious correlations (Gonzalez et al., 2023). Measurement error of PALs can also cause regression dilution (see Glossary).

Body mass versus TEE

The additive and stress models predict that more physically active individuals will have similar or transiently higher REEs, respectively, for a given body mass than more sedentary individuals. In contrast, the constrained energy model hypothesizes that more physically active individuals will have higher AEEs but lower REEs, and hence similar TEEs for a given body mass than more sedentary individuals. The latter predictions were used to support the constrained energy model in a cross-sectional comparison of TEE measurements of hunter-gatherers from Tanzania, subsistence farmers from Bolivia, and industrialized westerners from Europe and

North America (Pontzer et al., 2012). In this analysis, the hunter-gatherers had substantially higher estimated PALs yet similar TEE levels relative to FFM as the westerners; at the population level, hunter-gatherers also had similar TEEs relative to total body mass as westerners. Although the study measured only TEE, the more-active hunter-gatherers were inferred to have lower REEs for a given body mass because $TEE = AEE + REE + DIT$ (Pontzer et al., 2016a). This analysis, however, evaluated the effects of physical activity on metabolism only indirectly, because neither AEE nor REE were measured. In addition, although REE is primarily a function of FFM, TEE (the sum of REE and AEE) must be a function of some combination of FFM and M (as discussed above). Another potential confound is that the Tanzanian hunter-gatherers live in a considerably warmer environment than the other populations measured. Because REE is lower among organisms in colder environments (Speakman and Król, 2010), the hunter-gatherers' habitat may contribute to their lower REEs (hence also TEEs) for a given value of M , compared to westerners.

A more-detailed analysis that measured TEE and REE, and assessed physical activity using accelerometry, compared metabolic rates of Shuar forager-horticulturalist children from the Amazon with similar-aged children from the United States and United Kingdom (Urlacher et al., 2019). Although the Shuar children were ~25% more active than western children, they had similar levels of TEE relative to FFM. A subsequent study found that urban Shuar have lower levels of activity and lower levels of REE than rural Shuar (Urlacher et al., 2021). Neither of these findings support the constrained energy hypothesis that higher levels of activity decrease REE, but the authors hypothesize that the rural Shuar's higher mass-specific REEs compared to those of westerners result from greater energy allocation to immune function (which is upregulated in this Amazonian population), thus masking compensatory decreases in REE from AEE (Urlacher et al., 2019). It is also possible (but untested) that the Shuar children compensate for more walking and running by reducing levels of NEAT (Halsey, 2021).

Altogether, regressing TEE against body mass is an indirect way to evaluate competing models of how AEE affects REE (hence also TEE). This method is subject to misinterpretation because of multiple confounding factors. A better cross-sectional design is to regress AEE directly against REE and TEE while controlling for body mass effects on all these variables, as we discuss below.

AEE versus REE and TEE

A number of studies have tested the effects of physical activity on metabolic rates by regressing AEE or other measures of activity against either REE or TEE. This approach makes sense because the additive, constrained energy and stress models make contrasting predictions about the effect of AEE as the appropriate independent variable on REE (Fig. 3), thereby indirectly affecting TEE. Of the many such studies published, Careau et al. (2021) is one of two hypothesized to provide support for the constrained energy model. This study analyzed metabolic rates from 1756 elderly individuals measured twice (7 to 9 years apart). TEE was measured using DLW, REE was measured using respirometry, and AEE was calculated as $0.9\text{TEE} - \text{REE}$ (thereby assuming DIT is 10% of TEE). Within individuals, there was a significant negative association between AEE and REE after accounting for FFM, fat mass and age, suggesting that decreases in REE compensate for ~25% of the additional calories that normal-weight individuals spend on physical activity. Gonzalez et al. (2023), however, correctly highlighted that by subtracting REE from TEE to estimate AEE, this analysis mathematically coupled the supposedly dependent and independent variables, thus leading to a spurious negative correlation. Reanalysis of the study's results showed that the negative slope between AEE and REE is entirely explained by collinearity and regression dilution driven by error, and the results thus accord with predictions of the additive model (Gonzalez et al., 2023).

Ideally, cross-sectional studies that regress AEE and REE or TEE should use direct measurements of activity that are mathematically independent of REE or TEE, but as noted above, this is difficult. In the absence of 24-hour respirometry, the most common way to measure AEE directly is by using accelerometers that quantify intensity of activity as counts per minute (CPM). One study that used accelerometer data to test the constrained energy model reported that increases in CPM below a threshold of 230 CPM/day were independent of REE but positively correlated with TEE, whereas CPM and TEE and REE were independent above this threshold (Pontzer et al., 2016a). However, the relationship between CPM accelerometer measurements and direct measures of activity is nonlinear (Crouter et al., 2011) and generally has a low correlation (e.g. $r=0.26$ in Pontzer et al., 2016a), possibly indicating high error rates that make regressions prone to regression dilution. Furthermore, reanalysis of the data from Pontzer et al. (2016a) showed that CPM measurements of AEE are actually positively and significantly ($p<0.0005$) correlated with TEE (Gonzalez et al., 2023). Because TEE is the sum of REE and

AEE, this correlation suggests a significant positive correlation between AEE and REE, potentially supporting the stress model.

Metabolic quotients

Recently, Yegian et al. (2024) proposed a new metric, metabolic quotients (MQs), to compare whole-organism metabolic rates. Briefly, MQs are the ratio of an organism's or a taxon's observed metabolic rates (REE, AEE or TEE) relative to their predicted metabolic rates. Yegian et al. (2024) calculated predicted metabolic rates from an independent reference sample of 413 legged eutherian mammals for which DLW data were available and which were corrected using multiple regression for M , percent body fat and environmental temperature. This study excluded winged and marine mammals because their metabolic rates scale differently relative to M ; in addition, potential autocorrelations caused by relatedness were corrected using phylogenetic generalized least squares. This method yields three dimensionless MQs – resting metabolic quotient (RMQ), activity metabolic quotient (AMQ) and total metabolic quotient (TMQ). By definition, a MQ of 1.0 is typical for an average legged, eutherian mammal of the same size and body composition living in a similar environment.

MQs can also be affected by the sources of error noted above but have several advantages over metrics such as PALs that attempt to measure mass-specific metabolic rates. One useful characteristic is they are empirical descriptions that make no assumptions about scaling, and they control for the effects of M , percent body fat and environmental temperature, as well as any similarities caused by descent from a common ancestor. In addition, Yegian et al. (2024) validated MQs for both interspecific and intraspecific comparisons. As predicted for interspecific comparisons, R^2 of regressions of RMQ, AMQ and TMQ against M in the reference sample yielded values close to 0.0. In addition, as predicted for intraspecific comparisons, R^2 of regressions of RMQ, AMQ and TMQ for 273 adult humans against REE, AEE and TEE adjusted for size, age and sex yielded values close to 1.0 for all MQs.

Because MQs were proposed only recently, Yegian et al. (2024) is currently the only published study to use these quotients to evaluate indirectly the three different models of AEE effects on REE and TEE. This analysis, summarized in Table 1, reported that – after correcting for body size – humans from a wide range of populations that vary substantially in activity levels (AMQs) have nearly identical RMQs that are not significantly different. For example, the

average AMQ of highly active subsistence farmers from the Gambia is 1.80, twice as high as the AMQ of more-sedentary Americans from Louisiana (0.87), but RMQs of the two populations are nearly the same (1.76 and 1.65, respectively). As Table 1 shows, after correcting for size, body composition and environment, human populations with markedly different levels of activity allocate approximately equal amounts of energy to resting metabolism. Yegian et al. (2024) also found that humans have considerably higher RMQs than other mammals, including apes and monkeys who also have higher RMQs than similar-sized mammals; in addition, whereas apes and monkeys compensate for their relatively high RMQs with low AMQs (a metabolic trade-off), resulting in average TMQs of nearly 1.0, humans have unusually high TMQs because they devote higher than predicted amounts of energy to both AMQ and RMQ.

Life-history and health implications of the metabolic effects of physical activity

That physical activity can cause very short-term dose-dependent increases in REE as measured by EPOC is uncontroversial, but whether physical activity increases or decreases REE over the long-term or has no effect on REE remains unclear. In our view, the balance of evidence supports the additive model, whereas spurious results from autocorrelation, regression dilution and other analytical errors call into question much of the evidence used to support the constrained energy hypothesis. Clearly, testing all the models rigorously requires further study, ideally using longitudinal long-term experiments that independently and accurately measure all aspects of metabolism including DIT, as well as energy intake and other variables that can affect metabolic rates. Testing these models also depends on which metabolic rates one measures and how one models their effects. For example, because BMR needs to be measured in individuals who have not been physically active for 24 or more hours, humans and other organisms who engage in evolutionary normal levels of activity likely have higher and more variable REEs than BMRs.

Although further studies are needed to reveal whether, how and to what extent AEE influences REE, hence also TEE, the additive, stress, and constrained energy models have implications for how activity affects life history and health that are not always in accord. Physical activity, including exercise, unquestionably slows aging and reduces vulnerability to a wide range of diseases, but how it does so is not entirely understood.

According to life-history theory, when energy is limited, spending additional energy on AEE should cause trade-offs by reducing how much energy can be allocated to other functions,

namely growth, maintenance, storage and reproduction. Furthermore, because the ultimate target of natural selection is reproductive success, one expects selection to favor energy allocation tradeoffs that augment numbers of surviving offspring. These basic principles suggest two non-exclusive pathways by which activity benefits health (Lieberman et al., 2021). In one pathway, energy spent on AEE reduces energy allocation to certain functions that compromise long-term health; in the other pathway, the stresses that activity causes increase energy allocation to other repair, maintenance and capacity-building functions that improve long-term health. These ideas are discussed in more detail below.

Pathway 1: reduced energy allocation to functions that compromise long-term health

The first pathway is that sufficiently high levels of AEE prevent excess energy allocation to functions that increase short-term reproductive success at the cost of long-term health (a phenomenon sometimes termed ‘antagonistic pleiotropy’). One uncontroversial example of this trade-off is fat storage. Although dieting is more effective for weight loss than the low levels of physical activity most studies prescribe (~150 minutes/week of moderate exercise, such as walking), abundant evidence shows that similarly modest doses of activity can effectively prevent weight gain, and levels twice as high or more can also promote weight loss (Jakicic et al., 2019; Flack et al., 2020). Aerobic physical activity also prioritizes burning visceral fat, which is strongly associated with chronic, low-grade inflammation that contributes to a broad range of conditions including many cancers, heart disease, type 2 diabetes and Alzheimer’s (Furman et al., 2019). As a result, physically inactive individuals in energy-abundant environments are more likely to have excess visceral adipose tissue and be obese, in turn increasing their risk of morbidity and mortality (Valenzuela et al., 2023).

Lack of regular physical activity also can compromise long-term health by promoting excess energy allocation to certain reproductive hormones. In one study, women who engaged in moderate amounts of activity such as 20 km/week of running (~180 kcal/day of added AEE) had lower levels of estrogen and progesterone during the luteal phase of the menstrual cycle compared to healthy sedentary controls matched for age and body size (Ellison and Lager, 1986). Similar decreases in luteal phase progesterone and estrogen levels have also been documented among farmers compared to more-sedentary individuals in Poland (Jasienska et al., 2006). Because moderate levels of activity were normal for most of human evolutionary history and

have no measurably negative effect on fecundity, abnormally higher levels of reproductive hormones among sedentary women are likely to reflect adaptations to increase reproductive effort when surplus energy is available. However, because of their mitotic effects, elevated levels of estrogen and progesterone increase the risk of breast cancer, helping explain evidence that moderate activity levels decrease a woman's lifetime risk of breast cancer by 30–40% (Friedenreich and Orenstein, 2002).

Pathway 2: increased energy allocation to repair, maintenance and capacity-building functions

The second pathway by which exercise benefits health derives paradoxically from the fact that physical activity is physiologically stressful. As reviewed by Lieberman and colleagues (2021), at the cellular and tissue levels, physical activity increases the production and release of reactive oxygen species, damages DNA, thermally denatures proteins, creates metabolite byproducts, stimulates inflammation, induces hypoxia and upregulates the sympathetic nervous system. At a higher structural level, activity can generate forces that, for example, cause tears in muscles, interstitial damage to cartilage in joints, hemodynamic stresses in arterial walls, pressure load in the heart, increased intestinal permeability and microcracks in bones. With all this damage, one might think that exercise is so harmful it increases mortality and morbidity, but the opposite is true because activity simultaneously stimulates repair, maintenance and capacity-building responses that effectively counter these and other forms of damage. At the cellular level, for example, physical activity stimulates the production of antioxidants, increases the synthesis of enzymes that repair DNA, activates autophagy, induces heat shock proteins, upregulates anti-inflammatory cytokines, triggers angiogenesis and mitochondrial biogenesis, and activates the parasympathetic nervous system. At the tissue and organ levels, activity induces cartilage repair, arterial elasticity and elaboration, cardiac remodeling, mucus regeneration in the gut, and bone and muscle growth or repair.

The 'active grandparent' hypothesis proposes that these diverse responses to the stresses of physical activity slow senescence and promote health for two related reasons (Lieberman et al., 2021). First, repair and maintenance responses to activity-induced stresses not only restore homeostasis but also can overshoot whatever damage is caused, thus increasing capacity (allostasis). As examples, many capacity building mechanisms such as hypertrophy of muscle, replacing and increasing mitochondria, and augmenting the cardiovascular system lower

susceptibility to subsequent stresses. Second, because humans and other species never evolved not to be regularly physically active as they age, there was never selection to turn on these beneficial mechanisms to the same degree in the absence of physical activity. As a result, sedentary individuals senesce more rapidly and increase their vulnerability to many diseases by not building sufficient capacity and not repairing much of the damage that inevitably accumulates over time.

The evidence that insufficient lifelong physical activity is an evolutionary mismatch raises one last question: does energy allocation to AEE have different effects in humans than in other species? Humans have unusually long lifespans of about seven decades, usually including about two to three post-reproductive decades (Gurven and Kaplan, 2007). In contrast, only a handful of mammalian species survive after they stop reproducing. In addition, farmers and hunter-gatherers in non-industrial societies typically remain active as they age (evidence reviewed in Lieberman et al., 2021). It is therefore possible – but conjectural – that there was selection in humans for physical activity to differentially activate repair and maintenance mechanisms that slow senescence and extend healthspans, which largely determined lifespans before the era of modern medicine. This hypothesis is untested but merits scrutiny given limited evidence that most captive animal species – including great apes – have longer lifespans independent of the effects of predation than wild conspecifics, despite being less physically active (Tidière et al., 1996). In addition, after controlling for food intake and body weight, most experimental studies on laboratory rodents report that exercise leads either to modest or nonexistent effects on lifespan (Retzlaff et al., 1966; Goodrick et al., 1983; Holloszy et al., 1985; Garcia-Valles et al., 2013). It is therefore intriguing to speculate that exercise may have unique health benefits for humans.

Conclusion

To conclude, all forms of physical activity, including exercise, cost energy and thus affect metabolic rates. However, it is challenging to define and measure whole-organism metabolic rates accurately and to determine how the energy spent on being physically active, namely AEE, affects other aspects of metabolism after correcting for body mass and composition. Sources of error and differences of opinion on how to analyze metabolic rates have led to competing

hypotheses. The null hypothesis, the additive model, proposes that increases in AEE are independent of REE; the stress model proposes that increases in AEE temporarily increase REE (hence also TEE) over short timescales; and the constrained energy model proposes that increases in AEE decrease REE, thus keeping TEE approximately constant.

Our Review finds most support for the additive model, provides some potential support for the stress model, and concludes that most of the evidence for the constrained energy model arises from spurious correlations and regression dilution. Intuitively, this makes sense because TEE, by definition, is not an actual metabolic rate but instead the measured sum of AEE, REE and DIT – all of which should be able to vary independently. In addition, investing in REE mostly helps organisms maintain their bodies. It is therefore puzzling why TEE should or would be constrained below extreme levels among humans with access to unlimited energy intake. That said, more and better analyses are required to test all three models.

Perhaps the most important implication of these models is that the energetic costs of physical activity have multiple potential effects on energy allocation that can affect health. To some extent, spending more calories on AEE can prevent excess energy being stored as fat and being allocated to the production of hormones that compromise health at the expense of reproduction. At the same time, the stresses caused by physical activity stimulate energy allocation to mechanisms that repair, maintain and build capacity, thus potentially slowing senescence and reducing vulnerability to many diseases. Because organisms, humans especially, never evolved to be habitually inactive – including as they age – these beneficial repair and maintenance mechanisms are not activated to the same extent in the absence of regular, habitual physical activity. Lack of sufficient lifelong activity is therefore an evolutionary mismatch, with far-reaching implications for human health. Further work on this topic is important if we are to understand the mechanisms underlying these interactions.

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The authors declare no competing or financial interests

Author Contributions

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Glossary

Active energy expenditure (AEE) – the energy cost per day of all physical activities

Basal metabolic rate (BMR) – rate of daily energy consumption as measured in a dark, thermoneutral room immediately after waking in a fasted state and in the absence of much physical activity for the previous 24–48 hours.

Carry-over effects – when the effects of a treatment or condition, such as increased levels of physical activity, persist after the treatment ends, making it difficult to separate the impact of the next treatment or condition in a longitudinal study.

Diet-induced thermogenesis (DIT, also termed the thermic effect of food) – the post-prandial increase in metabolism that includes the cost of digestion.

Evolutionary mismatch – conditions that are more common or severe because organisms are inadequately or imperfectly adapted to novel environmental conditions (Lieberman, 2013).

Excess post-exercise oxygen consumption – the phenomenon by which physical activity causes transient, short-term increases in REE, usually lasting for a few hours but potentially for as long as 48 hours, depending on the duration, intensity and type of activity.

Non-exercise activity thermogenesis, NEAT – the amount of energy an individual expends through all physical activities other than deliberate exercise.

Resting/basal energy expenditure (REE) – the energy the body expends daily at rest in a non-prandial state.

Regression dilution – a bias that occurs in regression analysis when the predictor variable is measured with random error. This error weakens the estimated relationship, causing the slope of the regression to falsely appear closer to zero.

Total/daily energy expenditure (TEE or DEE) – the total sum of the organism's energy use over 24 hours.

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Figures and Tables

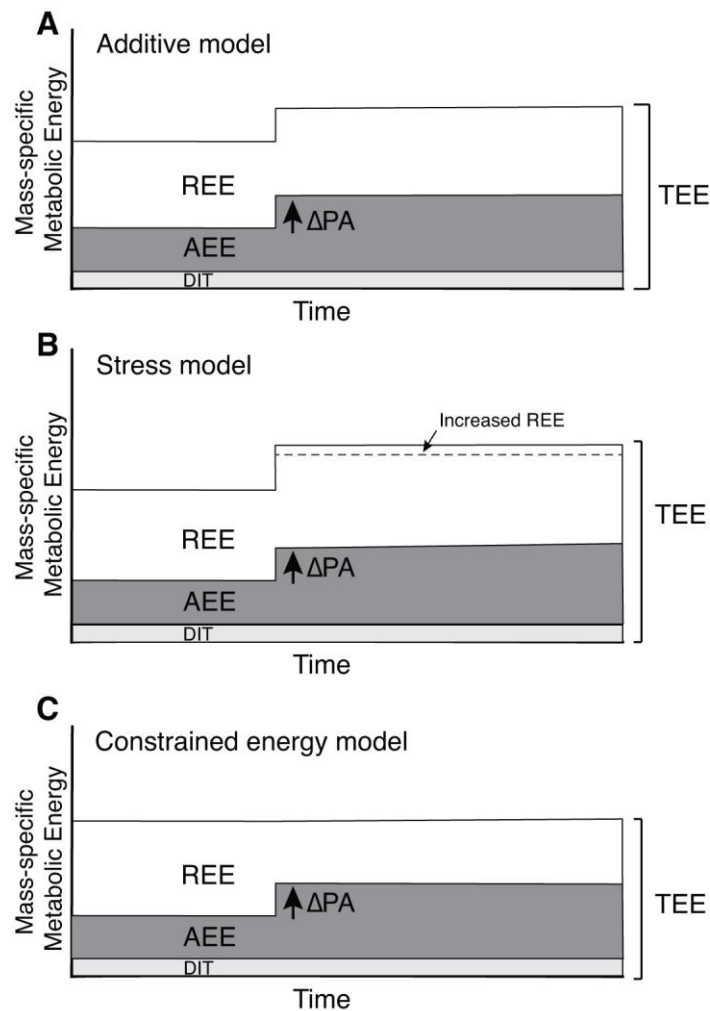


Fig. 1. Longitudinal models of AEE versus REE and TEE. The additive, stress and constrained energy models make different predictions regarding how a change in levels of physical activity (ΔPA) affects mass-specific metabolic rates. (A) According to the additive model, an $x\%$ increase in AEE has no effect on REE and thus increases TEE by $x\%$. (B) According to the stress model, an $x\%$ increase in AEE increases REE by $y\%$, and hence increases TEE by $x\%+y\%$. The $y\%$ increase in REE, however, is transient, and its magnitude and duration are a function of activity intensity, duration, frequency and type. (C) According to the constrained energy model, an $x\%$ increase in AEE decreases REE by $x\%$ to keep TEE constant. Note that in all models, metabolic rates are adjusted for changes in body mass and composition; DIT is diet-induced thermogenesis.

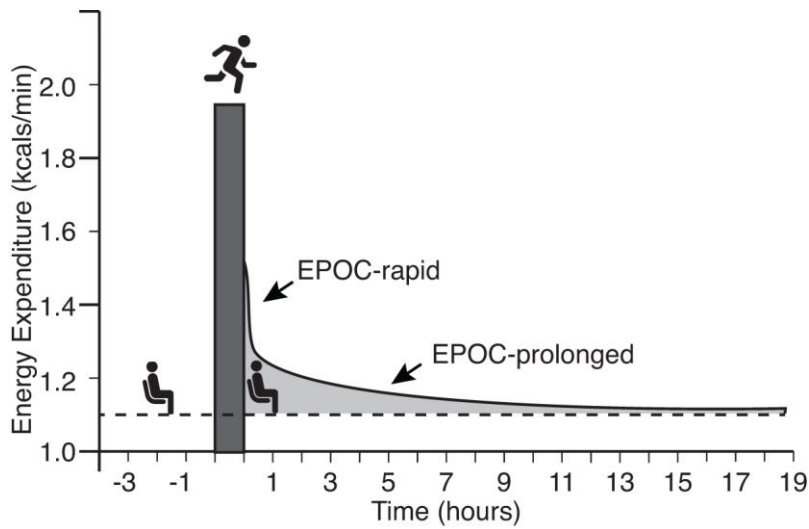


Fig. 2. Excess post-exercise oxygen consumption. Following a bout of physical activity (vertical bar), REE rises above basal levels (dashed line) in two phases. The short-term rapid phase is thought to primarily reflect the cost of replacing spent energy; the prolonged phase, whose magnitude and duration are a function of intensity, duration and type of physical activity, is hypothesized to reflect mostly the cost of repair, maintenance and capacity-building processes.

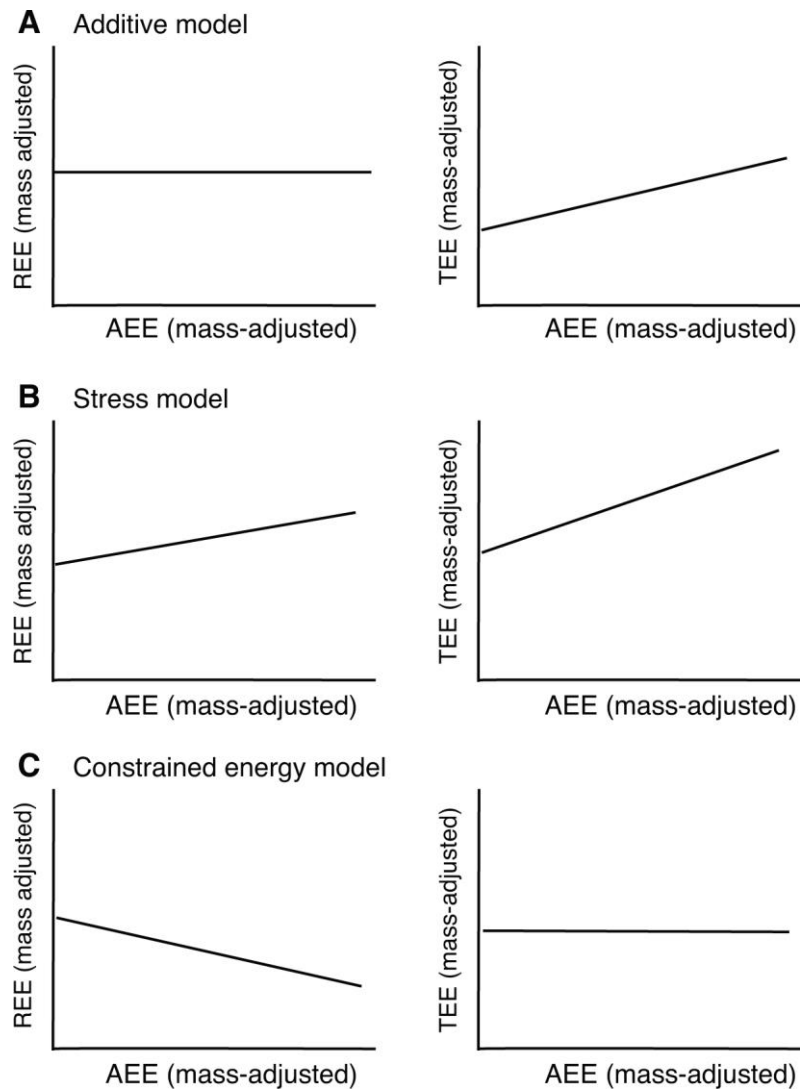


Fig. 3. Cross-sectional predictions of the additive, stress and constrained energy models. (A) According to the additive model, an $x\%$ increase in AEE is uncorrelated with REE but is associated with an increase of TEE by $x\%$. (B) According to the stress model, an $x\%$ increase in AEE is associated with a transient increase of REE by $y\%$, thus also leading to an associated TEE increase of $x\%+y\%$. (C) According to the constrained energy model, increases in AEE are associated with a decrease in REE to keep TEE constant. Note that metabolic rates in all three models need to control for variations in body mass and composition.

Table 1. Metabolic quotients of different populations (from Yegian et al., 2024)

Population	Way of life	<i>N</i> (m/f)	AMQ	RMQ	TMQ
Hadza	Hunter-gatherers	30 (13/17)	1.24	1.64	1.42
Aymara	Subsistence farmers	13 (6/7)	1.42	1.62	1.50
Sakha	Nomadic pastoralists	18 (14/14)	1.15	1.77	1.40
Tsimane	Subsistence farmers	40 (18/22)	1.31	1.57	1.42
Gambia	Subsistence farmers	15 (8/7)	1.80	1.76	1.78
Americans	Industrial	324 (138/186)	0.87	1.65	1.20
World Average	Mostly industrial	110 populations	1.04	1.78	1.34

AMQ/RMQ/TMQ, activity/resting/total metabolic quotient; f, female; m, male; *N*, number of individuals.