PERSPECTIVE

The active grandparent hypothesis: Physical activity and the evolution of extended human healthspans and lifespans

Daniel E. Lieberman[a,1], Timothy M. Kistner[a], Daniel Richard[a], I-Min Lee[b], and Aaron L. Baggish[c]

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The proximate mechanisms by which physical activity (PA) slows senescence and decreases morbidity and mortality have been extensively documented. However, we lack an ultimate, evolutionary explanation for why lifelong PA, particularly during middle and older age, promotes health. As the growing worldwide epidemic of physical inactivity accelerates the prevalence of noncommunicable diseases among aging populations, integrating evolutionary and biomedical perspectives can foster new insights into how and why lifelong PA helps preserve health and extend lifespans. Building on previous life-history research, we assess the evidence that humans were selected not just to live several decades after they cease reproducing but also to be moderately physically active during those postreproductive years. We next review the long-standing hypothesis that PA promotes health by allocating energy away from potentially harmful overinvestments in fat storage and reproductive tissues and propose the novel hypothesis that PA also stimulates energy allocation toward repair and maintenance processes. We hypothesize that selection in humans for lifelong PA, including during postreproductive years to provision offspring, promoted selection for both energy allocation pathways which synergistically slow senescence and reduce vulnerability to many forms of chronic diseases. As a result, extended human healthspans and lifespans are both a cause and an effect of habitual PA, helping explain why lack of lifelong PA in humans can increase disease risk and reduce longevity.

physical activity | exercise | lifespan | healthspan | evolution

Humans have known for millennia that physical activity (PA) promotes health and longevity. Over the last few decades, studies have shown that 150 min/wk of moderate- or 75 min/wk of vigorous-intensity aerobic PA reduces the average otherwise-sedentary person's relative risk of all-cause mortality by ~50%, and that additional PA has further but diminishing benefits (1–4). PA yields dose-dependent reductions in the risks of numerous diseases including hypertension, cardiovascular disease (CVD), type 2 diabetes, Alzheimer's, and many cancers. PA also slows senescence, defined as processes of accumulated deterioration that reduce the ability to respond to stresses and increase vulnerability to disease (5). As a result, PA significantly increases quality-adjusted life years and reduces disability-adjusted life years (6).

Despite the undisputed health benefits of PA, PA levels are decreasing worldwide as machines and technology replace human labor, contributing to the growing prevalence of morbidity among older individuals (7). As a result, there is an increased need to promote and prescribe PA including exercise—defined as voluntary, discretionary PA undertaken to sustain or improve health and fitness. In addition, there are intense efforts to understand better the mechanisms by which PA promotes health in order to harness its benefits pharmaceutically.

But why does PA decrease morbidity and mortality rates? Recent advances in medical science, physiology, and related fields have elucidated many biological processes by which PA helps people retain functional capacity and avoid disease as they age. As

[a]Department of Human Evolutionary Biology, Harvard University, Cambridge, MA 02138; [b]Division of Preventive Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02215; and [c]Cardiovascular Performance Program, Massachusetts General Hospital and Harvard Medical School, Boston, MA 02114

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[1]To whom correspondence may be addressed. Email: danlieb@fas.harvard.edu.

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examples, regular PA helps prevent weight gain, maintain normal blood pressure, lower levels of low-density lipoproteins and triglycerides, increase levels of high-density lipoproteins, reduce systemic inflammation, decrease stress levels, and stimulate the production of neurotransmitters and neurotrophins that maintain neurons and ameliorate mood (8). Although these and other consequences of PA are the proximate mechanisms by which exercise fosters healthy aging, they do not explain the underlying, ultimate reasons why PA stimulates these processes in the first place. Beyond the question of what level of PA is normal for humans, why do these beneficial mechanisms not operate to the same degree in the absence of PA, especially among older, sedentary individuals?

The axiom that nothing in biology makes sense except in the light of evolution is sometimes a cliché, but merits being applied to the relationship between PA and health. To understand fully why PA reduces morbidity and extends longevity requires evolutionary theory and data including recent advances in understanding the evolution of humans' unique, extended life history (9–11); how humans allocate energy to different physiological functions, including PA and maintenance, that affect health (12–15); and the levels and types of PA among hunter-gatherers and other small-scale societies (16, 17). Inspired by these and other insights, evolutionary explanations for why PA is healthy generally postulate that humans are mismatched to novel environments that permit habitual physical inactivity. The basis for this hypothesis is that mismatches arise because phenotypic adaptations result from gene-by-environment interactions but, while gene frequencies change slowly and gradually over many generations, environmental factors such as PA levels can change profoundly and rapidly, especially through cultural evolution. Since almost no humans were persistently physically inactive until a few generations ago, there was never selection to prevent dysregulation of physiological processes affected by PA such as levels of stress and reproductive hormones that can lead to disease (15, 18–20). The mismatch hypothesis, however, does not explain why habitual PA in and of itself is an important environmental variable that affects so many pathophysiological processes. In other words, why does PA affect proximate mechanisms that slow senescence and inhibit vulnerability to disease?

Here we review how integrating recent advances in biomedical research on exercise with evolutionary studies of human life-history theory and PA can deepen our understanding and foster new insights into why, how, and to what extent PA decreases rates of morbidity and mortality, even in contemporary high-income populations with access to modern medical care. We first review evidence that humans were uniquely selected to live several postreproductive decades while remaining physically active. We then review two nonmutually exclusive hypotheses for why there was selection for PA throughout the lifespan but especially in middle and old age to allocate energy toward physiological processes that extend healthspans, hence lifespans. We next apply predictions of these hypotheses to the two leading causes of morbidity and mortality in high-income countries: CVD and cancer. To conclude, we compare the effects of PA on humans and other mammals, and explore how integrating evolutionary biology and medical science can spur new ways of thinking about relationships among PA, aging, health, and disease.

Human Life History and Physical Activity

Most studies of the effects of PA on morbidity and mortality are from high-income industrial and postindustrial populations who typically engage in low levels of PA (Fig. 1). Large-scale studies using wearable sensors report that the average American adult takes 4,774 steps per day, ~3 km (21), engages in less than 30 min/d of moderate to vigorous physical activity (MVPA; defined as equivalent to brisk walking or more intense activity) (22), and has a physical activity level (PAL; daily energy expenditure/basal metabolic rate [BMR]) of about 1.6 to 1.7 (23). In contrast, adults in hunter-gatherer populations such as the Hadza average 15,800 steps a day, about 9 to 15 km, engage in 135 min/d of MVPA, and have PALs of about 1.9 (17, 24, 25). Similar or higher levels of activity characterize nonindustrial farming populations, indicating that until recently most human adults engaged in moderate levels of daily PA (16, 26).

Even though people in high-income industrial environments are many times less active than those in low-income nonindustrial environments, they are still more active than our closest ape relatives (Fig. 1). Adult chimpanzees travel on average 2 to 4 km/d and have PALs of ~1.4 to 1.5 (13, 27); gorillas and orangutans are even less physically active (28, 29). Because most mammals have PALs between 2 and 3 (30), we can infer

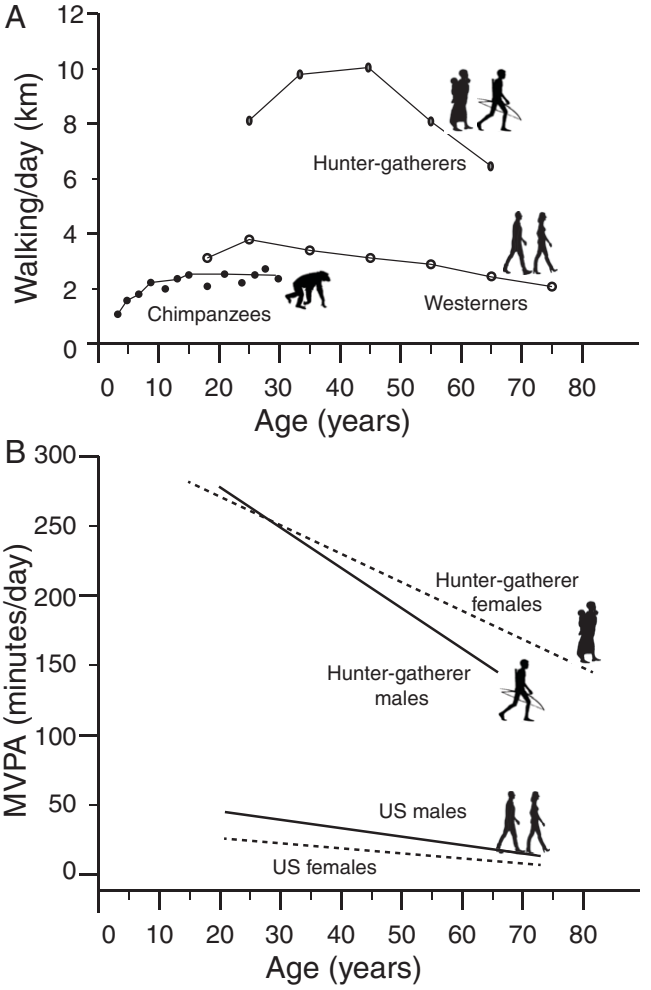

Fig. 1. Comparison of PA levels across the lifespan in different human populations and apes. (*A*) Daily walking distance (average of males and females) in chimpanzees, Westerners, and Hadza hunter-gatherers. (*B*) Min/d of MVPA in male and female Hadza hunter-gatherers and US adults. Chimpanzee data are from ref. 27; Hadza data are from refs. 24, 34, and 104; and data on Westerners are from refs. 21 and 22.

that the great apes were selected for low levels of PA, and that the last common ancestor of humans and chimpanzees was similarly sedentary. Selection for increased PA, especially aerobic PA, in the hominin lineage probably occurred by 2 million y ago with the origins of hunting and gathering.

Considering these differences in PA from a life-history perspective suggests the hypothesis that selection for increased PA in humans was linked to selection for extended lifespans. Female chimpanzees in the wild rarely live beyond the age of 35 to 40 (10). Contrary to the widespread belief that human lifespans until recently were short, hunter-gatherers who survive infancy and childhood tend to live on average seven decades, approximately 20 y past the age at which they cease reproducing (11), and fossil evidence indicates that extended human lifespans were common by 40,000 y ago (31). Lengthy postreproductive lifespans have been shown to be a critical component of the unique human life-history strategy in which grandparents enhance their reproductive success not just by imparting knowledge and skills but also by being physically active foragers who gather and hunt for food surpluses that they provide to their children and grandchildren (9, 10). Among Hadza hunter-gatherers, for example, postreproductive women forage on average 6 h/d, 20% more than younger mothers, and they devote as much or more effort as parents to preparing food, childcare, and engaging in other PAs such as digging, walking, and carrying (32). Overall, hunter-gatherer grandparents provision their offspring with 250 to 3,000 calories per day and decrease their children's PA costs by several hundred additional calories per day (10).

Because of intergenerational energy transfers, natural selection likely favored healthy postreproductive longevity in hunter-gatherers who continued to engage in moderate levels of PA as they aged. PA levels among postreproductive hunter-gatherers support this prediction (Fig. 1). While the number of daily steps older Americans take decreases by about half between the ages of 40 and 70, daily walking distances among hunter-gatherers such as the Hadza decline only modestly with age (33, 34). These differences in lifelong PA patterns are reflected in fitness measurements among age-stratified cohorts. By age 60, average Westerners walk 33% more slowly than they did in their 40s, and lose 25% of their grip strength and 22 to 25% of VO_2max levels—defined as the maximal rate of oxygen uptake during PA (35–37). In contrast, hunter-gatherer walking speeds barely decline with age, and their grip strengths and VO_2max levels deteriorate considerably less than similar-aged Westerners (34, 38, 39). For most of human evolutionary history, chronic disease was likely rare and functional capacity remained high in postreproductive individuals until just prior to death, highlighting how the extension of morbidity in old age is largely a recent phenomenon (40). Put differently, selection is unlikely to have favored longevity in unhealthy elderly individuals who were physically inactive because they would have been unable to forage, thus imposing an energetic cost on caregiving relatives.

The hypothesis that humans were selected for extended, healthy postreproductive longevity to engage in regular levels of moderate PA raises the related hypothesis that selection for PA to extend lifespans acted in part through selection for PA to extend healthspans, defined as how long an individual lives without serious, long-term illness or loss of functional capacity. We think of healthspan and lifespan as different but, prior to modern medicine, healthspan strongly influenced lifespan (41).

Selection for PA to increase healthspans and lifespans, however, raises a seeming paradox from the perspective of life-history theory, which predicts natural selection to favor adaptations that maximize fitness by differentially apportioning time and energy over the life cycle to five alternative functions including not just PA but also growth, maintenance, energy storage, and reproduction. Since energy is limited for almost all organisms (some humans in high-income countries are an unusual, recent exception) and a calorie cannot be spent twice, energy spent on PA diverts energy not just from reproduction but also from processes that counter senescence and prevent morbidity and mortality. These energetic tradeoffs, moreover, are considerable. An average Hadza hunter-gatherer mother allocates about one-third of her daily energy expenditure to PA (42). In addition, PA causes a broad range of well-characterized forms of physiological stress including damage at the molecular, cellular, and tissue levels, all of which need to be repaired (Table 1).

To resolve this paradox, we review two nonmutually exclusive energy allocation hypotheses to explain why lifelong PA, especially in middle and old age, tends to increase rather than decrease healthspan and lifespan. The first hypothesis, which has previously been recognized (e.g., refs. 15 and 20), is that energy spent on PA reduces overinvestments in fat storage and reproduction that potentially compromise health in abnormal modern environments with nearly limitless calories. The second, novel hypothesis is that the stresses of PA stimulate investments in healthspan-preserving somatic repair and maintenance processes that are activated less in the absence of PA. Together, these hypotheses suggest that selection for increased levels of PA not only helped make possible humans' uniquely slow and lengthy life history but also promoted selection for traits that allocate energy both away from processes that can compromise health and toward processes that slow senescence and decrease vulnerability to disease, thus extending both healthspan and lifespan.

Hypothesis 1: PA Allocates Energy from Excess Investment in Reproduction and Fat Storage. PA can be energetically costly. An average adult expends about 30 or 60 kcal/km to walk or run, respectively, plus hundreds of calories per day on other activities (43). Several researchers have thus proposed that a major pathway by which PA promotes health is to prevent potentially harmful excess energy allocation to fat and reproductive tissues under conditions of sustained positive energy balance (15, 20). To understand these widely appreciated benefits of PA, it helps to apply energy allocation theory to the pathways by which the body stores fat and invests in reproductive tissues in diverse human populations as well as nonhuman primates. These combined perspectives elucidate how and why lack of PA is a mismatch in sedentary individuals with access to abundant energy-rich food by diverting calories toward unhealthy overinvestment in reproduction and fat storage.

A starting point for this hypothesis is that while all animals differentially allocate energy to PA, growth, maintenance, fat storage, or reproduction, these tradeoffs are likely heightened in humans because of our unusually expensive reproductive strategy compared with our closest ape relatives. These elevated expenditures are most evident among females. Whereas chimpanzee mothers begin reproducing at age 12 to 15 and give birth every 5 to 6 y, hunter-gatherer mothers usually start reproducing around age 18 and average 3- to 4-y interbirth

Table 1. Major stresses and responses often induced by PA

Type of stress	Repair response
Structural	
Bony microcracks (106, 107)	Secondary (Haversian) remodeling and bone accretion (108, 109)
Muscle fiber tears (110)	Muscle fiber hypertrophy and myocyte apoptosis/autophagy (111, 112)
Hemodynamic arterial stress (113)	Increased endothelial progenitor proliferation and signaling, amplified NO production, angiogenesis, and reduced arterial stiffness (113–117)
Exercise-induced hemolysis (118)	Increased erythropoiesis (119)
Volume and/or pressure overload in the heart	Cardiac remodeling, thickening and/or expansion of ventricles and atria; increased cardiomyocyte contractile function (73, 120, 121)
Cartilage deformation and degradation, interstitial fluid loss (122)	Cartilage matrix synthesis and remodeling, articular cartilage turnover, synovial secretions (122, 123)
Increased respiratory exposure to airborne pathogens (124, 125)	Enhanced immunosurveillance in respiratory membranes; increased recirculation of natural killer and cytotoxic T cells (67, 126)
Increased intestinal membrane permeability (127)	Microbiome alterations that stimulate intestinal mucus production, provide energy to colonocytes, and drive T_{reg} differentiation; induction of antimicrobial peptides from host cells (128–132)
Cellular and molecular	
Elevated ROS production in active tissues (133, 134)	Enhanced antioxidant synthesis, autophagy, mitophagy, apoptosis (135–138)
Thermal protein denaturation (139)	Heat shock protein up-regulation, autophagy (135, 140)
Metabolite production (e.g., lactate, ammonia, inorganic phosphate, etc.) (141)	Lactic acid oxidation and use as a metabolic substrate (lactate shuttle), increased protein breakdown and resynthesis, proteinuria (141–143)
Increased energy flux and depletion of cellular energy reserves (141, 144)	Mitochondrial biogenesis, improved mitochondrial function, up-regulated glycogen and phosphagen synthesis (145–148)
Sympathetic nervous system activation (149)	Parasympathetic nervous system activation, lowered sympathetic nervous system reactivity (150, 151)
Acute DNA damage foci (152, 153)	Increased activation of DNA repair pathways, expression of repair enzymes, apoptosis (136, 138, 152–159), and release of systemic repair factors (85, 86, 160)
Acute inflammation and immune infiltration to damaged tissues (161, 162)	Anti-inflammatory myokine release, immune clearance of damaged/senescent cells (52, 160, 163–165)
Acute hypoxia (144)	Angiogenesis, improved cellular respiratory efficiency, improved cardiac output (120, 166, 167)

PA-induced stresses, and their associated repair responses, are summarized. ROS, reactive oxygen species; T_{reg}, regulatory T cell.

intervals (10). Consequently, a typical hunter-gatherer mother struggles to satisfy not only her own high energy needs but also obtain extra calories for the substantial costs of nursing (circa 500 kcal/d) as well as feeding and caring for several older but still immature juveniles—all with large brains that ceaselessly require as many as 400 kcal/d (10). Hunter-gatherer males also have high energy needs compared with other primates (13).

Humans' high energy costs have critical consequences for energy allocation that impact the effects of PA on healthspans. First, whereas chimpanzee mothers spend ~336 kcal/d on PA, typical hunter-gatherer mothers have been measured to spend ~635 kcal/d on PA (data from refs. 13 and 42). As a result, there was selection in humans for an enhanced proclivity to store fat to enable them to stay physically active as well as nurse and provision offspring during periods of extended negative energy balance. Whereas body fat comprises 2 to 9% of body mass in adult chimpanzees and other primates (13), male and female hunter-gatherers average 10 to 15% and 15 to 25% body fat, respectively, and males and females in high-income populations such as the USA average 23 to 31% and 32 to 42%, respectively (17, 44). Among Kalahari hunter-gatherers, skinfold thickness (a proxy for subcutaneous fat levels) declines 15% during lean seasons when PA levels increase (45).

Another important consequence of humans' high energy budget is to modulate energy allocation toward reproduction based on energy availability, especially in females. Ovarian function is highly sensitive to energy, causing variations in progesterone and estradiol levels, adaptively increasing or decreasing conception likelihood during periods of positive or negative energy balance, respectively (14). In addition, while investment in gestation and lactation tends to be buffered from fluctuations in energy availability, gestation length, birthweight, and interbirth intervals (through amenorrhea) are highly sensitive and responsive to energy balance and flux as regulated by leptin, estradiol, insulin, and cortisol (14). Human reproductive investment is so finely tuned to energy availability that PA levels independent of diet modulate reproductive hormone levels (46). Even moderate PA doses such as 20 km/wk of jogging (180 kcal/d) lower progesterone and estradiol levels in the luteal phase of the menstrual cycle by ~50% in weight-stable healthy young women relative to sedentary controls (18, 47). Although such reductions potentially impact fecundity, few women until recently were habitually physically inactive, suggesting that sedentary women from modern high-income countries have elevated reproductive hormone levels compared with less sedentary women with evolutionarily normal PA levels (48). Sustained endurance PA also lowers basal testosterone levels, and hunter-gatherers and subsistence farmers have lower testosterone levels than similar-aged less physically active males from high-income countries (49). As discussed below, elevated levels of these mitotic hormones from low PA levels are implicated in increased risk of several cancer types.

The mechanisms by which humans preferentially store energy as fat and increase investment in reproduction during periods of physical inactivity are unambiguously adaptive in evolutionarily normal conditions with high levels of energy flux

and substantial alternations between positive and negative energy balance. But in modern conditions of sustained energy abundance along with low PA, these tradeoffs can lead to mismatches, most critically excess fat storage. Using body mass index (BMI) as a proxy, less than 2% of African hunter-gatherers are classified as overweight but ~70% of Americans are overweight or obese (18, 44, 45). Although these BMI differences are predominantly a consequence of diet, regular PA has repeatedly been shown to help prevent weight gain from fat storage (50). Twin studies confirm that habitual physical inactivity is strongly associated with increased likelihood of obesity even after controlling for childhood environment and genetics (51). In turn, obesity, especially visceral obesity, in the context of physical inactivity provokes systemic inflammation as swollen adipocytes become dysfunctional and, along with invading macrophages, release proinflammatory cytokines and adipokines. Chronic, systemic inflammation then contributes to insulin resistance, endothelial dysfunction, dyslipidemia, atherosclerosis, and neurodegeneration, and thereby to mismatch conditions such as type 2 diabetes, CVD, Alzheimer's, and osteoarthritis (see below).

In addition to indirectly triggering inflammation via obesity, lack of PA also fails to suppress chronic inflammation through at least three important pathways. First, PA curtails systemic inflammation by reducing visceral fat levels as well as bloodstream levels of fat and glucose. Second, PA directly lowers inflammation because contracting skeletal muscles produce acute surges of proteins (myokines), especially interleukin-6 (IL-6), that regulate immune function (52). For example, PA-induced IL-6 increases glucose uptake in skeletal muscle, increases beta-oxidation in adipocytes and myocytes, and stimulates the production of anti-inflammatory cytokines such as IL-1ra and IL-10 (53). Since all humans until recently engaged in regular lifelong PA, lack of these myokine signals in physically inactive individuals has likely increased levels of chronic inflammation, hence many mismatch diseases. Overall, increased levels of PA are associated with lower levels of chronic inflammation even after correcting for BMI and other risk factors for inflammation such as smoking (54). Finally, PA not only lowers insulin levels, which play a strong role in adipose dysfunction and elevate the risk of cancer (see below), but also substantially reduces insulin resistance, a major cause of metabolic syndrome, by increasing insulin sensitivity in muscle, liver, adipocytes, and other cells and by altering insulin-independent glucose metabolism in various tissues (55, 56). These shifts in energy allocation illustrate how PA (or its absence) has generally more powerful effects on insulin resistance than visceral adiposity alone.

Hypothesis 2: PA Allocates Energy to Repair and Maintenance Processes. An alternative hypothesis for why PA was selected to promote healthspan is that PA is physiologically stressful. Beyond costing average nonindustrial adults many hundreds of calories a day, varying doses and types of PA can generate numerous forms of stress and damage at the molecular, cellular, and tissue levels, as summarized in Table 1. Since regular PA is necessary for all animals, there was likely strong selection for PA to stimulate processes that allocate energy toward an equally wide range of maintenance and repair functions (also summarized with references in Table 1) that ameliorate stresses and prevent or restore damage caused by PA. Many of these processes are homeostatic, such as restocking depleted energy stores, producing antioxidants, clearing metabolites, reducing inflammation, and stimulating the parasympathetic nervous system to down-regulate sympathetic activation. Others are allostatic mechanisms that promote stability by increasing capacities such as stimulating muscle and bone hypertrophy, inducing proliferation of mitochondria and glucose transporters, and enhancing cardiovascular function.

While PA induces many repair and maintenance processes, these consume energy and are thus expected to be subject to tradeoffs. Although impossible to measure directly, we can approximate PA-induced repair and maintenance costs from quantifying the short-term effects of PA on resting energy expenditure (REE). As shown in Fig. 2, REE following a bout of PA can be initially elevated by 3 to 20% and then take between 2 and 48 h to return to preexercise levels, with the total increase and duration dependent on factors such as PA dose, fitness level, and sex (57). This excess postexercise oxygen consumption (EPOC, or "afterburn") was initially thought to be an oxygen debt reflecting the cost of energy replenishment, but phosphagen restoration and lactate clearance comprise a modest fraction of EPOC, indicating that other repair and maintenance processes account for the majority of increased REE costs following PA (58). EPOC continues to occur as people age (59), and because EPOC levels increase exponentially with PA intensity and linearly with duration, the costs can be significant. In one controlled experiment, adults who exercised at 70% VO_2max for 80 min experienced an average 5% increase in REE over 24 h adding up to 125 kcal of EPOC (60). In another study of 10 fit young males who walked briskly for 3 h at 50% VO_2max, REE levels were elevated by 9% after 4.5 h and remained elevated by 4.7% after 18 h (61). Since foraging populations such as the Hadza and Tsimane average 2 to 4 h daily of MVPA (16, 24), it is reasonable to hypothesize that for most of human evolution, quotidian PAs stimulated similar levels of energy allocation toward repair and maintenance. As Fig. 2 models, a 70-kg person who is nearly sedentary or as active as an average hunter-gatherer is predicted to divert 4,380 and 17,540 kcal, respectively, per year toward EPOC-related repair and maintenance, causing the latter to invest 262,800 kcal more over 20 y.

One issue that requires further study is evidence from cross-sectional studies that total daily energy expenditure (DEE) relative to lean body mass is not higher in physically active non-Western populations, including Hadza hunter-gatherers, than in sedentary Westerners (42). This observation has led to the hypothesis that individuals compensate for higher levels of PA by lowering their BMR (62). The metabolic mechanisms underlying this hypothesized adaptation, however, have yet to be identified, and it is unknown whether evolutionarily normal levels of PA lead to lower BMRs or if sedentary individuals have disregulated BMRs. In either case, BMR is properly measured in a fasted state in thermoneutral conditions following at least 24 h of rest, thereby excluding any effects of EPOC, suggesting that metabolic compensation in more active individuals occurs through processes unrelated to repair and maintenance of PA-induced damage. In addition, it has been shown that more physically active, fitter individuals in Western populations have higher BMRs and REEs even after resting (63, 64). These data suggest that factors other than shifts in EPOC are responsible for cross-sectional differences in DEE between populations. This makes sense, because it would be maladaptive not to activate repair and maintenance

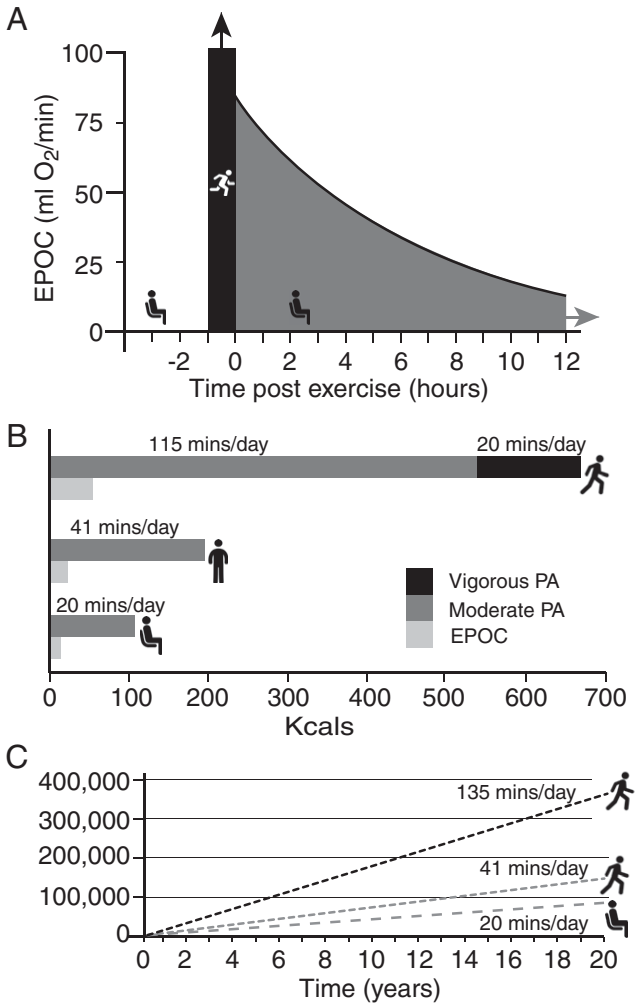

Fig. 2. Effects of PA on energy, repair, and maintenance. (*A*) Effect of PA on prolonged EPOC for a 70-kg male. The EPOC depicted here is from 71 to 80 min of PA at 69 to 78% VO_2max ($n = 12$) (57). (*B*) Estimated calories per day spent on moderate PA, vigorous PA, and EPOC invested in repair and maintenance by a 70-kg sedentary person who gets 20 min moderate PA per day, supplements this with 21 min/d of moderate PA and 2 min/d of vigorous PA, or is as active as a typical hunter-gatherer with 115 min/d of moderate PA and 20 min/d of vigorous PA. Estimates of EPOC are from ref. 105; repair and maintenance costs are estimated conservatively to be 80% of EPOC (58). (*C*) Model of cumulative investment in repair and maintenance (R&M) over 20 y for a 70-kg person who gets 20, 41, or 135 min/d of MVPA as modeled above in *B*. Leaving aside other potential aspects of metabolic compensation, over 20 y, repair and maintenance investment in someone as active as a typical hunter-gatherer totals 282,800 kcal more than the sedentary person.

processes in response to the widespread physiological damage PA induces (otherwise PA would shorten, not extend, healthspans).

The phenomenon of EPOC highlights another benefit of activating repair and maintenance processes in response to PA, which is to adjust capacity economically to demand, thus avoiding allocating excess energy to functions that do not ultimately benefit reproductive fitness. A well-known example is muscle, which costs 10 to 15 kcal/kg to maintain yet comprises 30 to 40% of body weight in average adult humans, about 20% of REE (65). These costs render it adaptive to minimize excess muscle through hypotrophy in the absence of demand and through hypertrophy in response to PA, especially from microdamage caused by contractions against high resistance. Adaptations to "use it or lose it," however, can be problematic in modern environments that enable individuals, especially the elderly, to be physically inactive. Returning to the example of muscle, physically inactive individuals tend to lose more muscle mass than active individuals, leading to sarcopenia, which in turn promotes in the elderly a vicious cycle of further physical inactivity and declining health, but these declines can be rescued by PA (66). Other traits selected to adjust capacity to demand from PA-induced stress include bone mass, mitochondrial density, capillary density, heart volume, and hemoglobin levels (Table 1). Another health-preserving example of matching capacity to PA-induced demand is transiently elevated investment in immune function. Moderate levels of PA stimulate increased immunosurveillance in both the innate and adaptive immune systems as evident from extravasation and recirculation of neutrophils, cytotoxic T cells, antibodies, and other immune cell subsets that are preferentially deployed to vulnerable locations such as the respiratory and digestive tracts (67).

Importantly, the short-term forms of damage PA causes including oxidation, metabolite production, and mitochondrial dysfunction are quickly repaired. For example, while high-intensity PA may transiently reduce mitochondrial function in skeletal muscle, PA rapidly stimulates muscle cells to restore and improve mitochondrial function and density, resulting in long-term benefit (68). In contrast, mitochondrial damage accrues more slowly over the normal aging process and without the activation of comparable repair and maintenance, contributing to gradual cellular senescence. Altogether, the inflammatory and oxidative stresses PA generates are countered by anti-inflammatory and antioxidative stress mechanisms. With continued PA, these compensatory processes amplify to the point at which habitual PA results in negligible amounts of net inflammation or oxidative injury (69). Further, because of allostasis (see above), PA stimulates tissues to increase their capacity and thus become better adapted to PA-induced stresses. It bears repeating, however, that while PA generates damage more acutely than aging, we hypothesize that PA also stimulates repair and maintenance mechanisms that are otherwise less strongly activated. Since long-term, habitual physical inactivity was rare until recently, including among the elderly, there was likely minimal selection to activate these mechanisms in the absence of PA. Consequently, the effects of PA on reducing morbidity and mortality appear to be greater in older than younger people (1, 2).

Effects of PA on Cardiovascular Disease and Cancer

To explore how integrating evolutionary and biomedical perspectives can advance our understanding of how and why PA helps slow some forms of senescence and reduce vulnerability to many diseases, we focus on two predictions of the nonmutually exclusive energy allocation hypotheses presented above. First, by augmenting and accelerating stresses, many of which also occur during the normal aging process, PA stimulates repair and maintenance responses less activated during prolonged physical inactivity. Consequently, lack of habitual PA, especially in postreproductive individuals, permits the accrual of pathogenic damage that might otherwise be repaired or prevented. Second, among individuals with access to abundant energy, regular PA prevents energy allocation toward excess fat storage and reproductive tissues that up-regulate inflammation and other pathogenic processes.

These two predictions apply to many causes of morbidity and mortality, but we apply them briefly to CVD and cancer, which together account for approximately two-thirds of deaths in high-income countries.

Cardiovascular Disease. CVD is currently the leading cause of mortality in high-income countries. Habitual physical inactivity is an undisputed, major risk factor for CVD along with hypertension, dyslipidemia, chronic inflammation, diet, stress, and genetics (70). The mechanisms by which PA provides protection from CVD are incompletely understood but include stimulating repair and maintenance processes that reduce pathophysiological damage to the heart and arteries, especially through a reduction in inflammation.

With regard to the hypothesis that PA promotes health by stimulating repair and maintenance in response to stress, the principal mechanical stresses PA exerts on the cardiovascular system are a combination of acute increases in arterial blood pressure and arterial blood flow. PA-induced surges in systemic blood pressure stress the vascular endothelium, leading to microdamage that triggers a wide range of beneficial growth, repair, and maintenance mechanisms. For example, PA-induced endothelial stress stimulates the release of nitrogen oxide (NO), which facilitates protective vasodilation and suppresses inflammation by inhibiting leukocyte chemotaxis and platelet aggregation (71). Repeated bouts of PA also stimulate the growth of capillaries and arterioles, thus lowering blood pressure during future PA as well as preventing hypertension during rest (72). Increases in arterial pressure and blood flow also stress the muscular walls of the heart chambers. Over time, repetitive bouts of aerobic PA stimulate adaptive cardiac remodeling characterized by balanced increases in left ventricular wall thickness and chamber volumes (eccentric hypertrophy) that reduce cardiac wall stress (73).

The sequence of pulsatile, time-limited pressure stress induced by PA followed by repair and recovery leads to an adaptive phenotype that contrasts markedly from the pathogenic effects of chronic hypertension. Like PA, chronic high blood pressure provokes the accumulation of microtears and endothelial dysfunction but, unlike PA, persistent hypertension does not stimulate significant repair. As a consequence, the progressively diseased endothelium, coupled with lipid dysregulation and vascular inflammation, is vulnerable to atherosclerotic plaque formation and its cardinal sequelae, chronic blood flow insufficiency and acute plaque rupture, leading to complete vessel occlusion. Similar differences occur within heart muscle. Whereas PA stimulates adaptive cardiac remodeling, chronic hypertension induces wall thickening without chamber dilation (concentric hypertrophy) and myocyte fibrosis, resulting in decreased diastolic compliance. This maladaptive phenotype is a leading cause of congestive heart failure (74).

The energetic tradeoffs PA causes also protect against CVD by down-regulating several pathophysiological processes predicted by the hypothesis that PA prevents energy allocation toward reproduction at the expense of health. Most obviously, energy spent on PA reduces energy allocation toward fat storage, especially ectopic fat in the liver and other visceral organs that is especially inflammatory and thus well-known to play a key role in the pathogenesis of arterial plaque formation (75). PA also reduces levels of chronic inflammation independent of body mass, largely because PA activates muscles to produce anti-inflammatory myokines (52, 54). Another energetic tradeoff by which PA helps prevent CVD is to reduce chronic elevation of sympathetic nervous system activity associated with sedentary behavior. PA transiently increases sympathetic activity to increase heart rate and cardiac muscle function, thus ensuring adequate blood flow delivery to active muscles, but habitual PA accentuates compensatory parasympathetic activity that facilitates rapid homeostatic recovery of heart rate and blood pressure following cessation of PA (76). As a result, habitual PA both improves autonomic recovery from isolated bouts of PA and enhances parasympathetic activity during rest, leading to lower blood pressure and heart rates as well as lower levels of resting cortisol.

Cancers. Cancers, the second-leading cause of death in high-income countries, are increasingly prevalent worldwide (7). Cancers arise from a perverse kind of natural selection within multicellular organisms: As cells accrue cancerous mutations they can become dysregulated, divide uncontrollably, migrate, and outcompete other cells. Cancers are more common with age, especially when cells have increased exposures to mutagens and when the immune system fails to recognize and eliminate them. Major risk factors for many cancers include smoking, alcohol, obesity, and systemic inflammation, but physical inactivity should not be underestimated: High-quality, prospective studies show a dose-dependent relationship between PA and several cancers, especially breast and colon cancer (3, 77, 78). According to some estimates, 3 to 4 h of moderate exercise per week reduces the risk of breast cancer by 30 to 40% in women and the risk of colon cancer by 40 to 50% in men and women (79).

Why PA helps prevent cancer partly makes sense in light of the hypothesis that PA favors energy allocation away from investments in fat and reproductive tissues. Energy spent on PA helps counteract excess accumulation of fat, especially visceral adipose tissue, a major contributor to chronic inflammation that can increase cancer risk via oxidative damage, hence DNA damage (80). By some estimates, overweight and obesity account for nearly one-third of breast cancer deaths in the USA (81). In addition, moderate levels of PA lower both adipocyte production of mitotic hormones like estrogen as well as ovarian production of estradiol and progesterone in normal-weight women by as much as 50% during the luteal phase of the menstrual cycle compared with sedentary women, thus significantly decreasing cancer risk in highly hormone-sensitive breast tissue (15). PA also lowers levels of insulin, which elevates the risk of several cancers (82). The energetic demands of PA also reduce bloodstream glucose levels, and thus may potentially retard tumor growth in cancerous cells with impaired oxidative phosphorylation that depend on glycolysis (83). PA is additionally theorized to help keep tumors quiescent by increasing their blood and oxygen supply, thus paradoxically preventing cancer cells from undergoing metabolic stress that activates their production of growth factors such as IGF1 (84).

The hypothesis that PA promotes health by stimulating repair also helps explain some of PA's preventive effects for many cancers. It bears repeating that PA generates copious free radicals (both reactive oxygen and nitrogen species) and proinflammatory cytokines that can contribute to DNA damage (Table 1). However, as Table 1 also summarizes (with references), PA has been shown in trained individuals to decrease DNA damage rates through three mechanisms. First, PA stimulates the dose-dependent production of antioxidants including superoxide

dismutase, glutathione peroxidase, and catalase. Second, PA stimulates skeletal muscle to produce short-term, abundant quantities of anti-inflammatory myokines (e.g., IL-6, IL-1ra, and IL-10), thus limiting unintended, largely nonspecific inflammatory damage. Finally, PA stimulates several DNA repair mechanisms including the TP53 tumor suppressor gene and the production and activity of key repair enzymes such as hOGG1, PARP1, and APEX1.

Importantly, many PA-induced DNA repair mechanisms act systemically and thus may protect against cancer growth in multiple tissues (85). PA has further been shown to modify the epigenome through DNA methylation and histone modifications (86–88), with some evidence suggesting that long-term methylation changes are retained with training (89). These modifications have been best studied at gene promoters through exercise-induced derepression of exercise- and metabolism-related genes such as PGC-1α, MEF2A, and TFAM (86–88), as well as alteration of the methylation status of cancer-associated genes (e.g., tumor suppressors such as L3MBTL1) (90). Overall, individuals who engage in regular levels of nonextreme PA have lower baseline levels of inflammation (e.g., CRP, IL-6, and TNF-α), oxidative damage (e.g., as measured by 8-OGdG and 8-oxodG), and both increased antioxidant and repair capacity.

Last, PA also helps protect against cancer by promoting repair and maintenance by the immune system. Because PA can generate plentiful cellular damage, it is unsurprising that there has been selection for PA to increase the production and mobilization of immune cells such as natural killer and cytotoxic T (CD8+) lymphocytes that seek out and clear damaged and decaying cells including precancerous and cancerous cells (91, 92). Rodent studies also indicate that PA helps redeploy these cells from the thymus and lymph nodes to the peripheral circulation, thus enhancing immunosurveillance (91). PA has been shown in mice to augment the influx of immune cells in tumors, and reduce tumor incidence and growth by an average of 60% (93). These mechanisms may also help clear deleterious senescent cells in many tissues.

Implications and Conclusion

All animals need to engage in regular PA but, at some point, hominins were selected to engage in significantly more PA than their comparatively sedentary ancestors to make possible our unique life-history strategy in which parents and grandparents gather and hunt surplus energy which they transfer to their children and grandchildren. A key component of this energetically intensive strategy is for postreproductive adults to stay healthy for several decades as they continue engaging in PA. These observations lead to the hypothesis that moderate levels of daily PA evolved not just as a consequence of humans' unique life-history strategy but also as a cause, because PA generates diverse stresses that induce manifold repair and maintenance mechanisms that are otherwise less activated because they cost energy and because humans were never regularly sedentary. In addition, PA diverts energy from excess fat storage and investment in reproductive tissues that can compromise long-term health in modern environments with superabundant energy. Altogether, PA stimulates the body to allocate energy in ways that slow senescence and prevent morbidity from CVD, many cancers, and numerous other chronic illnesses such as type 2 diabetes and Alzheimer's (7, 40). These conditions are rare among hunter-gatherers including the elderly (11).

Although it has long been known that PA extends both healthspans and lifespans, understanding why PA slows senescence and decreases vulnerability to many diseases has critical implications, most importantly to explain and emphasize why the older one gets, the more PA matters. According to Paffenbarger and colleagues' classic study, moderately active 70- and 80-y-olds have 50% lower all-cause mortality rates than sedentary individuals of the same age, sex, and socioeconomic status (1). In addition, PA levels need only be modest to confer significant benefits. The 2 to 4 daily hours of MVPA undertaken by elders in foraging populations (16, 17) is an order of magnitude greater than PA levels of average Westerners today (22), and more than six times the 150 min/wk of MVPA that major health organizations recommend as a minimum (4).

An evolutionary perspective also helps explain why a combination of endurance and resistance PA is beneficial (4). Given the importance of endurance PA for hunter-gatherers, it is unsurprising there was especially strong selection in the human lineage to adapt to the stresses aerobic PA induces. While resistance PA primarily benefits the musculoskeletal and cardiovascular systems, endurance PA stresses almost every system of the body and typically expends more calories, thus stimulating more widespread repair and maintenance responses and leading to enhanced energetic tradeoffs. High-intensity interval training is also beneficial by inducing elevated levels of stress and thus eliciting more acute responses (94). Some of the beneficial metabolic stresses PA induces are also stimulated by negative energy balance caused by intermittent fasting (95).

We recognize the challenge of finding epidemiological data to test definitively our hypothesis that the health benefits of PA derive not only from selection for humans to be physically active but also from selection for PA to allocate energy toward processes that extend healthspans. The ideal test would be a prospective comparison of two genetically similar populations, one sedentary and the other physically active, both of which lacked access to modern medical care. Although the sedentary population is predicted to have increased morbidity in older individuals along with reduced longevity, we know of no sedentary human populations that lack some degree of modern healthcare. Further, there is abundant evidence that lack of PA increases vulnerability to conditions such as hypertension, dyslipidemia, and insulin insensitivity that require medical treatment to prevent or mitigate premature mortality (2–8). In this respect, our hypothesis may help explain the seeming paradox of greater life expectancy in modern, sedentary Westernized populations than in traditional foraging societies. Leaving aside that greater life expectancy of modern, high-income-country populations stems largely from less infant mortality (11), increased lifespans in Western populations also result from access to medical care that has accompanied the extension of morbidities that are otherwise partly prevented by PA. Thus, as lifespan has increased in high-income countries, so has morbidity (40). Put differently, while sedentary individuals in industrialized environments with access to healthcare tend to have slightly longer lifespans than physically active foragers, we hypothesize they are less likely to have longer healthspans.

Phylogenetic comparative studies would be useful to test further the hypothesis that there was selection in humans for PA to allocate energy toward processes that extend healthspans. Although few species live beyond the age of reproduction and provide food as well as other resources not just to offspring but also to grandoffspring (F1 and F2 generations), more data are needed to compare the effects of PA on senescence and health in other long-lived species. In this respect, comparisons of wild versus captive animals are potential sources of

useful information. Compared with captive conspecifics, wild animals are generally more physically active, less likely to be overweight, and, although more vulnerable to predation, expected to have longer maximum lifespans. However, one study found that 84% of 59 captive animal species (males and females) have longer maximum lifespans with slower rates of senescence than wild conspecifics (96). Among apes, maximum lifespan of wild chimpanzees is 46 to 66 y, but captive chimpanzees can live up to 68 y (97, 98), and the maximum lifespans of wild and captive gorillas are 44 and 61 y, respectively (12, 99). In addition, experimental studies in rodents report either modest (100, 101) or nonexistent (102, 103) benefits of exercise for maximum lifespan, especially after controlling for food intake and body weight. These data highlight not just the limitations but also unrecognized potentials of animal models for studying the effects of PA on senescence and health. Since life history obviously differs between humans, rodents, and other species, looking for differences in the effects of PA on senescence between humans and model organisms may reveal vital targets of selection that help extend human healthspans and lifespans beyond the cessation of reproduction.

In conclusion, while more research is needed, integrating evolutionary and biomedical evidence to understand both how and why exercise is healthy is both useful and empowering. All animals evolved to be physically active when it was necessary and rewarding, but we propose that moderate levels of lifelong PA played a special role in the evolution of our species' uniquely extended life history. Today, billions of people no longer need to engage in much PA and thus have to choose to do PA—not just when they are young, but also as they continue to age. It is thus constructive to appreciate that exercise is not so much a magic bullet that guarantees good health and a long life but instead a normal, healthy form of physiological stress not unlike being occasionally hungry or exposing a child's immune system to enough challenges to develop appropriately. While modern medicine can cope with many of the mismatches caused by a lack of PA, and some mechanisms by which PA promotes health are pharmaceutical targets, it is impossible to put all the benefits of exercise in a pill. No medicine could possibly generate the diverse range of healthy stresses nor the equally diverse range of beneficial physiological responses PA stimulates. Fortunately, thanks to our evolutionary history, only modest levels of PA yield substantial benefits, especially if we keep them up as we age.

Data Availability. There are no data underlying this work.

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