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REVIEW ARTICLE

Potential Long-Term Health Problems Associated with Ultra-Endurance Running: A Narrative Review

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Abstract
It is well established that physical activity reduces all-cause mortality and can prolong life. Ultra-endurance running (UER) is an extreme sport that is becoming increasingly popular, and comprises running races above marathon distance, exceeding 6 h, and/or running fixed distances on multiple days. Serious acute adverse events are rare, but there is mounting evidence that UER may lead to long-term health problems. The purpose of this review is to present the current state of knowledge regarding the potential long-term health problems derived from UER, specifically potential maladaptation in key organ systems, including cardiovascular, respiratory, musculoskeletal, renal, immunological, gastrointestinal, neurological, and integumentary systems. Special consideration is given to youth, masters, and female athletes, all of whom may be more susceptible to certain long-term health issues. We present directions for future research into the pathophysiological mechanisms that underpin athlete susceptibility to long-term issues. Although all body systems can be affected by UER, one of the clearest effects of endurance exercise is on the cardiovascular system, including right ventricular dysfunction and potential increased risk of arrhythmias and hypertension. There is also evidence that rare cases of acute renal injury in UER could lead to progressive renal scarring and chronic kidney disease. There are limited data specific to female athletes, who may be at greater risk of certain UER-related health issues due to interactions between energy availability and sex-hormone concentrations. Indeed, failure to consider sex differences in the design of female-specific UER training programs may have a negative impact on athlete longevity. It is hoped that this review will inform risk stratification and stimulate further research about UER and the implications for long-term health.

Key Points

Physical activity is preventative against all-cause mortality, but there is growing evidence that ultra-endurance running (UER) may have pathological implications for multiple body systems.

In susceptible individuals, the most noteworthy maladaptations occur in the cardiovascular system (particularly right ventricular dysfunction), and the renal and musculoskeletal systems.

More epidemiological studies with larger cohorts are needed to better elucidate the complex pathophysiology of long-term health problems in UER.

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1 Introduction

Ultra-endurance running (UER) can be defined either by running distance (races that exceed the marathon distance of 42.195 km) or running time (exceeding 6 h), including multi-day or multi-stage events [1]. The popularity of UER has increased over the last 2 decades [2] and, in 2019 alone, over 669,000 runners contested more than 7000 UER events around the world [3]. Participation in UER decreased significantly in 2020 due to the worldwide coronavirus disease 2019 (COVID-19) pandemic [4]. To date, research in UER has focused predominantly on acute injuries and medical problems, as well as physiological, biochemical, nutritional, performance, and training-related aspects [5–11]. More recently, researchers have inquired into the long-term effects of prolonged and strenuous exercise, particularly as UER is one of the most physiologically demanding sports that can potentially lead to long-term health-related issues [12, 13].

Although it is well established that regular physical activity confers important health benefits and can prolong life [14, 15], there is a growing body of knowledge suggesting that repeated bouts of extreme exercise (such as UER) may have negative implications on long-term human health [13, 16]. Long-term health problems have been defined as conditions that last at least 1 year and that require ongoing medical attention and/or limit activities of daily living [17]. However, owing to a lack of longitudinal data, the extent of long-term health issues related to UER is not decisively known. A further unknown is the extent to which pre-existing conditions may increase athlete susceptibility.

Participation of youth (< 19 years of age), masters (> 35 years of age), and female athletes in UER has increased exponentially over the last few years [18–22], and each group deserves special consideration owing to their greater potential for long-term health issues in this sport [23]. For example, young and physiologically less mature UER athletes may suffer more exercise-related injuries than their older and more experienced peers, and extreme bouts of exercise starting at a young age resulting in stress on an immature and developing body may lead to long-term health issues [24, 25]. Similarly, masters athletes may also be at increased risk due to pre-existing health conditions that may be exacerbated by prolonged training and racing [26, 27]. Special consideration should also be given to the female athlete due to interactions between menstrual function and bone health [28].

This article will review the available evidence underpinning the potential long-term health problems associated with UER. To contextualize the main discussion, we first provide a short overview of the participation trends, training demands, and performance aspects, to better understand the demands and trends of UER. Thereafter, we present a synopsis of some of the most influential studies examining the possible association between UER (and endurance sports in general) and clinical health problems. This is organized by key organ systems (e.g., cardiovascular, pulmonary, musculoskeletal system) that, according to available data, are most likely to be influenced by UER, with key findings summarized in Table 1. The authors present considerations for the prevention, monitoring, and management of these potential health problems, and offer directions for future research into the pathophysiology of UER. It is hoped that this review will inform medical best-practice in UER, as well as stimulate more open debate about the potential implications for long-term health.

2 Methods

The first author (VS) organized the author group in January 2021 to include recognized experts in UER from different regions of the world and with a variety of backgrounds (sports scientists and medical specialists from family medicine, sports medicine, cardiology, internal medicine, pediatrics, and orthopedics). In a series of online meetings, and via email correspondence, the authors conceived the aims and objectives of the review. Thereafter, each author drafted a section that aligned with their respective expertise and a first draft of the manuscript was subsequently developed and reviewed by all other authors. After several rounds of discussion and refining the document, each author approved the final work. All communications and discussions were performed electronically.

UER is defined as any running distance over the standard marathon (> 42.195 km), timed events over 6 h, or multi-day, multi-stage events [1]. Youth athletes are defined as athletes under the age of 19 years [24] and masters athletes as those over the age of 35 years [29]. Long-term health problems have been defined as conditions that last 1 year or more and/or require ongoing medical attention or limit activities of daily living or both [17].

For the review to be comprehensive, the authors opted not to restrict studies to any given race type (e.g., single-stage vs multi-stage, road vs trail, uphill vs downhill), and while the literature search focused on responses specifically to UER (i.e., footraces), data from other ultra-endurance sports (with similar pathophysiology) were included where necessary to inform expert opinion. Articles were found primarily via three online databases (PubMed, MEDLINE, Google Scholar; with no date restrictions) with search-terms comprising the relevant body system (e.g., cardiovascular, respiratory, etc.) alongside various combinations of the following: long-term; chronic; ultra-endurance; ultra-marathon; ultramarathon; running; extreme-endurance; physiology; pathophysiology; injury; illness; disease. The reference lists of those articles included were then manually searched for additional literature. All relevant article types (meta-analyses, systematic reviews, randomized controlled trials [RCTs], exploratory studies, confirmatory studies, and case reports) were included but precedence was given to high-quality research (meta-analyses and RCTs). We have also provided details in the text regarding the nature of any given study.

3 Participation Trends

Participation in UER has increased considerably over the last 2–3 decades, exhibiting an exponential increase that has slowed slightly since ~ 2016 [2]. In adults, the increased participation is largely attributed to female and masters athletes [2, 18, 30, 31]. The 50-km distance is the most popular, with most finishers originating from the USA and France [2], followed by the 100-km event wherein most finishers originate from Europe, especially France [2, 32]. Relevant

Table 1 Summary of key findings from the reviewed literature by organ system, with expert opinion on mitigation, management, screening, and future research

Organ system	Main findings	Mitigation/management	Screening	Future research
Cardiovascular	UER is generally safe with respect to cardiovascular health. In susceptible people, possible cardiac damage, myocardial inflammation/fibrosis, increased risk of AF.	Follow-up of susceptible individuals (e.g., previous cardiac issues). Consider adequate rest after UER events. Consider role of alcohol and other factors as contributors to AF.	Currently under debate. Possibly required in youth and masters athletes with long history of training.	What makes an athlete susceptible? Studies to determine if pathology due to training or periodic racing.
Respiratory	Acute respiratory dysfunction is common. Plausible that UER athletes exhibit similar (or higher) rates of cold-air-induced airway damage versus other endurance sports.	Chronic issues more likely when training in cold/dry conditions. Be cognizant of air quality.	Individuals with pre-existing respiratory disorders (e.g., asthma) and/or those with respiratory symptoms (e.g., cough, wheeze, phlegm).	Epidemiological studies on incidence of airway damage in UER. Interactions of lung edema with pulmonary circulation.
Musculoskeletal	Acute issues are common and, if untreated, may have long-term effects. Stress fractures are possible with high-mileage training and/or in those with poor nutrition.	Consider nutritional intake and caloric balance. Ensure adequate recovery (e.g., rest, nutrition, sleep).	High-risk athletes, those with poor nutritional health, gait modifications, and/or history of poor bone health.	Whether UER leads to long-term osteoarthritic changes.
Renal	Acute issues are common, but they are generally minor and recover quickly. Repetitive kidney injury may lead to CKD due to renal scarring and maladaptive repair.	Follow hydration guidelines, especially in the heat. Optimally manage high mechanical workload. Avoid NSAIDs during training/racing.	Those exhibiting repeated renal injury and/or pre-existing renal issues.	Mechanistic studies on the link between acute renal injury and chronic maladaptation.
Gastrointestinal	Acute GI issues are common, but chronic issues linked to UER are rare.	Follow hydration guidelines, especially in the heat. Practice nutrition in advance of racing.	Athletes with new or long-term, unresolved GI symptoms.	Studies on incidence of long-term gut issues in UER. Whether gut training mitigates risk of GI injury.
Immune	High-mileage training/racing associated with increased oxidative stress and inflammatory cascade. Overtraining will compromise immune health.	Consider nutritional intake and caloric balance. Ensure adequate recovery (e.g., rest, nutrition, sleep)	Immunodeficient athletes and/or those exhibiting frequent acute infections.	Epidemiological and mechanistic studies into the effect of UER on chronic immune function.
Neuropsychological	Training generally has beneficial effects on mental health. Acute dysfunction of neurological system is common following UER. No data regarding chronic implications.	Formulate a psychological support network. Be cognizant of mental health initiatives.	Athletes with poor mental health and/or long-term anxiety/depression.	Studies exploring long-term mental health in large cohorts of UER athletes.
Integumentary	Increased risk of malignant skin lesions due to prolonged exposure to ultraviolet rays.	Cover up during training/racing. Diligent use of sunscreen.	Athletes with unusual skin lesions or changes to skin health.	Studies exploring link between skin surface pH and skin barrier homeostasis on integumentary issues.

AF atrial fibrillation, *CKD* chronic kidney disease, *GI* gastrointestinal, *NSAID* nonsteroidal-anti-inflammatory drug, *UER* ultra-endurance running to the present review on long-term health concerns, youth participation (< 19 years of age) in UER has also increased exponentially over the last few decades, albeit in far lower numbers when compared to adults [20–22]. The most popular running distances among youths are 50-km and 100-km [21], with most young UER athletes between 16 and 18 years, but some were younger than 13 [21]. Collectively, these data show a considerable increase in UER participation around the world, especially in female, youth, and masters athletes.

4 Training and Performance

Ultra-endurance running requires high mileage training that can lead to excessive strain on the body. Average training distances in adult UER are between 66 and 83 km/week [9, 33, 34] and around 57 km/week in youth athletes [24].

Ultra-endurance running performance is underpinned by a complex interplay among numerous physiological systems [35]. Moreover, several other variables affect UER performance such as physiological determinants, training, experience, anthropometric data, and race performance [36]. UER performance is related to average running speed in training, maximal aerobic speed [37], peak treadmill running speed [38], maximum oxygen uptake [38], average weekly running training hours [39–43], average weekly running kilometers [34, 40–42, 44–46], and other variables such as years as an active runner [34, 42], longest training run [38, 45], number of finished marathons [39, 40, 43], ultramarathons [39–41, 43], multi-stage ultramarathons [43], pre-race records for marathon [41, 45] and specific ultramarathons [43], and personal best time in shorter races [34, 41, 44, 47] such as 5 km [34], 10 km [34], half-marathon [34], and marathon [41, 41, 44, 45]. Often, for very long UER events, previous experience is more important than training [48].

Furthermore, the influence of both training (e.g., high running speed and high training volume [mean weekly running kilometers]) and anthropometric variables (e.g., body fat and muscle mass) on UER performance have been investigated [34, 40, 44–49] and seemed to be related to UER race performance [46]. Overall, training characteristics such as a high running speed and high training volume were more important than anthropometric characteristics for a successful race outcome [41, 44, 45, 48]. Multi-variate regression analyses including both anthropometric and training characteristics reduced the predictor variables mainly to body fat and speed during training units [48]. Weekly running kilometers and personal best time in 5 km, 10 km, and half-marathon were all associated with UER performance in women [34]. For men, however, age, body mass index, years as active runner, running speed during training, and personal best time in both 5 km and marathon were all associated with UER performance [34].

5 Long-Term Health Implications: Key Aspects by Organ System

5.1 Cardiovascular System

Regular aerobic exercise confers various health benefits, including reduced risk of cardiovascular disease and all-cause mortality [50, 51]. Longitudinal studies specifically studying former world-class [52, 53] or leisure-time [54] athletes showed a dose–response beneficial effect in various endurance sports, including running. However, it is also established that chronic endurance exercise training has a substantial structural and functional impact on the heart, including morphological and histological cardiac remodeling, arrhythmias, sinus node dysfunction, and high coronary artery calcium (CAC) scores, although the significance and consequences of such alterations are still debated [55].

The endurance athlete's heart typically exhibits eccentric remodeling of the left ventricle (LV) and a large increase in the size of the right ventricle (RV) and atria [56–59]. Owing to a higher wall stress in the RV than in the LV during exercise [60], more than 50% of endurance athletes exhibit RV enlargement [61]. This remodeling is concomitant with the development of maximal aerobic power [62]. Potentially, some individuals with large increases in myocardial mass may also exhibit some fibrosis scars [63, 64]. Indeed, animal models of chronic endurance training show that the larger cavity size is associated with myocardial fibrosis [65, 66] and significant ventricular arrhythmia. There is growing evidence to confirm this histological remodeling in humans [63, 64]. A higher prevalence of LV myocardial fibrosis has been reported in apparently healthy marathoners compared to matched sedentary counterparts [63, 64]. In fact, such alterations may be related to training experience (i.e., years of practice) [67]. Cardiac fibrosis has been described in different localizations (RV insertion point, subendocardial, subepicardial, mid-wall, or diffuse) suggesting that there is no clear relationship with endurance training, per se. In the general population, myocardial fibrosis was related to arrhythmias and mortality [68]; however, the incidence of myocardial fibrosis in UER athletes and any associated long-term consequences are yet to be comprehensively explored. The improvement in myocardial imaging (high-resolution magnetic resonance imaging [MRI]) showed that fibrosis may be localized in all cavities [63]. Unlike in the LV, fibrosis in the RV or atria is clearly associated with potential adverse events. Ventricular arrhythmias, mainly originating from the RV outflow tract in endurance athletes [69], are often associated with an impaired RV function and RV fibrosis [70, 71].

Atrial arrhythmia, mainly atrial fibrillation (AF), can be encountered in highly trained endurance male athletes, and this abnormality may typically occur after several years of training, with a risk multiplied three- to five-fold when compared to sedentary individuals [72, 73]. A recent meta-analysis found that younger athletes and athletes participating in mixed sports had a higher risk than those involved in endurance sports [74]. The underlying mechanisms comprise a combination of increased vagal tone, exercise dose, and anatomical and functional atrial remodeling, including atrial fibrosis [75–77]. The overall risk for exercise-related AF is, however, low; nevertheless, there is a U-shaped relationship with lifetime-accumulated high-intensity endurance training and the risk of developing AF [78, 79], and it is worth communicating this risk to UER athletes. Atrial node dysfunction [80] or exercise-induced atrio-ventricular block [81] may be further complications associated with fibrotic remodeling of the conduction system.

Another surprising finding in endurance athletes, mostly runners [82], is a high prevalence of CAC score (> 100) on coronary computerized tomography (CT) angiography compared with sedentary controls [83, 84]. The atherosclerotic plaques are, however, calcified and stable in athletes, leading to less rupture [84]. Although speculative, this may arise from long-term mechanical flexing of the epicardial coronary arteries during exercise, triggering inflammation and atherogenesis [85]. As for the LV fibrosis scars, a high CAC score might poorly predict future coronary events in athletes [86].

5.2 Respiratory System

The respiratory system is partially composed of conducting airways that warm, humidify, and purify inspired air before it reaches the lung parenchyma [87]. Although achieved adequately at rest, the capacity of the upper airways to condition ambient air is exceeded at minute ventilations above 35–60 L min^{-1} [87, 88]. Thus, moderate-intensity exercise, as observed in UER, exposes the distal airways to unconditioned air that cools and dehydrates the epithelial surfaces [89]. The resulting inflammation can stimulate bronchial smooth muscle constriction, airway narrowing, and subsequent obstruction [90]. Such a mechanism of exercise-induced bronchoconstriction (EIB), while incompletely understood, may be important in the pathophysiology of acute lung function decline following UER [91]. Importantly, repeated acute exacerbations—particularly those involving cold/dry air—may cause injury and remodeling of the bronchial smooth muscle [89, 92].

EIB, which causes asthma-like symptoms in response to prolonged hyperpnea, has a prevalence of 5–20% in the general population and its prevalence is considerably higher in people with pre-existing asthma [93]. Endurance athletes are potentially at a greater risk of EIB owing to high levels of pulmonary ventilation sustained in training [94]. Although there are no epidemiological studies on the prevalence in UER, data from non-asthmatic endurance runners show that biomarkers of both airway inflammation and oxidative stress increase with exercise duration [95, 96]. The only available data relating to exercise-induced asthma in UER suggest a prevalence that is similar to that seen in the general population [97]; however, these data are limited by the self-selection of participants, the self-reporting of data, and the lack of a control group.

A further pulmonary consideration for the UER athlete relates to the potential effects of mild and transient post-race lung edemas that have been reported in marathon runners [98–100], which, in most cases, have a neurogenic pathogenesis (e.g., exercise-associated hyponatremia) [98, 101]. Competitors in a 100-mile (161-km) footrace were shown to exhibit a mean increase in the frequency of echocardiographic “comet tails” (indicative of extravascular lung water) congruent with decreased lung diffusing capacity and alveolar-capillary membrane conductance [102]. That decreases in lung diffusing capacity occurred simultaneously with decreased RV function [103] suggests that UER confers a disproportionate hemodynamic load on the pulmonary circulation [60]. While pulmonary edema may be a normal response to strenuous endurance exercise, the short- or long-term consequences of repeated occurrences are currently unknown.

5.3 Musculoskeletal System

Musculoskeletal injuries are common in UER and may affect bones, joints, cartilage/menisci, muscles, tendons, ligaments, and bursae [104–107]. Around 90% of injuries in UER are overuse in nature [104, 105, 108–110]. Most injuries are minor and affect the lower limbs, especially the foot, ankle, and knee [108, 111, 112]. Risk factors are multifactorial and include history of previous injuries, higher body mass index, advanced age, running volume, and biomechanics [105, 113, 114]. Despite the injury prevalence in UER, the long-term and cumulative effects have not been adequately studied [115]. Although recreational running in general may have positive effects on bone strength, regular high-volume running may decrease foot bone strength and increase the risk of osteopenia and/or stress fracture [116]. It has been shown that stress fractures are relatively common in UER [24, 105, 115, 117] and may require prolonged medical treatment and absence from sporting activities. Stress fractures usually develop through overuse strain on healthy bone [118–121], with reported incidences of between 5.5 and 22% [97, 117]. Approximately 21% of female endurance runners, including those contesting UER, developed stress fracture that was attributed to increased energy expenditure concomitant with inadequate nutrition [122].

Several small investigations using MRI showed no evidence of acute changes in patella-femoral and tibio-fibular joint structures pre- to post-UER [123–127]. Athletes starting the race with tendinopathies demonstrated worsening MRI images after the race [123]. Tendon injuries (e.g., Achilles tendinopathy or patella tendinopathy) are relatively common in UER athletes [104, 106, 110], and although most are minor, they can become chronic and result in prolonged and recurring absences from sport [112, 128, 129].

There may be a dose-dependent association between competitive level of running and knee and hip osteoarthritis [130, 131]. A moderate (recreational) running regimen has been shown to be associated with a lower occurrence of hip and knee osteoarthritis compared to that seen in the general population [130, 131]. However, endurance (competitive) running has been associated with a higher occurrence of hip and knee osteoarthritis compared to that seen in the general population [130, 131].

Other lower extremity injuries such as ligament strains, ankle sprains, iliotibial band syndrome, and plantar fasciitis, which may occur as a result of running injuries, usually have a good long-term prognosis [104, 110]. Back pain is a common chronic condition and has been reported in 12–14% of UER athletes [97, 117]. Nevertheless, the origin of the pain is not necessarily related to UER and may instead be the result of activities of daily life [117]. In fact, running is often seen as protective against the development of lower-back pain [132].

5.4 Renal System

During exercise, renal blood flow is reduced as cardiac output is redirected to the muscles, resulting in diminished renal function [133]. Severe decreases in renal function and renal failure are rare during UER [134–137]. The risk of kidney injury can be exacerbated by factors such as endurance running in extreme environments (e.g., hot and/or humid conditions, racing at altitude), severe muscle damage due to high biomechanical loads, low rates of fluid intake resulting in dehydration, the ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs), and genetic predisposition [134–140]. Conditions such as hyponatremia, bilirubinuria, proteinuria, hematuria, hemoglobinuria, myoglobinuria, and cylindruria can predicate acute renal issues and are indicators of acute kidney injury (AKI) in long-distance runners [133, 141–147]. These renal issues (cumulative incidence of 15–45%) [134, 135] are generally minor in UER and recover to baseline values within 1–10 days [134, 145, 147–149]. Considering that AKI is usually asymptomatic, it is likely that many cases remain undetected during and after UER.

An important consideration is the extent to which AKI is associated with UER and might evoke chronic kidney damage. While individual or cumulative AKI could contribute to future chronic damage in general populations [150, 151], there is no clear association in UER, and a better understanding of the physiological cascade of events is needed [140]. Any link between AKI in UER and long-term renal issues could be strengthened by certain risk factors, including age, race, genetics, and other pathological conditions.

In the general population, some evidence links acute and chronic renal failure due to potential maladaptive repair [152], and progressive renal scarring [153] due to cumulative AKI events. In this sense, there is a growing scientific literature also providing evidence that AKI accelerates the progression of chronic kidney disease (CKD) [152], that AKI repeated episodes are associated with CKD, and that the severity of AKI could lead to long-term renal issues [153]. Besides, severe cases of AKI in non-runners may require dialysis and are especially vulnerable to worse long-term renal outcomes [154]. Occasionally, AKI is detected in combination with rhabdomyolysis that may lead to a more complex condition in UER [144, 155–157]. It is currently unknown if severe renal dysfunction in UER, or repetitive renal insults that meet the criteria of AKI, lead to an accelerated progression of long-term renal issues in UER [134, 145, 147, 158].

5.5 Gastrointestinal System

Acute gastrointestinal (GI) issues are common during UER training and racing, with 50–80% of runners experiencing nausea, vomiting, and/or diarrhea [159–161]. Prolonged running has also been shown to evoke small intestinal damage and increased intestinal permeability [162]. However, these symptoms typically resolve with the cessation of exercise and do not appear to result in any long-term health issues; nevertheless, in extreme cases, dehydration and splanchnic hypoperfusion during exercise can lead to ischemic colitis, which in turn rarely requires surgical intervention [163]. In rare examples, chronic GI issues can lead to iron and other nutritional deficiencies [164].

In general, endurance exercise is associated with long-term benefits to the GI system, like reversal of non-alcoholic fatty liver disease and lower rates of colon cancer [165, 166]. These findings may be in part due to beneficial effects of exercise on the gut biome [167, 168]. Gut biome changes are typically associated with improvements in microbiota diversity, inflammatory markers, metabolic profiles, and immune responses [167–169].

5.6 Immune System

The stress produced by endurance exercise can significantly impact immune function in the short term. The immune system generally works more efficiently in athletes in whom the activity of natural killer cells is increased. Following UER, there is a transient immunosuppression for several hours, which could increase the risk of acute subclinical and clinical viral and bacterial infections. In fact, as a result of high-volume training and racing, UER athletes may be more prone to acute infections (due to reduced immunoglobulins, e.g., IgA) [170–173]. UER also results in indicators of oxidative stress (e.g., F(2)-isoprostane and lipid hydroperoxides), which increase linearly with race duration [96], in addition to increased cytokines (e.g., granulocyte colony-stimulating factor [G-CSF], interleukin [IL]-10, IL-1ra, IL-6, and IL-8), increased immune cells leading to leukocytosis, neutrophilia, and monocytosis [174], and increased cortisol, and decreased testosterone and luteinizing hormone [175].

In athletic populations, periods of overreaching may result in longer lasting immune alterations and dysfunction [176]. Importantly, physiological/psychological overload evoked from training and racing that is disproportionate to recovery may lead to non-functional overreaching, contributing to a long-term performance deficit known as under-performance syndrome [176]. Some physiological (proteomic) and perceptual (e.g., training distress score) measures could be monitored to assess non-functional overreaching in athletes, including in UER [177]. The classic physiological symptoms of overreaching include an increase in cytokines and oxidative stress as inflammation and muscle damage indicators. Consequently, it seems relatively clear that there is a link between inflammatory responses and endurance exercise, immune dysfunction, and overreaching and overtraining syndrome [178, 179]. Also, these conditions may compromise resistance to common minor illnesses, resulting in a greater incidence of infection [180].

5.7 Neurological and Psychological Function

Although the long-term effects of UER on the brain are unclear, MRI data collected before and after a UER event lasting 2 months (4487 km; Trans European Foot Race) showed a substantial (6%) reduction in brain volume possibly attributable to transient loss of protein and electrolyte disturbances [181]. However, brain volume had returned to baseline at the 8-month follow-up, with no signs of permanent lesions or damage [181]. A short-term decrease in cortical activity in the frontal cortex has also been observed during 6-h UER, showing no effect on cognitive performance [182]. There are data suggesting benefits of UER on cerebral function. Indeed, a single-subject case report showed that a patient with Parkinson's disease exhibited a partial correction of abnormalities and decreased demand on medication after training for a 100-km UER event [183]. Moreover, lifelong endurance training helps maintain the cortical brain reserve [184]. As such, endurance training is most likely to have a positive impact, rather than a negative impact, on neurological health later in life.

With respect to psychological wellbeing, endurance exercise has well-documented positive effects on depression and other mental health issues [185–187]. However, UER athletes tend to exhibit significantly greater exercise dependence relative to marathon runners or athletes contesting races of shorter distances or the general population [188–190], and this could have a subsequent negative impact on health [191, 192]. The prevalence of depression and mental health issues in UER athletes is equal to or higher than that exhibited in the general population [188, 189], although this may not be causative, and it could be that people with underlying depression, anxiety, and/or other mental health issues are drawn to sports like UER, perceiving it as a way to "self-medicate."

5.8 Integumentary System

Dermatological problems can occur due to potential exposure to UV rays (resulting from prolonged outdoor exercise and/or high-altitude running) in addition to immunosuppression due to long-term intense exercise [193, 194]. UER athletes may be at higher risk of pre-malignant and malignant skin cancers and other UV-related health risks, e.g., adverse effects on ocular structures [193–196]. In general, athletes should be encouraged to use clothing that blocks UV radiation, use sunscreens, and wear sunglasses with UV protection to help lower the risk [193, 194, 197]. However, only ~ 62% of UER athletes use sunscreen, a hat (52%), or other protective clothing (7.4%), and so clearly further education is needed [198].

6 Special Considerations

6.1 Youth Athletes

Participation of youth athletes in UER is increasing, and UER may impact growth and development in key organ systems (e.g., the cardiovascular, pulmonary, and musculoskeletal systems) during maturation in youth athletes [25]. It is currently unknown if UER is safe or poses an increased risk of acute and/or chronic injuries in youth athletes [25]. Of concern is that chronic health issues may develop earlier in susceptible individuals when participating in UER at a young age [20, 23, 24]. To date, only one retrospective observational study has described longitudinal health changes in 78 adults who participated in UER as youths [24]. Approximately one-quarter of youth athletes suffered from lower-limb musculoskeletal injuries (mostly knee, ankle, foot), and 6.4% developed a stress fracture [24]. As adults the overall lifetime incidence of stress fracture increased to 14% [24], which is much higher than the 5.5% previously reported in adult UER athletes [97]. Thus, the longer physiological stress evoked by lifelong UER participation may increase the risk of injury. Only 27% of youth athletes continued running UER into adulthood, the main reason being injuries [24]. Interestingly, this study showed that most participants reported positive effects from running ultras as youth athletes, but only ~ 21% would recommend youth athlete participation in UER [24]

To help parents, athletes, coaches, race directors, and medical professionals to reach an informed decision, a recent consensus statement [25] reviewed the evidence on health implications of youth athlete participation in UER and provided a decision-making algorithm for appropriate youth participation based on age, developmental stages, medical and psychological wellbeing, training status, and race-specific factors [25]. Until data on long-term consequences are available, youth participation in UER is not recommended on a large scale without comprehensive and individualized assessment [25].

6.2 Masters Athletes

A masters athlete is defined as an athlete ≥ 35 years of age who trains for, or participates in, athletic competitions that are sometimes specifically designed for older athletes [199]. The average age to contest a first ultra-marathon is 35 years [188], and so peak performance in UER is generally achieved at an older age (i.e., between 35 and 50 years) [31, 200, 201]. Experience is a crucial component of success in UER [200], and older age seems to be an advantage regarding mitigating overuse injuries in long-distance running (i.e., younger and less experienced UER athletes are at a higher risk for exercise-related injuries such as a stress fracture) [97].

Masters UER athletes are generally a healthy population, with a lower all-type mortality and increased life expectancy compared to the general population [97, 202]. From the limited and self-reported data available, UER athletes exhibit good health, with few chronic illnesses and low use of the medical care system [97]. Whether this is due to the regular exercise or a predisposition of healthier individuals participating in UER in this relatively older age group [31, 200, 201] is not fully understood.

6.3 Female Athletes

There are limited data on female UER owing to reduced female participation [2, 203], possibly lesser interest in volunteering for applied research [204], and possibly because of exclusion of female subjects on the (sometimes erroneous) basis that menstrual phase might confound the physiological response [205]. Nevertheless, a recent review highlighted several key aspects of female athlete physiology that warrant careful consideration in periodized UER training plan [122].

Arguably, the most important long-term consideration for females in UER relates to interactions of energy availability and sex-hormone concentrations. The primary nutritional challenge in UER is the ability to meet daily caloric requirements [206]. A relative energy deficiency can sometimes occur due to high training volumes and/or restriction of dietary energy intake (deliberate or inadvertent); the syndrome of relative energy deficiency in sport (RED-S) refers to physiological impairments that may result [207]. Although the negative effects of low energy availability can affect both male and female athletes, its consequences are more rapid and profound in females owing to the downstream interactions with menstrual function and bone health (as described in the Female Athlete Triad [28]). A particular concern is that estrogen associates positively with bone mineral density [208]. Thus, diminished estrogen levels (e.g., in amenorrheic athletes) may increase the risk of stress fracture [209]. Even eumenorrheic females may be more susceptible than males to adverse changes in bone health following short-term low energy availability [210]. While this likely has implications for high-mileage training, it has not yet been studied in female UER. Finally, because peak performance in UER generally occurs mid-life (e.g., at ~ 44 years in the 24-h run [211]), female athletes should be mindful of the potential adverse changes in bone health and increased risk of osteoporosis that occur during menopause [212]. Accordingly, the data suggest there are important differences in male and female physiological function [122]. Failure to consider these differences in the design of female-specific UER training programs may have a negative impact on athlete longevity.

6.4 Organizational Issues

UER events often take place in remote locations and under challenging environmental conditions, with the inherent risk of severe pathologies, life-threatening injuries and occasional deaths of competitors [6, 106, 213]. Deaths have occurred from exercise-associated hyponatremia, cardiac issues, hyper/hypothermia, wildfires and other environmental hazards during competitions [6, 106, 213, 214], but are generally isolated occurrences that can often be prevented with appropriate pre-event medical planning [6].

7 Future Considerations

Moderate physical activity is well known to have positive effects on health, being preventative against numerous life-style–related diseases and reducing all-cause mortality. Similarly, many of these benefits can be derived from participation in UER, and the sport can generally be considered a safe and healthy pastime. However, it should also be recognized that with increased participation in UER comes an increased risk that susceptible individuals may experience chronic maladaptations leading to adverse effects on health and possible long-term health problems in later life (see Fig. 1). Although this review provides the current state of evidence of UER and its impact on long-term health, there remain many unknowns that warrant further exploration (see Table 1).

With regard to the cardiovascular system, UER appears generally safe; however, some susceptible UER athletes may exhibit cardiac damage, myocardial inflammation, myocardial fibrosis scars, and a higher risk of AF with prolonged participation. This should be explored further in UER, especially in longitudinal studies.

Similarly, long-term epidemiological studies are needed to explore the prevalence of EIB/exercise-induced asthma in ultra-marathon runners, the long-term implications of recurrent pulmonary edema associated with UER, and the implications of chronic UER-mediated RV dysfunction on the pulmonary circulation. Longitudinal studies may also provide a better understanding of kidney function through a running season and/or the lifespan, and how to prevent and treat these acute and chronic kidney conditions in a timely manner. New technological developments such as wearable devices [145, 215, 216] could allow researchers to monitor adverse changes in real-time, particularly when athletes are competing in extreme environments that are more likely to increase the incidence of AKI. Studies are also needed to explore how situational, contextual, and individual factors influence the incidence of AKI, and how this temporary loss of kidney function is related to possible long-term kidney problems [140, 145, 157]. Considering the ongoing debate regarding the use of traditional biomarkers for detection of AKI in sports, a more in-depth analysis of alternative indicators of kidney damage (e.g., neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule [KIM]-1, cystatin C, albumin, proenkephalin [PENK]), before and after UER events, is also warranted [156, 217, 218].

With regard to GI-related disorders, there are data suggesting that moderate-intensity exercise may be of benefit,

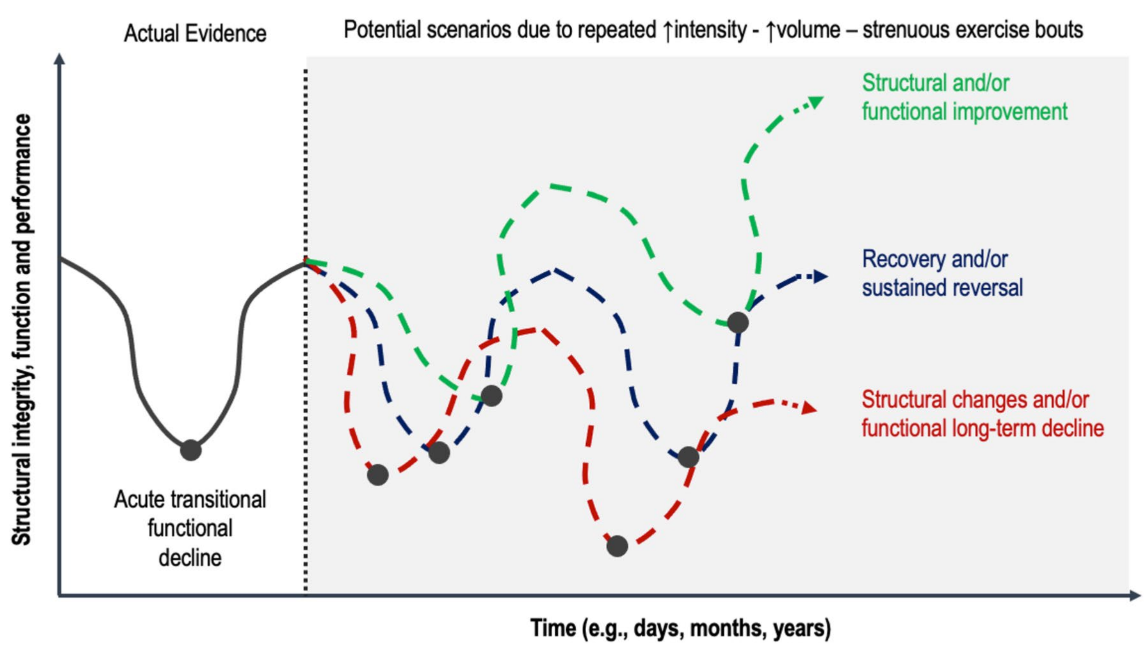

Fig. 1 The potential impact of repeated high-intensity/volume bouts of ultra-endurance running on key organ systems with potential maladaptations in susceptible individuals. Adapted by permission from BMJ Publishing Group Limited, *BMJ Open Sport Exerc Med*, Scheer V and Rojas-Valverde D [16], Vol. 7, e001131, 2021

but the limited data on the health effects of more strenuous exercise like UER suggest it may be detrimental. Moreover, further research is needed to establish whether acute GI disturbances associated with UER lead to chronic GI issues.

Long-term impact of UER on the musculoskeletal system should also be considered, especially with regard to stress fractures and potential osteoarthritic changes, which may occur to a greater extent in youth and female athletes.

Finally, medical screening and long-term follow-up of athletes engaging in regular UER may be an important component of risk stratification and in the early detection of long-term health concerns, but this is an ongoing point of contention. As such, careful scrutiny of the feasibility, advantages and disadvantages of screening in UER must be considered. The notion of shared decision making is relevant for UER in that clinicians and athletes should work cooperatively to consider the evidence and make an informed decision that balances the risks/expected outcomes of UER with patient preferences and values [13]. This is especially pertinent given that some of the long-term health changes may not be reversible (e.g., cardiac chamber remodeling).

8 Conclusions

UER is growing in popularity, particularly for youth, masters, and female athletes. There are many health benefits of participation, and UER rarely evokes serious adverse events. However, there is a growing body of evidence suggesting that UER may have implications for long-term health, particularly affecting the cardiovascular, respiratory, and musculoskeletal systems. Whether this applies only to susceptible individuals, and whether this results from high training volumes or rather the periodic stress of racing, requires further study. Future studies are needed to help better elucidate disease prevalence and pathophysiology in UER athletes.

Declarations

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Conflict of interest Volker Scheer, Nicholas B. Tiller, Stéphane Doutreleau, Morteza Khodaee, Beat Knechtle, Andrew Pasternak, and Daniel Rojas-Valverde declare that they have no conflicts of interest relevant to the content of this review.

Availability of data and material Not applicable.

Authors' contributions VS and DRV conceived and designed the paper. VS organized the contributors. VS, NBT, and DRV provided the first draft, with all authors contributing to the written content, and multiple rounds of review. All authors approved the final version.

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