CHAPTER

1 Exercise and sport: Definitions, classifications, and relevance to population health

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Introduction

When the human (and prehuman) genome was naturally selected, daily physical activity was critical for obtaining food and ensuring survival. For the most part, calories were obtained by hunting, scavenging meat, and foraging for vegetables and other staples.[1] Modern hunter-gatherer tribes also expend considerable energy in accomplishing a range of other activities. For example, both males and females have been observed walking several kilometers each day, navigating hilly and rocky terrain, to collect water and firewood, search for camp resources, and visit neighboring tribes.[2] The Hadza, a modern hunter-gatherer population residing in Northern Tanzania, exhibit levels of moderate-to-vigorous physical activity (MVPA) that are approximately 14-times greater than that of subjects participating in large epidemiological studies in the United States.[3] Accordingly, expending energy through physical activity was once a prerequisite for daily life, and such codependency shaped the cardiorespiratory, metabolic, and musculoskeletal systems of modern man (for review, see Ref.[4]). Physical activity and exercise are very much part of our DNA.

Presently, human genes and human lives are incongruent. Physical activity is no longer necessary to secure calories, our jobs are largely sedentary, and scarcely is a predominance of leisure time devoted to structured exercise. Instead, much of contemporary culture is characterized by a surplus of energy availability, inactive lifestyles, and all the technological contrivances the modern world can afford. In evolutionary timeframes, the cultural shift in modern society has been rapid, far outstripping the ability of genetic evolution to respond. Our misplaced lifestyles and behavior have birthed an obesity epidemic we cannot stem, and an increased incidence of noncommunicable diseases including cardiovascular disease, coronary heart disease (CHD), type II diabetes mellitus, and lifestyle-related cancers.[5] Indeed, with the exception of cigarette smoking, the leading risk factors for mortality (e.g., high blood pressure, high blood glucose, obesity) are directly associated with physical inactivity.[6] With growing concern for public health, there is now a greater emphasis on increasing population health through various lifestyle interventions including physical activity, structured exercise regimens, and participation in competitive sports which, collectively, reduce the risk of cardiovascular disease (CVD) and all-cause mortality.[7–9] A more robust understanding of the mechanisms underpinning disease, and the applied physiological adaptations associated with chronic exercise, is crucial for students, graduates, and practitioners alike.

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In this opening chapter of *Epigenetics of Exercise and Sport*, we first make a distinction among *physical activity*, *exercise*, and *sport*, overview the scientific consensus on the physical activity/exercise guidelines, and assess the disparity between those guidelines and the current estimates of population engagement. We then overview the myriad physiological benefits of regular exercise, with a focus on the individual responses to diet and exercise and our capacity for physiological adaptation, both of which are genetically and epigenetically determined. The question of how to determine the intensity of exercise prescription is addressed, with a focus on the various exercise intensity domains. Finally, we collate some novel data on exercise at the extremes, with an emphasis on the juxtaposition between the benefits of exercise and the pathophysiological consequences of long-term participation in ultraendurance sport. This chapter provides a framework for the remainder of the book and serves to contextualize the later discussions pertinent to epigenetics.

Defining physical activity and population categories

In an effort to mitigate the risks associated with physical inactivity, many are now implementing lifestyle changes to reduce sedentary time. But such changes may manifest in several forms. For example, structured exercise and competitive sport are both considered physical activities, but clearly not all physical activities (to include activities of daily living: ADLs) manifest as exercise or sport. Moreover, the organism will experience distinct physiological responses (both acute and chronic) depending on the nature of the activity. As such, it is first important to definitionally distinguish physical activity, exercise, and sport, and consider more broadly our conceptualizations of the "active lifestyle." The effectiveness of any intervention will also depend on its appropriateness for the individual; therefore, the population fitness subcategories warrant brief consideration.

Physical activity, as defined by the World Health Organization, is *any bodily movement produced by skeletal muscles that requires energy expenditure – including activities undertaken while working, playing, carrying out household chores, travelling, and engaging in recreational pursuits.*[10] Many individuals meet the physical activity guidelines through vigorous gardening, grocery shopping, and other manual tasks. Striving to augment levels of physical activity becomes more pertinent given the increased sitting time associated with sedentary jobs.[11] The primary distinction between physical activity and exercise is that the latter is planned, structured, and repetitive, and specifically undertaken for the propose of developing fitness in one-or-more body systems (e.g., cardiovascular, musculoskeletal). To obtain the benefits of exercise, it should be regular (at least 3–5 days per week, depending on the intensity) and considered of moderate-to-vigorous intensity. Examples include strength and/or aerobic exercise in the gym, jogging or running, cycling, swimming, and team sports. There is a gray area between the definitions because whether an intervention is considered *physical activity* or *exercise* will depend on the health/trained status of the individual. For instance, interventions centered on increasing daily steps (i.e., walking interventions) are likely to be very effective for improving health outcomes and facilitating weight-loss in individuals previously sedentary and/or overweight; and middle-aged and overweight individuals appear more likely to lose weight in the short-term (< 6 months) by following weight-loss interventions using activity trackers when compared to standard weight-loss programs.[12] Nevertheless, such interventions may not evoke substantial improvements in cardiovascular fitness in those who already exhibit above-average levels of activity (e.g., young, physically-active individuals) because the physiological stress may be insufficient.

In addition to regular exercise, many turn to competitive sport to maintain positive physical and mental health, and examples may include football, netball, hockey, competitive running/cycling/triathlon, racquet sports, etc. But the notion of a *sport* has also been contested, with a degree of ambiguity in the accepted definitions. The International Olympic Committee recognizes nonathletic events (like chess and bridge) as sports, but these do not bestow any physical health benefits beyond those associated with stress relief and psychological wellbeing, both of which are outside the scope of this discussion. Thus, definitionally-speaking, the sport does not necessarily confer a benefit to physical health. The sports contested at the Olympic Games are determined using five criteria set by the 90 members of the International Olympic Committee (IOC): (i) Olympic proposal (history of the sport, whether it has previously been included, the current level of worldwide participation); (ii) institutional matters (financial status of the sport, governance, and gender equity); (iii) value to the Olympic movement (the sport's image and whether it represents Olympic values); (iv) popularity (spectator number, sponsorship, media interest); and (v) business model (the potential income it will generate, costs of staging the sport). However, none of these criteria state physical prowess or technical skill as prerequisites. Given the importance of physical *exertion* for population health, the forthcoming chapters will invoke the term "sport" as *those activities requiring high levels of exertion, physical athleticism, or dexterity, which confer a benefit to physical health when practiced with sufficient frequency*.

Finally, whether you are a practitioner delivering coaching services to a client, a researcher embarking on data collection, or a clinician treating a patient, the fitness categorization of your subject warrants careful consideration. Indeed, an obese and sedentary individual with poor cardiorespiratory capacity—despite being at an increased risk of CVD—may have no preexisting illness. Similarly, a patient with a respiratory disorder or spinal cord injury may be an experienced competitive athlete. Depending on a holistic consideration of their trained status, exercise history, and long-term goals, the fitness category will largely inform the way in which one engages and works with the individual. Populations can generally be categorized into five groups based on their physical activity/exercise behaviors: (i) sedentary individuals; (ii) physically-active individuals; (iii) exercisers; (iv) amateur athletes; and (v) elite athletes. Sedentary individuals have inactive jobs (with long periods spent sitting), but they also do not regularly engage in physical tasks in the house or yard, and do not participate in structured exercise programs. Consequently, their physical fitness is usually quite low, which is considered an independent risk factor for noncommunicable disease (along with being overweight and sedentary). Estimates are that up to a quarter of American adults fall into this category.[10] Physically-active individuals are those who meet (but do not exceed) the minimum conservative guidelines for physical activity but do not engage in structured exercise regimens. So-called *exercisers* are concerned with maintaining and/or improving their health and fitness by engaging in semiregular exercise (~three sessions per week) through a structured or unstructured program but, importantly, they may still fall short of the physical activity guidelines. Individuals in this category, who also manage to meet or exceed the physical activity recommendations, likely exhibit the greatest benefits to health, along with those in the next group. Amateur athletes are interested in sporting performance although not at the elite level. They likely train in their chosen sport(s) for one-or-more hours per day, indirectly meeting the physical activity guidelines. Finally, elite athletes are concerned primarily with sports performance. They may train most days of the week, often several times per day, meeting and vastly exceeding the guidelines for physical activity. Despite a positive relationship between the amount of physical activity and reduced risk of CVD, athletic groups are often at risk of overtraining and/or relative energy deficiency (RED-S)[13] which can affect both males and females and may lead to chronic malnutrition

and/or insufficient recovery. Giving special consideration to the individual's exercise history, as well as clearly defining the nature of the intervention (physical activity, exercise, performance), will be crucial in further understanding the physiological adaptations likely to manifest with chronic training.

What are the physical activity guidelines, and are we meeting them?

Given the overwhelming data pertaining to the benefits of regular physical activity, exercise, and sport, particularly as preventative factors in all-cause mortality (see later), it should be incumbent on us to be familiar with the broad participation guidelines, and whether we (as a population) are following them. The American College of Sports Medicine (ACSM)—a longstanding authority for students, academics, practitioners, and physicians—no longer publishes physical activity recommendations but instead defers to the US Department for Health and Human Services (HHS) and their Physical Activity Guidelines for Americans.[14] Therein, the HHS makes four key statements. First, it is suggested that health benefits can be achieved by *moving more throughout the day* while avoiding long periods of sitting or sedentary behavior. Second, substantially greater physical benefits can be obtained by engaging in at least 150–300 min (2.5–5 h) of moderate-intensity aerobic physical activity per week (see section "Exercise intensity domains" for how to classify exercise intensity). Moreover, similar benefits may be seen with 75–150 min (1.25–2.5 h) of vigorous-intensity aerobic physical activity per week. Third, aerobic activity should preferably be spread throughout the week; i.e., participating in a single, very long (5 h) cycle ride once per week at a moderate intensity is less favorable than five daily bouts of 1 h. Fourth, additional health benefits are obtained by engaging in muscle-strengthening activities of moderate or greater intensity (on two-or-more days of the week) that involve all the major muscle groups of the body. These guidelines, while lacking specificity, reflect a scientific consensus among governing bodies and are mirrored by the American Heart Association (AMA) and the World Health Organization (WHO). Others suggest that daily exercise expending ~500 kcal/day most closely approximates the Paleolithic standard,[4] which approximates that required to perform 75 min vigorous exercise.

There are comprehensive statistics available on population-specific public health practice. From the Centre for Disease Control: *Public health surveillance is the ongoing systematic collection, analysis, and interpretation of outcome-specific data for use in planning, interpretation, and evaluation of public health practice.*[15] Yet, current estimates suggest that even the modest targets for physical activity are not being met. Approximately 27% of worldwide cases of diabetes and approximately 30% of cases of ischemic heart disease are the result of physical inactivity.[10] The Bureau of Labor Statistics reports that <20% of US adults were engaged in sport, exercise, or other active leisure pursuits each day in 2017; and of those regularly participating in exercise or physical activity, the most popular outdoor activities were jogging/running, fishing, and cycling.[16] When presented by country, the prevalence of insufficient physical activity was >50% in Kuwait, American Samoa, Saudi Arabia, and Iraq, and with physical inactivity generally greater in females versus males (Fig. 1A and B).[17] Moreover, in 2016, more than 80% of school-going adolescents did not meet the current recommendations for daily physical activity (Fig. 1C and D),[18] although a greater number (51%) participated in muscle strengthening exercises (e.g., push-ups, sit-ups, weight lifting) on three-or-more days of the week. In contemporary society, our interest in physical activity appears fleeting and dictated by cultural trends. For example, a 2018 survey of American adults found that "exercise more" comprised 13% of New Years resolutions,

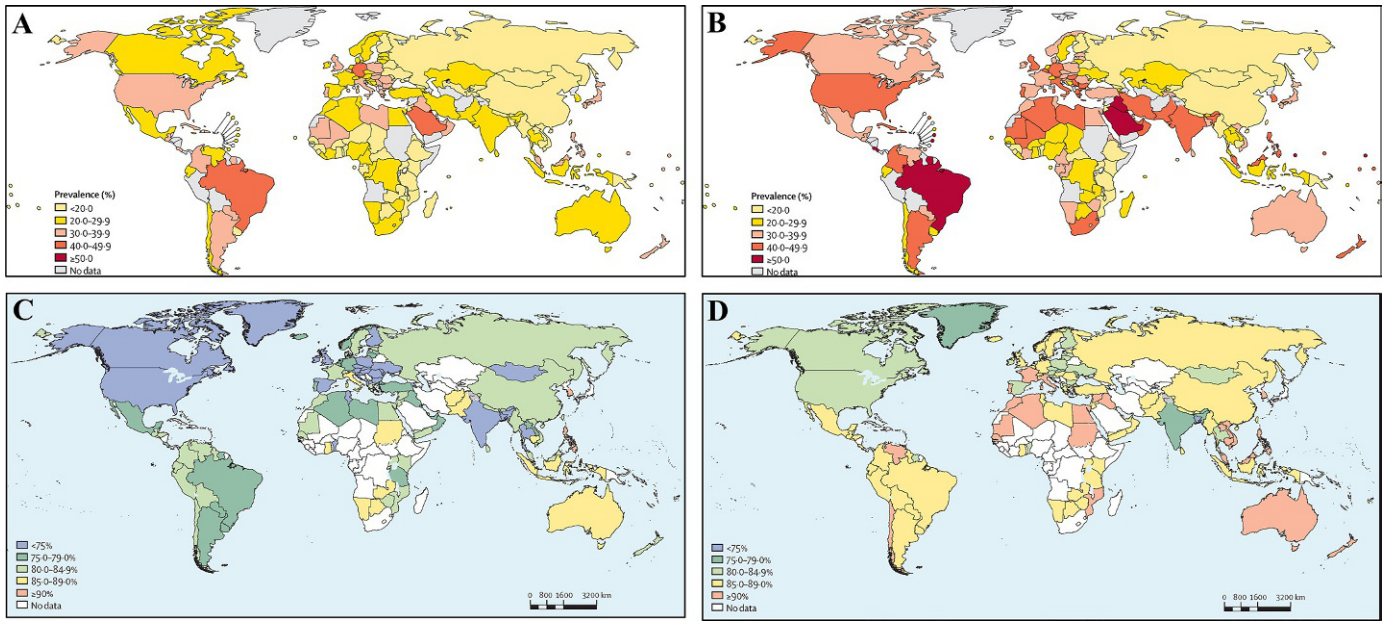

FIG. 1

Worldwide prevalence of insufficient physical activity among adult males (panel A), adult females (panel B), adolescent males (panel C), and adolescent females (panel D) in 2016. Adults aged 18+ years. *Lighter shades* represent countries more physically-active.[17,18]

closely followed by "quit smoking" and "lose weight".[19] Nevertheless, those with gym-memberships are significantly more likely to meet the recommended physical activity guidelines than nonmembers,[20] assuming continued use throughout the year. [21]

Notwithstanding the current statistics on underengagement, the trends appear to be improving. Data from the Centre for Disease Control reported population physical activity from 2008 to 2018.[15] In 2008, ~36% of American adults participated in no leisure-time physical activity, which decreased to ~30% by 2013, and to around ~26% by 2018; thus, reflecting a decrease of approximately 1% per year. These data are congruent with the numbers of people meeting the minimum aerobic physical activity guidelines, those meeting high aerobic physical activity guidelines, and those meeting muscle-strengthening guidelines. While the trend is encouraging, overall numbers meeting or exceeding the recommendations are still low and is reflected also in young people and adolescents. The guidelines for older adults (>65 years) are similar in duration and magnitude, relative to their younger counterparts, but statistics suggest that only 28%–44% of older adults are physically-active.[15] This, in turn, may accelerate the age-related decrease in skeletal muscle mass and functional capacity (sarcopenia) sometimes seen in older adults.[22] With such low numbers meeting the activity targets, there is clearly a need for better education on the benefits of physical activity, along with initiatives aimed at better understanding the reasons underpinning poor engagement and adherence.

Physiological implications of physical activity and inactivity

The association of regular physical activity and decreased risk of noncommunicable disease is ubiquitous. But before closer scrutiny of the specifics, it is worth noting that much of the exercise literature has focused on physical inactivity (manifesting as prolonged sitting) that characterizes modern lifestyles. Recent epidemiologic studies suggest that sitting time evokes cardiovascular and metabolic maladaptations that are independent of whether or not adults meet the physical activity guidelines. This is pertinent for individuals who engage in structured exercise but who are otherwise sedentary. Sedentary behaviors have been categorized by leisure time (e.g., watching television, playing video games, reading), occupational time (e.g., prolonged sitting at work in an office environment), and transportation time (driving or taking public transport), all of which are independently associated with increased risk and prevalence of cardiovascular diseases.[23] In a cohort of nearly 8000 men, Warren et al. found that riding in a car (and combined time riding in a car and watching television) were significant CVD mortality predictors; crucially, death rates due to CVD were notably lower in those who were otherwise physically-active.[24] As such, the physical activity helped to mitigate the sedentary-related increased risk of CVD. Collectively, these data suggest that interventions should focus on reducing sitting time, increasing daily time spent in MVPA, and adhering to a structured exercise/sporting regimen. Moreover, there is a dose-response in that more is generally better, although there are emerging data suggesting that extreme exercise behaviors may have detrimental effects (see section "Exercise at the extremes"). Given the independent association between prolonged sitting and CVD risk, several interventions have been proposed to reduce sedentary time, particularly, in the workplace.

A recent review from the Cochrane database studied workplace interventions for reducing sitting time.[11] Utilizing sit-stand desks (either alone or in combination with education and counseling) reduced sitting time by up to 100 min/day in short-term (3-month) follow-ups; nevertheless, most of the available evidence was deemed to be of low-quality due to limitations in study methodologies and small

sample sizes. Moreover, it remains to be seen if such a reduction in workplace sedentary time evokes physiological adaptations that translate to improved in long-term health. The review also reported that active workstations (e.g., treadmill or cycle desks) resulted in unclear or inconsistent effects on overall sitting time. One study utilizing sit-stand workstations to provoke frequent changes in body position observed reduced perceptions of lower-back pain in their subjects,[25] but more research in populations with preexisting lower-back pain is warranted. There are currently no studies evaluating the efficacy of standing or walking meetings for reducing sitting time at work although such data may prove insightful. In terms of reducing nonoccupational sedentary behavior, interventions may be effective in the short-to-medium term, but no significant effects have been observed chronically.[26] Accordingly, more high-quality data are needed before interventions like sit-stand/treadmill desks can be deemed efficacious, and more targeted approaches to increasing daily physical activity are, thus, worthy of consideration.

With respect to long-term weight-management, while many scientists and exercise professionals continue to debate the optimal means of weight-loss, it is likely that an overweight individual commencing a new exercise regimen will lose body fat by following any number of interventions. For example, there is robust evidence that pedometer-based walking initiatives lead to effective weight-loss,[27] as does resistance-training performed in conjunction with a calorie-restricted diet in overweight/obese patients with type II diabetes[28]; moreover, combined resistance-training and calorie-restriction was more effective than calorie-restriction alone.[28] Swimming also evoked decreases in body mass in obese women, as did walking, and water-walking, with no differences among groups after a 13-week intervention.[29] Overweight and/or obese individuals are likely, therefore, to exhibit decreases in body mass irrespective of the exercise regimen they follow, assuming it is prolonged and congruent with a healthy diet. The crucial component, therefore, is a structured program to which the individual will chronically adhere.

While physical activity that expends 1000 kcal/week results in a significantly reduced risk of all-cause mortality,[9] it appears that physical fitness is more strongly correlated with risk reduction than physical activity. Indeed, a meta-analysis published in the *Journal of the American Medical Association* (*JAMA*) studied published data from the last 40 years to further explore the association between cardiorespiratory fitness (quantified using maximal aerobic capacity; VO_2max) and the risk of cardiovascular events in healthy adults.[30] The authors calculated the risk ratio (RR; the probability of cardiovascular events) in a group with higher fitness levels relative to those with lower fitness levels. In practical terms, an RR of 0.5 denotes a relative risk half that of the norm (50% lower risk), and an RR of 1.5 indicates a 50% greater-than-average risk. The analysis showed that a 1-MET increase in maximal aerobic capacity reduced the RR to 0.87 and 0.85 for coronary heart disease/cardiovascular disease and all-cause mortality, respectively. In other words, having a maximal aerobic capacity that was 1-MET higher was associated with a ~15% decrease in CHD/CVD risk (Fig. 2). Such a reduction is likely to be clinically meaningful. Another review of studies with follow-up intervals ranging from 3 to 26 years reported a dose-response in which the incidence of mortality and cardiovascular disease (specifically, ischemic heart disease) was inversely related to physical activity; i.e., the greater the levels of physical activity, the lower the incidence of CVD.[8] Moreover, the findings were reported in a variety of populations and using a range of physical activity assessment modes. Notably, research suggests that modern hunter-gatherer tribes (The Hazda, discussed earlier) spend a mean of 134.9 ± 8.6 min/day in moderate-to-vigorous physical activity, which was estimated to be over 14-times greater than that observed in subjects participating in large contemporary epidemiological studies; the Hazda, in turn, exhibit no evidence of risk factors for cardiovascular disease across their lifespan.[3]

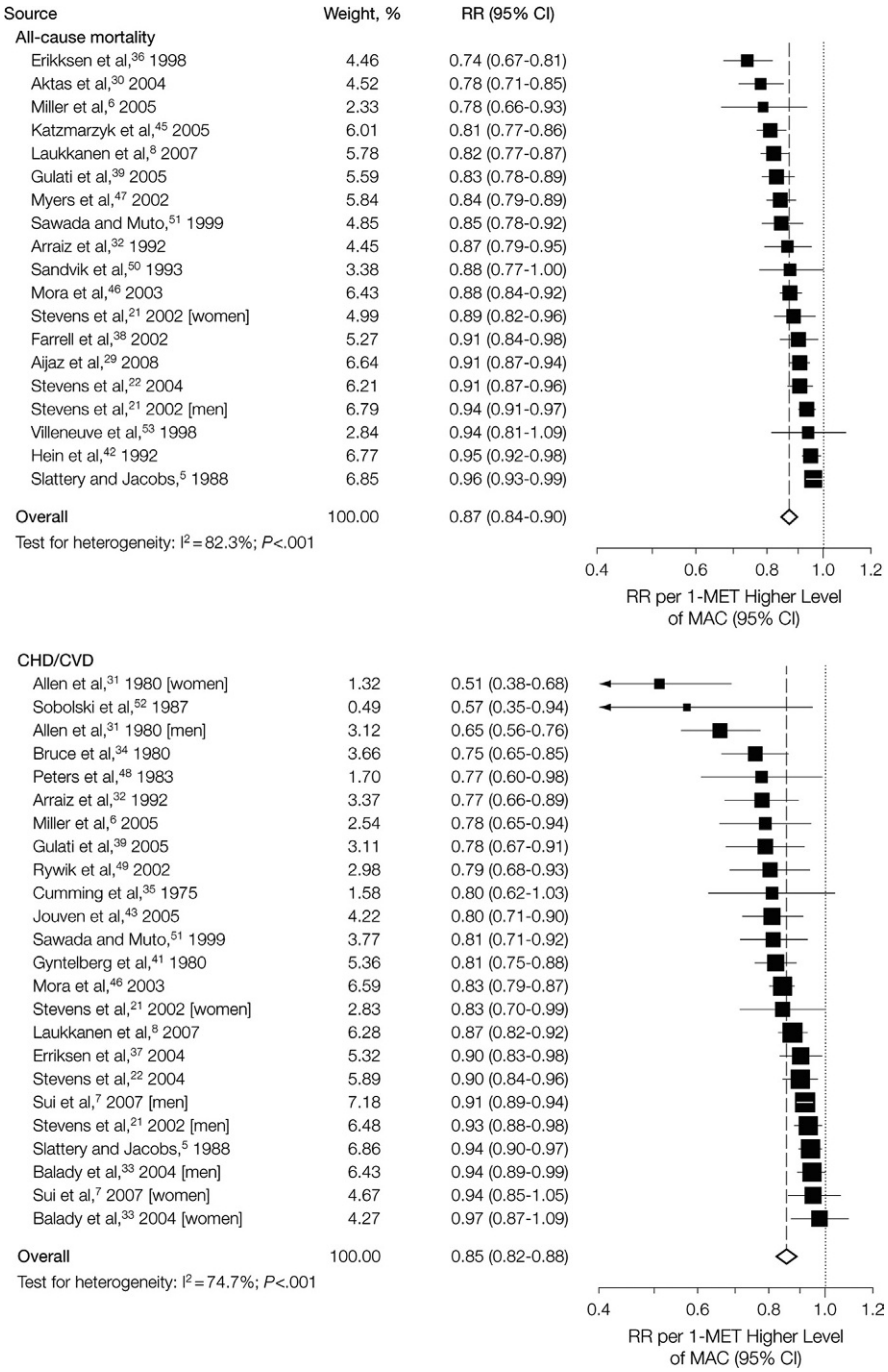

FIG. 2

A meta-analysis of all-cause mortality and CHD/CVD per 1-MET higher level of maximal aerobic capacity. A maximal aerobic capacity that increased by 1-MET would reduce RR by ~15%. *CHD*, coronary heart disease; *CI*, confidence interval; *CVD*, cardiovascular disease; *MAC*, maximal aerobic capacity; *MET*, metabolic equivalent; *RR*, risk ratio. The area of each square is proportional to the study weight.[30]

Exercise and physical activity have been widely studied as a means of addressing the worldwide obesity epidemic. In a review of databases for studies published between 2000 and 2015, Chin et al. determined that walking and low-intensity habitual physical activity (without additional dietary changes) evoked a weight-loss of 1%–1.5% body mass at 3–6 months postintervention; moreover, moderate-to-high-intensity exercise interventions resulted in 2%–3% weight loss within 6 months.[7] However, combined diet and exercise was associated with the greatest weight loss of between 8% and 11%.[7] According to the analysis, therefore, only diet and exercise in combination were sufficient to evoke the decrease in body weight deemed necessary for obese individuals.[31] Similar interventions have been studied in young people. Research from Kwon et al.[32] reports on the association between accelerometer-derived measures of physical activity and dual-energy X-ray absorptiometry (DEXA)-derived measures of body fat percentage, in a group of 493 healthy 5–19-year-olds (51% female). Those individuals who exhibited decreased physical activity with age had a greater risk of becoming obese in young adulthood relative to those who were consistently active throughout childhood and adolescence. Moreover, the authors reported that 45 min daily MVPA was sufficient to mitigate the risk of obesity in young adults. So, simply meeting the established physical activity guidelines may substantially reduce the prevalence of obesity during young adulthood in the West. While studies are short-term and conducted in educational settings, children and adolescents may significantly increase their walking time when utilizing goal-setting, planning, feedback and monitoring, social support, and repetition and substitution.[33]

The abovementioned research suggests that regular MVPA has a preventive role in cardiovascular disease, obesity, and several other noncommunicable diseases. It has been recommended that adults strive to emulate the routine physical activity patterns of our hunter-gatherer ancestors (in terms of frequency, intensity, time, and type; FITT) whose genome we largely share[34]; in turn, this may optimize epigenetic mechanisms of physiological adaptation, thereby conferring more robust health. A discussion of the numerous strategies of increasing population physical activity and exercise participation is outside the scope of this book; needless to say, any activity which increases daily energy expenditure and that requires moderate-to-vigorous physical exertion is likely to assist with long-term weight-management and improved cardiovascular outcomes, respectively, especially when such activity meets or exceeds the guidelines aforementioned. The optimal strategy should be individualized but must emphasize long-term adherence.

Exercise intensity domains

When engaging in/prescribing exercise, the FITT principle is a framework often utilized to encourage careful consideration of the frequency (how often the exercise is performed), intensity (how hard the workout is and, more specifically, how close one is working to their maximal capacity), time (the duration of the session), and type (the mode of exercise; e.g., cycle ergometry, treadmill ergometry, team-sport, etc.). All factors will vary depending on the trained status of the individual, and whether they have any preexisting medical issues or musculoskeletal injuries. For example, with respect to the frequency and duration of exercise, it is axiomatic that one must ensure a slow progression when embarking on a new exercise regimen, to allow sufficient time for physical adaptations that mitigate the risk of injury. Moreover, when considering type, it would be prudent for an overweight individual—with no history of exercise training—to avoid high-impact activities like running due to increased impact forces transmitted through the lower limbs[35] which may predispose them to pain and/or injury. However, relatively

less consideration is given to the exercise intensity at which sessions will be conducted. This is a crucial consideration for two reasons. First, while high-intensity training has been shown to be safe and effective for many, such exercise is contraindicated for those with chronic cardiometabolic conditions including unstable angina pectoris, uncompensated heart failure, recent coronary bypass intervention, exercise-limiting heart failure, complex ventricular arrhythmias or heart block, severe chronic obstructive pulmonary disease (COPD), uncontrolled diabetes mellitus, uncontrolled hypertension, severe neuropathy.[36] Second, the physiological adaptations associated with exercise training are unlikely to be optimal unless intensity is congruent with the targeted outcomes; indeed, different exercise intensities evoke different acute and chronic adaptations. This notion of duration and intensity-mediated adaptations has been comprehensively reviewed by MacInnis and Gibala[37] although the precise physiological responses associated with each exercise intensity are unclear owing to a lack of agreement in how such intensities are defined. It is, however, worth briefly noting the general adaptations associated with each intensity domain as this will also inform exercise prescription. Exercise, in general, is likely to positively influence mitochondrial content to improve aerobic capacity. Low-intensity exercise (that typically performed below the gas exchange threshold, and which may also be considered as an exercise of a *moderate-intensity*) is associated with improved aerobic endurance; increased distribution of slow-twitch (type I) muscle fibers, mitochondrial oxidative capacity, aerobic enzyme activity, substrate efficiency, and metabolic flexibility to aid in ATP resynthesis. Exercising above the gas exchange threshold, or engaging in exercise considered *heavy* in nature, will evoke more general increases in maximal aerobic capacity. Interestingly, at the whole-body level, $\dot{V}O_2$max is increased more by participating in high-intensity exercise (that characterized by short-duration sprint activity) when compared to moderate-intensity exercise for a given training volume.[37] There is less concrete information regarding the influence of exercise intensity on skeletal muscle capillary density, maximum stroke volume and cardiac output, and blood volume, but such adaptations are usually observed following a period of aerobic exercise training. The actual exercise intensity chosen will depend, therefore, on the goals of the exercise training program, and careful consideration should be given to the acute and chronic bodily responses associated with the various training intensities. To aid the reader, a graphical depiction of the principal types of aerobic exercise are shown (see Fig. 3).

Determining exercise intensity can be problematic because the training literature employs various classification tools, many of them nonspecific. Early exercise prescription was based on the Karvonen formula.[38] In their landmark 1957 paper, target heart rates for aerobic training were proposed based on various percentages of the heart rate reserve (HRR), which is first calculated by subtracting resting heart rate from maximum heart rate (HRmax − HRrest), the latter of which is established during an exercise stress test or estimated as 220 − age. Exercise target heart rate was then calculated with the following formula:

$$\text{Target HR} = \text{resting heart rate} + (\text{HRR} \times K)$$

Where K is a coefficient denoting the required intensity; light-intensity exercise is defined as that which elicits a heart rate of 30%–40% HRR ($K = 0.3$–0.4), moderate-intensity exercise elicits a heart rate of 40%–60% HRR ($K = 0.4$–0.6), and vigorous-intensity exercise elicits a heart rate of 60%–90% HRR ($K = 0.6$–0.9). Thus, an individual with a maximum heart rate of 200 b/min, and a resting heart rate of 60 b/min, exhibits an HRR of 140 b/min. For such an individual, the light-intensity exercise would be performed between 102 and 116 b/min while vigorous exercise would be performed at a work rate eliciting up to 186 b/min. Karvonen also assessed the physiological response to training at each intensity, finding that chronic training at high intensity was associated with a decrease in *working* heart rate, now understood to be the result of increased aerobic capacity and oxygen economy. Most importantly,

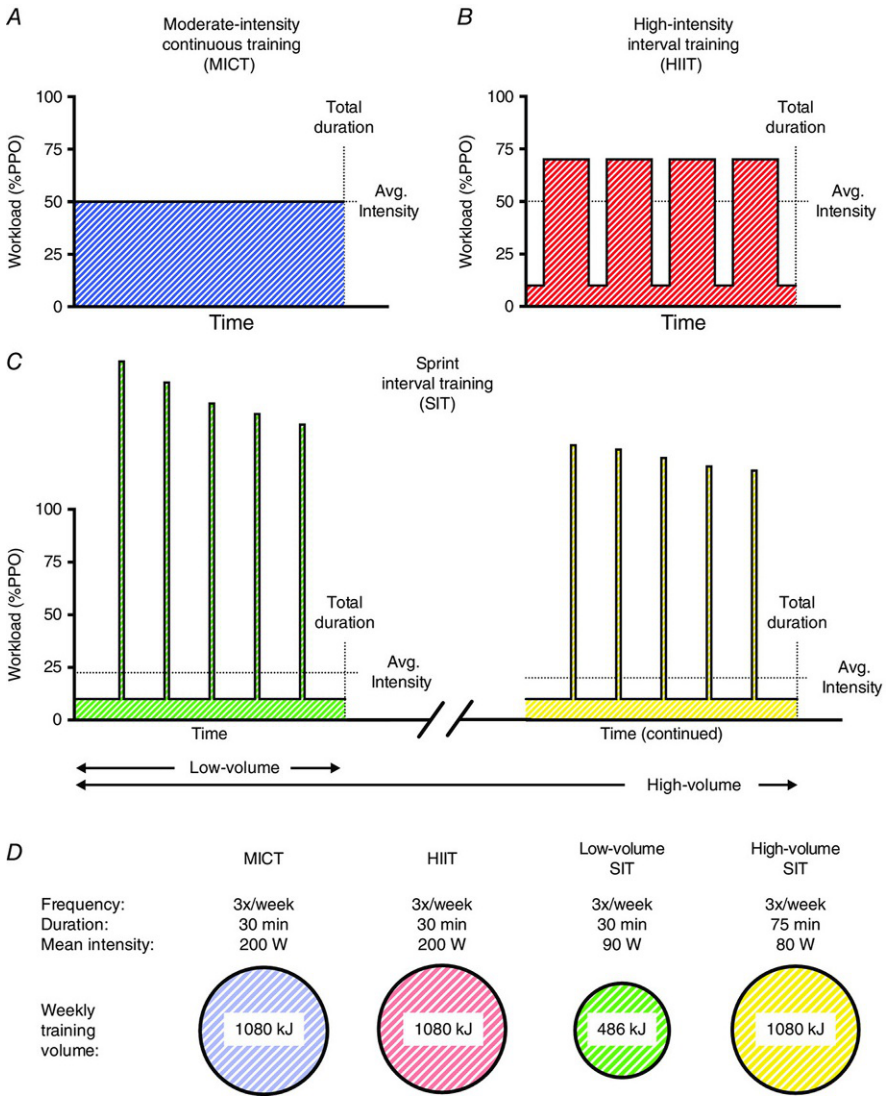

FIG. 3

Examples of moderate-intensity continuous training (MICT, panel A), high-intensity interval training (HIIT, panel B), and low and high volumes of sprint interval training (SIT, panel C). Example frequency, intensity, and durations for each session type (panel D). The intensity is depicted as a percentage of the peak power output (PPO) obtained during a standard incremental ramp test.[37]

it was Karvonen's study that identified 60% of HRR (vigorous-intensity exercise) as the critical threshold beyond which the greatest improvements in cardiorespiratory fitness were observed. While this simple formula might under- or overestimate exercise intensity in patients, the Karvonen formula was considered a general *rule-of-thumb* for many decades, especially in the absence of more accurate and comprehensive methods.

Many governing bodies prescribe exercise intensity in terms of the metabolic equivalent (MET). A MET is the ratio of energy expenditure during a given activity relative to the energy expenditure at rest; thus, the MET is a useful tool for quantifying the actual energy requirement of a task. Sedentary behavior evokes a MET of 1.0, while an activity of 5.0 METs requires an energy expenditure five times the resting rate. Physical activities have been compiled and categorized by their estimated MET values; leisurely cycling at 5.5 mph is estimated to evoke 3.5 METS while washing dishes has a MET value of 1.8.[39] The HHS Office of Disease Prevention and Health Promotion, in *Physical Activity Guidelines for Americans*, define light-intensity exercise as that evoking <3.0 METs (a slow walk), moderate-intensity activity is characterized by 3.0–5.9 METs (a brisk walk), and vigorous-intensity activity (>6.0 METs) can generally be achieved with a steady run.[14] The American Heart Association offers further examples of *moderate-intensity aerobic activities*, including brisk walking (at least 2.5 miles per hour), water aerobics, dancing (ballroom or social), gardening, tennis (doubles), and biking slower than 10 miles per hour. Examples of *vigorous-intensity aerobic activity* include hiking uphill or with a heavy backpack, running, swimming laps, aerobic dancing, heavy yard work like continuous digging, tennis (singles), cycling 10 miles per hour or faster, and jumping rope. While the above examples are broad and lack individualization, they are clearly written with the intention of making decisions about exercise intensity easy and accessible to all. The HHS also suggest rating the perceived "effort level" on a numbered scale, where moderate-intensity activity would be denoted by an effort level of 5–6 out of 10 (where "0" reflects the level of effort of sitting and 10 is maximal effort), and vigorous-intensity activity begins at 7–8.

Exercise training according to *perceived exertion* is common across all levels of ability, particularly when heart rate data are unavailable. Structured tools like the Borg Scale of Perceived Exertion[40] have proven very effective in both clinical and performance environments, as well as in the research context. The scale associates perceptions of exercise exertion with a 6–20-numbered scale anchored by "no feeling of exertion" (6) and "very, very hard" (20), which were selected to approximate resting heart rate (60 b/min) and maximum heart rate (200 b/min), respectively. Multiplying the Borg score by 10 gives an estimation of heart rate for a particular level of exertion. Indeed, activities evoking a *moderate intensity* register 11–14 on the scale (i.e., *fairly light* to *somewhat hard*), while *vigorous activities* are rated >15 (i.e., *hard* to *very, very hard*). The Borg Scale was published with a clear set of instructions about the accurate interpretation of the perceptual scale, on the premise that the instructions be read, in their entirety, to subjects before exercise (Fig. 4). The scale has been modified and updated several times over the last few decades, with independent scales developed for surveying dyspnoea (breathlessness) during exercise. There are advantages and disadvantages to the perceived exertion scales aforementioned. On the one-hand, such numbered charts are accessible, intuitive, and require no complex equipment or costly technology; thus, it can serve as a basic tool for estimating perceived exertion and exercise intensity in lieu of more sophisticated means. However, the scale has been criticized for its lack of appreciation of individual variations in resting and maximum heart rates, as well as concerns that accurate ratings require a nuanced understanding of the perceptual scale, as well as exercise experience and knowledge-of-self. Perceived exertion can also be influenced by mood and other psychological factors.

Any method that fails to account for interindividual variance in heart rate and metabolic thresholds is in danger of leading to the erroneous prescription of exercise intensity. From a scientific perspective, exercise intensity domains can be harnessed to a greater level of accuracy by utilizing a

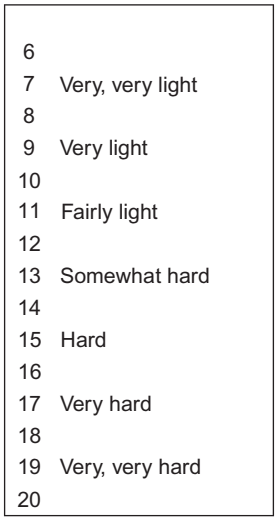

FIG. 4

The Borg 6–20 scale of perceived exertion, and the instructions offered to exercise subjects to aid in the subjective interpretation of the scale.[40] Instructions: "While doing physical activity, we want you to rate your perception of exertion. This feeling should reflect how heavy and strenuous the exercise feels to you, combining all sensations and feelings of physical stress, effort, and fatigue. Do not concern yourself with anyone factor such as leg pain or shortness of breath, but try to focus on your total feeling of exertion. Look at the rating scale below while you are engaging in an activity; it ranges from 6 to 20, where 6 means "no exertion at all" and 20 means "maximal exertion." Choose the number that best describes your level of exertion. This will give you a good idea of the intensity level of your activity, and you can use this information to speed up or slow down your movements to reach your desired range. Try to appraise your feeling of exertion as honestly as possible, without thinking about what the actual physical load is. Your own feeling of effort and exertion is important, not how it compares to other people's. Look at the scales and the expressions and then give a number."

Modified by the CDC from Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med. 1970;2(2):92–98.

physiology testing laboratory and congruent interpretive expertise. If such facilities are available, then the individual may choose to undergo ramp incremental or step testing in order to determine their submaximal and maximal capacities. The lactate threshold test has become a staple for endurance exercisers in the developed world, particularly at the elite level. The test involves performing steady-state exercise on a cycle, rowing, or treadmill ergometer in 3–4 min bouts of steadily-increasing work rate; heart rate, rating of perceived exertion (RPE), and pin-prick blood lactate samples are collected at the end of each stage for further analysis. After interpretation by a qualified exercise physiologist, the two lactate thresholds can be used to determine precise heart rate zones for training at predetermined intensities to elicit a given adaptation. Indeed, by determining the individual gas exchange and/or lactate threshold,[41] more targeted and individualized approaches can be prescribed to maximize the physiological adaptation to exercise.

More recently, a new model for the normalization of exercise intensity was proposed by Lansley et al.[42] Using gas exchange data derived from an incremental ramp exercise test, moderate-intensity exercise was determined as that which would elicit 80% of the gas exchange threshold. The heavy and severe exercise was deemed to be performed at a power output or speed equivalent to 20% and 60% of the difference between gas exchange threshold and VO_2max, respectively. While these physiological measures may not be accessible to all, such data allow for further individualization of exercise intensity.

Exercise at the extremes

Despite the robust empirical association between regular exercise and a decreased risk of mortality and myriad noncommunicable diseases, data are emerging to suggest that long-term participation in extreme exercise behaviors may result in disease pathology due to substantial physiological stress on multiple body systems. Ultraendurance exercise is that which lasts for more than 6 h in a single bout.[43] Participation in ultramarathon running, specifically, has steadily increased over the last 30 years.[44] In response to both Ironman triathlon and ultramarathon running, there are reports of acute (transient) reductions in right ventricular ejection fraction,[45] with long-term participation causing pathological changes in cardiac structure, function, and electrical activity (for review, see Ref.[46]). Evidence of myocardial fibrosis was observed in 6/12 veteran endurance athletes when compared 0/12 in age-matched veteran controls or young athletes.[47] Moreover, fibrosis prevalence was not associated with age, height, weight, or body surface area but was significantly associated with the number of years spent training, the number of completed marathons, and ultramarathons.[47]

Single-stage ultramarathon also provokes a pre- to postrace respiratory muscle fatigue, and postrace reductions in pulmonary function (for review, see Ref.[48]); while postrace decreases are rarely observed to be clinically significant, there may be clinical manifestations in individuals with below-average baseline function, or those with preexisting respiratory disorders (e.g., asthma). Finally, gastrointestinal (GI) distress is a commonly-cited reason for ultramarathon noncompletion[49] and is associated with intestinal tight-junction damage, and the acute release of endotoxins into the systemic circulation,[50] the repeated exposure to which may lead to a low-grade inflammatory state.[51] Collectively, the literature suggests that ultraendurance exercise is sufficient to cause acute physiological dysfunction and may be associated with chronic maladaptations of the respiratory, cardiovascular, digestive, and immune systems.[52,53]

Importantly, not all individuals exhibit pathological outcomes with chronic participation in ultraendurance sport, and we must be cautious not to deter individuals from regular, demanding exercise by failing to contextualize the possibility of pathological maladaptations. It is most likely that only certain individuals, or lifelong athletes, are susceptible to negative outcomes, and more research is needed to identify these subgroups, in addition to elucidating the mechanisms that render them more vulnerable. And while there is a much greater risk of pathology with chronic physical inactivity, there is likely a compromise between the two extremes that will offer the greatest physical and psychological benefits for the greatest number of people.

Individual responses to diet and exercise

Exercise is known to affect the body systems in some fairly predictable ways. Acutely, for example, physical activity will evoke an increase in both heart rate and stroke volume (to augment cardiac output), with few exceptions among individuals. Chronically, the exerciser will likely exhibit increases in cardiovascular health, oxygen uptake capacity, and muscle strength. Nevertheless, the extent to which an individual might adapt is finite and largely dependent on their inherited genetic predisposition. For this reason, the population-level data we have at our disposal should not be confused with how exercise affects the individual. It is axiomatic that some individuals have a greater propensity for training-induced adaptations, be it strength or endurance. For instance, Kenyan and Ethiopian athletes have dominated distance running events for several decades; their success is postulated to be the result of several factors, but predominantly a better running economy mediated by somatotype,[54] and also perhaps chronic exposure to altitude.[55] Importantly, there is a conservative limit on the extent to which their physical makeup can be influenced by training.

To further explore this notion of genetic predisposition, this section will highlight four compelling examples from the domain of exercise physiology/nutrition. Caffeine is a potent ergogenic aid, used as a stimulant for sports performance.[56] Its primary mechanism is to block adenosine-binding in the brain, thereby improving alertness and cognitive function. But caffeine metabolism is largely mediated by the cytochrome enzyme P-450 1A2, which itself is genetically variable. Recent studies in humans and other animals suggest that polymorphisms in adenosine A_1 and A_{2A} receptors mediate the individual response to caffeine, dictating behavioral responses, its effects on the sleep cycle, and arousal.[57] Indeed, A_{2A}-knockout mice exhibit no changes in wakefulness in response to caffeine.[58] Accordingly, genetic predisposition largely mediates caffeine sensitivity at the individual level, thereby mediating its potential as an ergogenic and explaining the range in individual sensitivity.

The response to carbohydrate (CHO) ingestion and other aspects of substrate metabolism are also in large part genetically-determined. Carbohydrate plays a crucial role in high-intensity exercise performance, with athletes recommended to consume 60% of their energy from CHO.[59] Nevertheless, there are data to suggest a range of individual tolerances to CHO intake. Amylase is a digestive enzyme produced in the salivary glands and pancreas that breaks the molecular bonds of starch molecules into smaller saccharides (sugars) including small amounts of glucose.[60] But salivary amylase content is highly variable and, of the genetic factors that mediate salivary concentration, copy number variation (CNV) in the AMY1 gene that codes for salivary amylase appear to play the predominant role. A paper published in *The Journal of Nutrition* found that, following the ingestion of starch, individuals with high salivary amylase activity exhibited significantly lower postprandial blood glucose concentrations relative to those with low amylase activity,[61] a difference that remained for at least 75 min. Interestingly, when pure glucose was ingested, high and low amylase groups showed no difference in terms of glucose response. Moreover, dietary carbohydrates, particularly sugars, contribute to increased liver fat accumulation, and recent genome-wide studies implicate several polymorphisms that increase liver-fat accumulation. Specifically, the patatin-like phospholipase domain-containing protein 3 (PNPLA3) gene, highly prevalent in Hispanic populations, contributes to excessive liver fat.[62] Genetic factors, therefore, are largely responsible for differences in both caffeine and CHO tolerance among individuals.

Congruent with CHO sensitivity, genetics influence the various rates at which individuals oxidize fat. While there are numerous studies that have made mechanistic links among obesity, genetics, and diet/physical activity, only recently was a model proposed on how to utilize these data to make individualized diet and exercise recommendations. A study published in *Nutrients* examined the interaction between genetic variation and changes in dietary ($n=4293$) and exercise ($n=3343$) habits that influence body fat.[63] From nearly 700 obesity-related single nucleotide polymorphisms (SNPs), a total of 100 were used to calculate genetic risk scores (GRS; 37 for carbohydrate, 19 for fat, 44 for total calories, and 25 for exercise onset). Based on the GRS distribution, the population was then categorized by sensitivity, with the main finding that mean body fat loss became larger when the sensitivity level increased. The authors concluded that genetic variants influence the effectiveness of dietary regimens for body fat loss (Fig. 5). Their research paved the way for genome-based personalized fat-loss programs based on the nutritional or exercise components that require modulation, and a greater appreciation of epigenetic influences on health and performance. Not only might such data have major implications for the growing obesity epidemic, but also for endurance exercise performance which is, to a very large extent, dependent on the individual capacity for fat oxidation.

Finally, studies related to the angiotensin I-converting enzyme (ACE) polymorphism have elucidated how a single genetic factor might mediate a complex phenotype associated with sporting ability. The gene was discovered around the turn of the millennium and was the first genetic element demonstrated in studies to potentially impact human performance. The ACE insertion/deletion polymorphism, specifically the I-allele, has been associated with endurance events including triathlon and metabolic efficiency in elite mountaineers. The D-allele has been associated with performance in sports with an emphasis on strength and power.[64] With respect to the present discussion, the ACE gene has been shown to act at a local level, influencing left ventricular cardiac mass in response to a training stimulus, and those with the D-allele likely exhibit a more potent cardiac response. Despite these findings, the importance of the ACE gene has been contested,[65,66] and other molecular mechanisms likely play an important role in physiological adaptation to training. Epigenetics is the study of processes that evoke changes in the functioning of an organism by modifying gene expression but without altering DNA code sequence. Not only have epigenetic factors been shown to regulate ACE expression,[67] but such molecular mechanisms likely have a powerful influence on exercise and sports performance (for review, see Ref.[68]). It is these epigenetic factors that are the focus of the forthcoming discussions.

In summary, the aim of this chapter was to introduce the topic of exercise and sport, discuss the statistics of participation, and highlight some of the physiological benefits to human health. Perhaps most importantly, we have revealed how the responses to exercise training are individual, and there is no one optimal strategy for all. Maximizing physiological adaptations—either to improve health or enhanceperformance—will depend on an understanding of scientifically-derived guidelines on exercise training, congruent with an appreciation of individual needs and responses. Importantly, the highlighted research emphasizes the importance of genetic predisposition but also points to ways in which nongenetic gene expression (epigenetics) might be a crucial means of influencing and optimizing individual outcomes. This, in turn, will allow for more bespoke recommendations with respect to exercise training and diet.

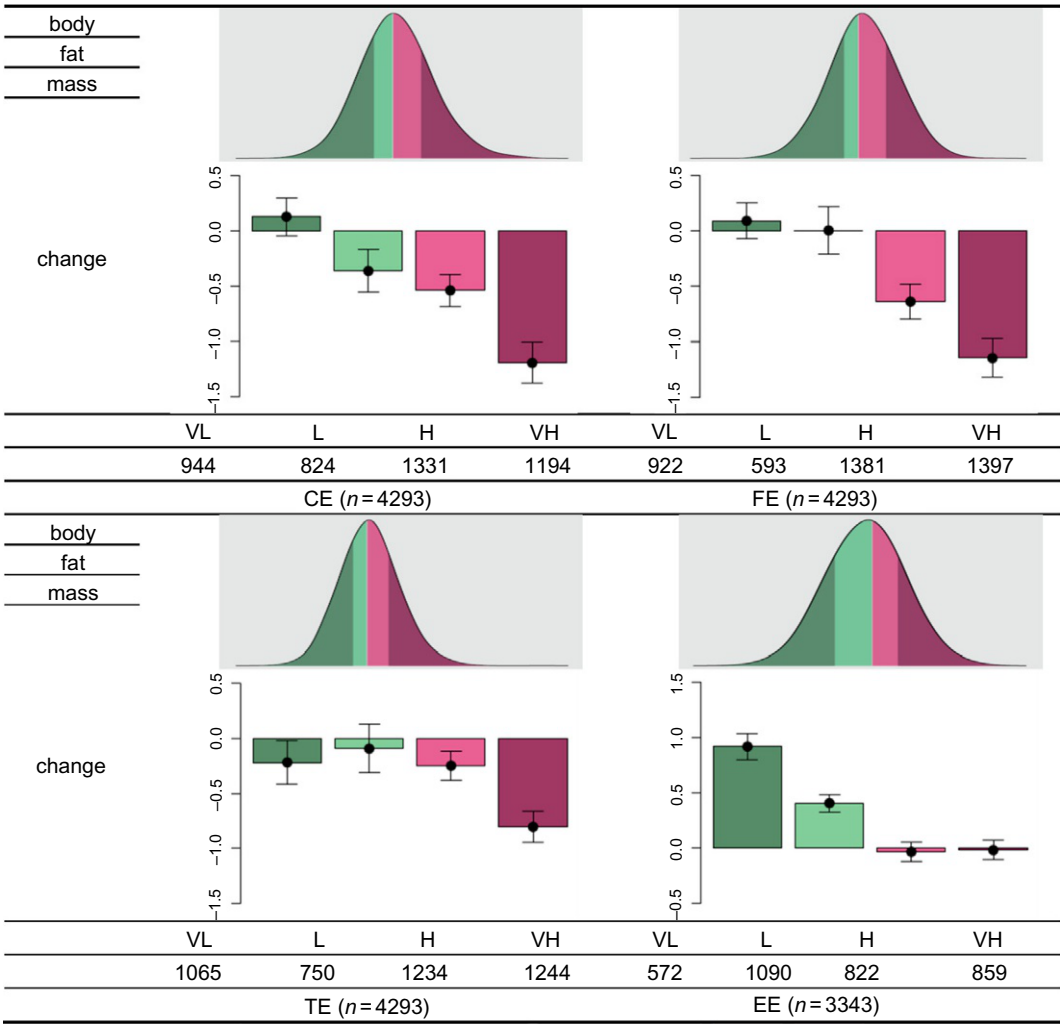

FIG. 5

Distribution of genetic risk scores (GRS) and within-group changes in body fat as a function of changes in diet or exercise regimen. Each individual's GRS can be calculated to measure changes in carbohydrate intake (CE), fat intake (FE), total calorie intake (TE), and exercise status (EE). To determine the effectiveness of body fat loss, "very low" (VL) was defined to range from the minimum of GRS and the value less than the 25th percentile. The "low" (L) level ranges from the value larger than or equal to the 25th percentile and 50th percentile, "high" (H) includes values larger than or equal to the 50th percentile and less than the 75th percentile, and "very high" (VL) corresponds to values larger than or equal to the 75th percentile. Among individuals with greater than 75 g reduction in carbohydrate intake, the mean change in body fat in individuals grouped to CE-VL was 0.13, −0.37 for the group CE-L, −0.54 for the CE-H group, and −1.19 for the CE-VH group. Among individuals with at least 13 g reduction in fat intake, the mean changes in body fat were −0.22, −0.095, −0.25, and −0.80 for the groups FE-VL, FE-L, FE-H, and FE-VH, respectively. Among individuals with at least 478 kcal reduction in total calorie intake, the mean changes in the body fat were 0.093, 0.0055, −0.64, and −1.14 for the groups TE-VL, TE-L, TE-H, and TE-VH, respectively. Among individuals who experienced exercise onset, the mean changes in body fat were 0.92, 0.41, −0.033, and −0.018, respectively.[63]

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