BINDAS, Jan, HAMOUTA, Jakub, DOROSZUK, Wiktor, DŁUGOSZ, Patrycja and JERZAK, Marika. Physiological Effects and Adaptations of Marathon Running: A Comprehensive Review. Journal of Education, Health and Sport. 2025;83:66745. eISSN 2391-8306.
https://doi.org/10.12775/JEHS.2025.83.66745
https://apcz.umk.pl/JEHS/article/view/66745

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 19.11.2025. Revised: 30.11.2025. Accepted: 30.11.2025. Published: 05.12.2025.

Physiological Effects and Adaptations of Marathon Running: A Comprehensive Review

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Abstract

Background. Marathon running is one of the most popular and rapidly expanding forms of endurance exercise. It provides well-documented cardiovascular, metabolic, and musculoskeletal benefits. Understanding the systemic adaptations and potential health risks associated with long-distance running is essential in sports medicine and physiology.

Aim. The aim of this review is to summarize current scientific knowledge on the physiological effects of marathon training and participation, focusing on cardiovascular, metabolic, musculoskeletal, renal, respiratory, and immune responses, as well as training strategies and performance-enhancing methods.

Material and Methods. This narrative review is based on a comprehensive literature analysis conducted through PubMed from 2018 to 2024. Keywords used included: "marathon", "endurance running", "cardiovascular remodeling", "exercise physiology". Studies involving both professional and amateur marathon runners were considered.

Results. Regular marathon training induces numerous systemic adaptations, including increased VO_2max, improved lipid profile, enhanced musculoskeletal efficiency, and neurohormonal regulation. However, acute and chronic health risks such as arrhythmias, renal stress, respiratory fatigue, and musculoskeletal injuries have also been observed. The degree of physiological strain is strongly correlated with training volume, experience, and recovery strategies.
Conclusions. Marathon running, when properly managed, promotes global health and physical performance. However, excessive or inadequately supervised training may lead to adverse effects, particularly in less experienced athletes. Individualized approaches to training, screening, and recovery are essential to maximize benefits and minimize risks.
Keywords: marathon running, endurance training, cardiovascular adaptation, VO_2max, sports physiology, running injuries, metabolic response, respiratory fatigue, recovery strategies

1.Introduction

One of the most popular forms of physical activity, with continuously growing interest, is running. From 2008 to 2018, global participation rates in male amateur marathon running grew by 46.91%. Moreover, a greater proportion of marathon participants are men (65.18%) compared to women (34.82%), with 41.90% of recreational runners residing in Europe, according to a report on recreational marathon runners (O'Riordan et al., 2023). Conversely, ultra-endurance running may impose considerable physiological stress, largely due to the extensive training volumes necessary for preparation. Young athletes often average approximately 57 km per week, whereas adult ultra-endurance runners may reach weekly distances ranging from 66 to 83 km (Scheer et al., 2022). The main beneficial effects of regular physical exercise include improvements in lipid profiles, reductions in resting blood pressure, enhanced carbohydrate homeostasis, favorable modulation of blood coagulation, increased cardiac output, and improved myocardial perfusion (Vitiello et al., 2021). Since the late 1990s, endurance activities have gained increasing popularity, likely due to their emphasis on personal challenge and the opportunity to spend more time outdoors. Prolonged physical exercise can be categorized based on duration and intensity. Moderate-duration events include races such as half-marathons and marathons, which typically last between 1 to 4 hours. In contrast, long-duration events include competitions like the half-Ironman (approximately 5–8 hours) and the full Ironman triathlon, which involves 3.8 km of swimming, 180 km of cycling, and 42.195 km of running.

2.Research materials and methods

This narrative review is based on a comprehensive literature analysis conducted through PubMed from 2018 to 2024. Keywords used included: "marathon", "endurance running", "cardiovascular remodeling", "exercise

physiology", "injury", "training", "VO_2max", and "biomarkers". Studies involving both professional and amateur marathon runners were considered.

2.1 AI.

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning106narratives to identify linguistic patterns associated with specific logical fallacies. Assistance107in refining the academic English language of the manuscript, ensuring clarity, consistency,108and adherence to scientific writing standards. AI were used for additional linguistic109refinement of the research manuscript, ensuring proper English grammar, style, and clarity in110the presentation of results. It is important to emphasize that all AI tools were used strictly as111assistive instruments under human supervision. The final interpretation of results,112classification of errors, and conclusions were determined by human experts in clinical113medicine and formal logic. The AI tools served primarily to enhance efficiency in data114processing, pattern recognition, and linguistic refinement, rather than replacing human115judgment in the analytical process.

3.Discussion

Cardiovascular system

Physical activity has demonstrated protective benefits in evidence-based pleiotropic research on the cardiovascular system, with the most significant positive health outcomes observed in individuals engaging in moderate physical activity compared to those leading a sedentary lifestyle. However, research has also found that in certain individuals, aerobic exercise—especially when excessive—may produce harmful cardiovascular effects such as coronary atherosclerosis and atrial fibrillation (AF) (O'Riordan et al., 2023; Scheer et al., 2022). Highly trained male endurance athletes, particularly after several years of training, develop atrial arrhythmias—primarily atrial fibrillation (AF)—three to five times more often than their sedentary counterparts (Scheer et al., 2022). Contrarily, a meta-analysis presented by Newman et al. (Risk of Atrial Fibrillation in Athletes: A Systematic Review and Meta-Analysis, 2021) found that endurance athletes have a lower risk of AF compared to younger athletes participating in mixed sports. Increased vagal tone, anatomical and functional atrial remodeling—including atrial fibrosis—and training load (exercise dosage) have been proposed as mechanisms underlying this correlation (Scheer et al., 2022). Lifetime training hours likely play a critical role in left atrial (LA) remodeling, as they are associated with LA enlargement and prolonged P-wave duration, both of which may indicate altered cardiac conduction (Braschler et al., 2025). It is worth mentioning this concern to ultra-endurance athletes, even if the overall probability of exercise-related AF is low, since a scientifically proven U-shaped association exists between lifetime accumulated high-intensity endurance training and the likelihood of developing AF (Scheer et al., 2022). Furthermore, atrial fibrosis may impair the

cardiac conduction system, potentially leading to sinoatrial node dysfunction or exercise-induced atrioventricular block (Scheer et al., 2022).

Evidence-based research has consistently shown a reduction in cardiovascular morbidity and mortality among individuals who exercise regularly (O'Riordan et al., 2023; Scheer et al., 2022); therefore, health promotion campaigns encourage consistent physical activity. Compared to inactive controls, endurance athletes exhibit significantly lower resting blood pressure values, which exert protective effects on the vasculature of various organs and the heart (Braschler et al., 2025). Moreover, endurance runners also demonstrate significantly lower resting heart rates than inactive individuals, suggesting that regular physical activity alters autonomic nervous system (ANS) function (Braschler et al., 2025). Electrocardiogram (ECG) studies have revealed decreased sympathetic and enhanced vagal tone to the heart in endurance athletes (Braschler et al., 2025). This is reflected on ECG as sinus bradycardia, observed in approximately 80% of trained athletes, compared to only 19% of non-athletes who exhibit a resting heart rate below 60 beats per minute (Braschler et al., 2025). Such adaptations benefit cardiovascular health and reduce the risk of cardiovascular events.

Nevertheless, running can be harmful to health, especially for less experienced runners (O'Riordan et al., 2023; Scheer et al., 2022). Consequently, participants should carefully consider what constitutes too much, too soon, and too fast, while remaining cognizant of the potential risks associated with vigorous exercise (O'Riordan et al., 2023). Another study observed a reduced risk of all-cause mortality and cardiovascular disease among the many health benefits associated with regular aerobic exercise (Scheer et al., 2022). Positive health effects have been documented across multiple endurance disciplines—not limited to running—with evidence of a dose-response relationship in both elite and recreational athletes (Scheer et al., 2022). In contrast, it has also been shown that athletes' hearts undergo morphological and histological remodeling, sinus node dysfunction, arrhythmias, and elevated coronary artery calcium scores (CAC >100) in computerized tomography (CT) angiography as adaptations to chronic endurance training (Scheer et al., 2022). However, the clinical significance and long-term consequences of these abnormalities remain under debate. Long-term mechanical flexing of the epicardial coronary arteries during exercise is thought to trigger inflammation and promote atherogenesis, although this hypothesis remains speculative. As a result, the main difference between athletes and sedentary individuals is that atherosclerotic plaques in athletes are more frequently calcified and stable, making them less prone to rupture (Scheer et al., 2022). Moreover, a high CAC score—particularly when accompanied by left ventricular (LV) fibrotic scarring—may be a poor predictor of future coronary events in athletes (Scheer et al., 2022).

Typical cardiac adaptations in endurance athletes, due to higher wall stress in the right ventricle (RV) compared to the left ventricle (LV) during exercise, include a significant increase in RV size (with more than 50% of endurance athletes exhibiting RV enlargement), right atrial enlargement, eccentric remodeling of the LV, increased LV wall thickness, and an overall gain in myocardial mass (Braschler et al., 2025; Scheer et al., 2022). These changes, driven by reduced filling time, enhance diastolic function and lead to an increase in cardiac output during endurance exercise (Braschler et al., 2025).

Amateur athletes represent a unique subset of the population who may be at increased risk of cardiovascular disease due to their involvement in vigorous exercise combined with underlying risk factors. Several components impact the health of amateur athletes, including age, level of fitness, physical demands, and cardiovascular health status (O'Riordan et al., 2023). A study by Kim JH et al. (Cardiac arrest during long-distance running races. N Engl J Med. 2012) showed that half marathon participants are predisposed to a lower health risk compared to full marathon runners. However, the dose-response relationship between exercise and cardiovascular disease outcomes, including coronary artery disease, has been questioned by evidence-based research (O'Riordan et al., 2023). Due to their often asymptomatic nature, many subclinical events—such as neurohormonal activation, hypercoagulability, precipitating plaque rupture, and endothelial erosion—may often go unnoticed, all of which have been linked to cardiac events during endurance sports.

A precipitating factor contributing to exercise-induced cardiovascular events may be excessive vigorous marathon running, particularly in individuals with pre-existing modifiable risk factors who may be susceptible to undiagnosed cardiovascular disease, especially among middle-aged men who begin running later in life (O'Riordan et al., 2023). According to current research, men are at a higher risk of experiencing sudden cardiac arrest and sudden cardiac death during a marathon and directly afterward compared to women (O'Riordan et al., 2023). One plausible explanation for this phenomenon is the earlier onset of atherosclerosis in men.

The most common causes of sudden cardiac death in young athletes (under 35 years old) are electrical and structural disorders of the heart, such as cardiomyopathies, coronary anomalies, ion channel disorders, and acquired cardiac conditions. In contrast, older amateur athletes (35 years and older) present with different cardiovascular risk factors, mainly atherosclerotic coronary artery disease, which may lead to cardiovascular events (O'Riordan et al., 2023). Despite this, research findings remain inconclusive regarding the clinical implications of marathon participation and the amplification of physiological parameters related to cardiovascular strain and cardiac responses.

Worldwide, cardiovascular screening is not routinely recommended for amateur athletes prior to marathon participation. There is ongoing debate surrounding routine preparticipation screening, as undiagnosed atherosclerotic coronary artery disease is the leading cause of exercise-related cardiac events in older athletes (≥35 years old); however, concerns remain about the accuracy and predictive value of such screening. It is therefore crucial to evaluate health outcomes specifically among male amateur marathon runners (O'Riordan et al., 2023). Cardiac arrests occur in marathon running at an estimated rate of approximately 1.01 per 100,000 runners (O'Riordan et al., 2023). Although such events are rare, it is essential to assess the modifiable risk factors for cardiovascular diseases in experienced male amateur marathon runners. This assessment includes evaluating the prevalence of these risk factors, the screening and assessment approaches used, as well as the associations between marathon running characteristics and cardiovascular disease.

Due to cultural, social, and legal differences within Europe and the United States, there are notable discrepancies in recommendations on cardiovascular disease prevention in sports, as issued by the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) (O'Riordan et al., 2023).

Marathon running appears to significantly reduce the myocardial lipid pool in endurance-trained men. In a comparative study, healthy individuals who followed a fat-rich diet for three days prior to a two-hour session of moderate-intensity aerobic cycling (at 50%–60% of maximal oxygen uptake) exhibited a 17% reduction in myocardial lipid content (Aengevaeren et al., 2020). In contrast, endurance-trained men demonstrated a 30% reduction under similar preloading conditions (Aengevaeren et al., 2020). These findings suggest that the greater exercise intensity and duration characteristic of marathon running lead to a more pronounced depletion of the myocardial lipid pool, in a manner that appears to be dose-dependent with respect to exercise load. It is important to note that the intracardiomyocellular lipid pool is a highly dynamic energy reservoir. During prolonged, high-intensity exercise, enhanced myocardial lipolysis and mitochondrial fatty acid β-oxidation are stimulated, resulting in an energy-demanding state that exceeds the capacity of triacylglycerol synthesis to replenish lipid stores (Aengevaeren et al., 2020).

After training for and completing their first marathon, novice marathon runners showed no significant changes in left ventricular (LV) trabeculation (D'Silva et al., 2020). The quantification methods used to determine the prevalence of excessive LV trabeculation remain highly inconsistent, even within the same individual, and demonstrated minimal variability over the study period. Previous research has suggested that apical trabeculation occurs more

frequently in younger individuals; however, no study to date has established age-specific normative or pathological cutoff values for LV trabeculation (D'Silva et al., 2020). Notably, the LV apex remains the most commonly affected region in cases of excessive trabeculation, a finding consistently observed across studies (D'Silva et al., 2020).

Athletes, particularly competitive soccer and rugby players, exhibit a higher prevalence of LV trabeculation compared to non-athletes, as indicated by a cross-sectional study (D'Silva et al., 2020). Reported prevalence rates vary significantly among different athletic populations, ranging from 1.4% to 18.3%. One proposed explanation for this phenomenon is that intense physical training may induce acquired LV trabeculation, potentially overlapping with subclinical cardiomyopathy in genetically predisposed individuals. However, it is important to note that not all cases of acquired LV trabeculation are pathological. Differentiating between benign and pathological trabeculation requires a comprehensive evaluation of additional cardiac parameters (D'Silva et al., 2020). Furthermore, there is currently no longitudinal evidence establishing a definitive cause-and-effect relationship between exercise and the development of increased LV trabeculation (D'Silva et al., 2020).

The majority of studies report a decrease in left ventricular (LV) diastolic function—observable after as little as one hour of exercise—and right ventricular (RV) diastolic function following marathon running (Vitiello et al., 2021). More recent research has confirmed that both LV and RV dysfunction can occur post-marathon and are closely associated with exercise-induced cardiac fatigue, which is more pronounced compared to resting conditions (Vitiello et al., 2021). These findings suggest that exercise intensity during a marathon is a more critical factor in the development of cardiac fatigue and myocardial alterations than the duration of the event alone. The observed decrease in ventricular relaxation is linked to impaired LV and RV diastolic function and is considered a consequence of prolonged physical exertion (PPE) (Vitiello et al., 2021).

A transient decline in cardiac function, often accompanied by elevated levels of biomarkers indicative of myocardial stress or degradation, can occur in some athletes as a result of PPE. According to the findings of a recent study, marathon running in recreational athletes exerts only a mild effect on both left and right ventricular (LV and RV) systolic and contractile function, while a more noticeable negative impact was observed on LV diastolic function (Vitiello et al., 2021). The study population exhibited a limited degree of myocardial involvement, characterized by transient inflammatory and damage-related responses, which supports the notion that cardiac fatigue and functional alterations following marathon running are largely physiological and reversible in nature, rather than pathological (Vitiello et al., 2021).

The degree of cardiac function impairment and the extent of biomarker release following a marathon are strongly influenced by both the training status of the athlete and the intensity of the run (Vitiello et al., 2021). A study conducted between 2018 and 2019, focusing on marathon runners over the age of 40, revealed that 20% of this population exhibited evidence of underlying coronary artery disease (CAD) (Vitiello et al., 2021). These findings underscore the importance of individualized risk assessment, particularly in older athletes, as subclinical cardiovascular conditions may be unmasked or exacerbated by the physiological stress of endurance events.

An analysis using echocardiographic ReVISION software examined the impact of marathon running on right ventricular (RV) mechanics in amateur athletes and demonstrated a significant reduction in RV systolic function, accompanied by transient RV enlargement following the race (Lewicka-Potocka et al., 2022). The underlying pathophysiology relates to the fact that the RV typically pumps blood into a low-resistance, low-pressure pulmonary circulation. However, during exercise, the reduction in pulmonary vascular resistance is relatively smaller compared to that in the systemic circulation. As a result, the RV faces a substantial increase in afterload to overcome the elevated pulmonary arterial systolic pressure (PASP) (Lewicka-Potocka et al., 2022). Additionally, the pressure overload increases proportionally with the augmented cardiac output (CO), contributing to heightened RV wall stress (Lewicka-Potocka et al., 2022). These elevated PASP values persist for a short period during and after exercise. In this study, the left ventricle (LV) appeared to tolerate marathon running well, while the RV exhibited a decrease in radial contraction, deterioration in global systolic function, and increased chamber volumes during and after the marathon (Lewicka-Potocka et al., 2022).

Animal studies using a rat model demonstrated that fibrosis in the right ventricle (RV) and both atria was induced by changes in ventricular function following four months of forced training. This pathological remodeling led to an increased susceptibility to ventricular arrhythmias (Lewicka-Potocka et al., 2022). In amateur athletes, post-run impairment of RV function was found to be transient, with a return to baseline observed within two weeks (Lewicka-Potocka et al., 2022). However, chronic and repeated endurance exercise may result in non-physiological remodeling of the RV, ultimately altering its function over time.

Elevated cardiac biomarkers such as high-sensitivity cardiac troponin I (hs-cTnI), B-type natriuretic peptide (BNP), and stress-related markers including growth differentiation factor-15 (GDF-15) and galectin-3 (Gal-3) suggest a "biochemical storm" that occurs following marathon running (Lewicka-Potocka et al., 2022). The release of these biomarkers is believed to originate primarily from the most mechanically strained cardiac chambers, which may attempt to compensate through fibrotic repair processes (Lewicka-Potocka et al., 2022).

A higher number of completed endurance competitions and more years of training are associated with an increased prevalence of myocardial fibrosis. Studies have shown that up to 50% of veteran endurance athletes exhibit signs of myocardial fibrosis (Lewicka-Potocka et al., 2022). Supporting this, the right ventricle (RV) appears to play a key role in the origin of ventricular arrhythmias in athletes, likely due to increased RV volume and reduced right ventricular ejection fraction (RVEF), often visualized as delayed gadolinium enhancement in the interventricular septum near the RV insertion point (Lewicka-Potocka et al., 2022).

Training volume during the preparation period plays a significant role in post-race right ventricular ejection fraction (RVEF) changes. One study demonstrated that a marked post-race reduction in RV radial contraction was more likely in athletes training 47 km or more per week (Lewicka-Potocka et al., 2022). A “U-shaped curve” is commonly used to illustrate the relationship between weekly training distance and cardiovascular outcomes, highlighting that both insufficient and excessive training volumes may increase cardiovascular risk. Higher pulmonary pressures, greater RV dysfunction, and elevated levels of cardiac troponin T (cTnT), N-terminal pro-brain natriuretic peptide (NT-proBNP), and galectin-3 (Gal-3) following competition have been observed particularly in individuals with lower fitness levels (as indicated by lower VO_2peak in cardiopulmonary exercise testing, CPET) or lower training volumes (Lewicka-Potocka et al., 2022). These factors may increase susceptibility to marathon-induced myocardial injury.

In contrast, several studies have demonstrated preserved right ventricular (RV) function in endurance athletes. This may be attributed to long-term, low-intensity training during the preparation period, although the exact time frame required for RV adaptation to increased hemodynamic load remains unknown and is likely highly individual (Lewicka-Potocka et al., 2022). The so-called "athlete's heart" is typically characterized by preserved right ventricular ejection fraction (RVEF) alongside increased RV dimensions, reflecting physiological rather than pathological remodeling.

The ReVISION method allowed researchers to detect significant changes in right ventricular (RV) function among amateur marathon runners, including increased RV volumes and reduced contractility. The observed RV dysfunction was primarily attributed to a transient reduction in radial shortening, while longitudinal and anteroposterior motion components remained preserved (Lewicka-Potocka et al., 2022). Additionally, elevated levels of galectin-3 (Gal-3), a biomarker associated with myocardial fibrosis, correlated with more pronounced RV dysfunction as assessed by the ReVISION echocardiographic analysis (Lewicka-Potocka et al., 2022). These findings emphasize the importance of proper training during the preparation phase. The authors also addressed the increasingly discussed concept of cumulative RV damage in endurance athletes, noting that higher Gal-3 concentrations were found in less fit individuals—likely due to either overtraining or insufficient training—and that these athletes exhibited a more marked reduction in RV radial contraction (Lewicka-Potocka et al., 2022).

An increase in cardiac biomarker levels is commonly observed following long-distance running and is possibly related to myocardial remodeling or temporary alterations in cardiac function. Research has shown a strong correlation between post-race echocardiographic abnormalities and elevated cardiac biomarkers; however, these elevations are typically short-lived and subject to high variability (Le Goff et al., 2022). Whether these changes represent pathological processes or physiological adaptations to endurance exercise remains under debate, and further studies are needed to fully understand the underlying mechanisms and long-term implications of these findings. Myocardial necrosis is most accurately indicated by elevated levels of cardiac troponin T (cTnT), considered the gold standard biomarker due to its high sensitivity and cardio-specificity. According to definitions provided by the European Society of Cardiology (ESC) and the American Heart Association (AHA), heart-type fatty acid-binding protein (H-FABP) may also serve as a marker of myocardial ischemia (Le Goff et al., 2022). Some studies suggest that elevated high-sensitivity troponin T (hs-cTnT) levels following strenuous exercise may reflect benign and reversible physiological changes, though this remains uncertain. Other studies have shown that post-exercise troponin elevations can follow kinetics similar to those observed during cardiac events, but typically with lower peak values and a more rapid return to baseline (Le Goff et al., 2022).

The COVID-19 pandemic highlighted the importance of considering infections as potential risk factors for cardiac events in endurance athletes. One serious complication of SARS-CoV-2 infection is myocarditis, which should lead to the exclusion of affected athletes from

competition for 3 to 6 months due to the increased risk of life-threatening cardiac events. However, many professional athletes ignored medical recommendations—often due to concerns about disqualification or loss of performance. This underlines the importance of appropriate risk stratification using markers such as high-sensitivity troponin T (hs-cTnT) or cardiac MRI (Le Goff et al., 2022). Other biomarkers may also provide insight into cardiac strain during endurance events. Copeptin and NT-proBNP levels can rise in response to myocyte stretching caused by increased cardiac volume, pressure, and neurohormonal activation during marathon training (Le Goff et al., 2022). Cardiac remodeling and fibrosis are best reflected by the biomarker suppression of tumorigenicity 2 (ST2), which has been proposed as a novel gold standard for early detection of heart failure. ST2 levels may increase due to various mechanisms, including elevated cardiac load, fibrosis, and structural remodeling, and importantly, these changes may signal a predisposition to arrhythmias related to fibrotic processes (Le Goff et al., 2022). Although ST2 and other cardiac biomarkers typically return to baseline within seven days post-marathon, it is concerning that post-recovery levels can remain elevated above pre-race baselines, suggesting a potential cumulative effect of repeated strenuous endurance activity (Le Goff et al., 2022).

Many studies have shown that strenuous exercise, such as participation in the Ultra-Trail du Mont-Blanc (UTMB), initiates a non-specific inflammatory response due to muscle damage, with elevated concentrations of C-reactive protein (CRP) typically peaking shortly after the event (Le Goff et al., 2022). The study showed that no permanent structural damage to the myocardium occurred after the ultramarathon, and all biomarker values tended to return to the normal range within seven days after the UTMB. However, most of them returned at slightly higher levels compared to baseline, which may be explained by the half-life and elimination time of the biomarkers (Le Goff et al., 2022). CKMB, HFABP, and hsCRP were the only markers that did not return to baseline, though the study does not exclude the possibility of a full return to baseline levels if samples were taken after a longer period; further research is necessary (Le Goff et al., 2022). These findings also suggest a potential cumulative effect of repeated endurance running, and additional studies—especially those investigating biomarkers such as ST2 in correlation with cardiac MRI—are recommended.

Cardiovascular remodeling associated with long-distance running—particularly more pronounced in elite and professional athletes—includes increased left ventricular (LV) mass, enlargement of both atria, increased LV myocardial wall thickness, and a greater bi-ventricular diameter. Despite these structural adaptations, systolic and diastolic function typically remain preserved. In studies analyzing the hearts of first-time marathon runners, researchers observed

predominantly concentric bi-ventricular remodeling, which was less pronounced than expected. Notably, eccentric LV hypertrophy was not observed in these runners, suggesting that such adaptation likely develops only after many years of sustained endurance training (Tsarouhas et al., 2022).

Exercise-induced inflammation is characterized by changes in inflammatory markers and is commonly observed in marathon and ultramarathon runners. This response results from microdamage to muscle tissue during prolonged exertion, which triggers local inflammation as part of the repair process. Consequently, there is an accumulation of leukocytes and activation of a systemic response, primarily manifesting as an acute-phase reaction and leukocytosis (Tsarouhas et al., 2022). The acute-phase response involves the release of cortisol, adrenocorticotropic hormone (ACTH), cytokines, and acute-phase proteins, such as C-reactive protein (CRP). In addition, alterations in endothelial function—particularly the depletion of nitric oxide (NO)—are currently under scientific investigation due to their potential implications for vascular health and recovery (Tsarouhas et al., 2022).

Strenuous exercise is characterized by several physiological stressors, including oxidative stress, glycogen depletion, muscle damage, increased plasma levels of cortisol and catecholamines, and the release of endotoxins. These factors collectively trigger the release of pro-inflammatory cytokines and can further amplify their concentrations. Interleukin-6 (IL-6), which exhibits both pro- and anti-inflammatory properties, is particularly sensitive to exercise intensity and energy availability (Tsarouhas et al., 2022). Its production is modulated by muscle contractions, the extent of muscle damage, and fatigue. In addition, circulating monocytes and activated macrophages contribute to the release of tumor necrosis factor-alpha (TNF-α), which partially counteracts IL-6 activity and promotes the production of cytokine inhibitors such as interleukin-1 receptor antagonist (IL-1ra) (Tsarouhas et al., 2022).

Augmented LV and RV chamber sizes, which are typical in endurance athletes, may lead to volume overload during marathon running or other high-intensity dynamic exercises (Tsarouhas et al., 2022). This volume load, in proportion to increased LV wall thickness, may contribute over time to the development of eccentric LV hypertrophy. One study also found that structural changes in the RV begin early in training and intensify with increasing training volume, while LV volumes tend to increase after approximately six months of sustained endurance training (Tsarouhas et al., 2022). Notably, the first six months of adaptation are primarily characterized by concentric hypertrophy; however, with continued high-intensity and prolonged training, eccentric hypertrophy emerges as the LV progressively dilates (Tsarouhas

et al., 2022). In summary, marathon training induces both LV and RV remodeling, progressing from concentric to eccentric hypertrophy in response to training duration and intensity.

A recent study confirmed similar findings, reporting that mild eccentric myocardial hypertrophy was present in ultramarathon runners (Tsarouhas et al., 2022). In contrast, a moderate training program involving 40 km per week in middle-aged marathon runners led to an increase in peak oxygen consumption (VO_2peak) during cardiopulmonary exercise testing over an 18-week period, but resulted in less pronounced myocardial adaptations (Tsarouhas et al., 2022). Diagnosing early cardiac disease in older athletes remains challenging due to a higher prevalence of cardiovascular risk factors compared to younger athletes, as well as the lack of well-defined criteria for distinguishing physiological cardiac adaptations ('athlete's heart') from early pathological changes. In elderly runners, increases in left ventricular (LV) mass and volume may be attributed to age-related factors such as elevated blood pressure rather than exercise alone. A potentially promising indicator of subclinical cardiac alterations—unrelated to training adaptations—is the presence of isolated left ventricular hypertrophy without a corresponding increase in LV mass, which may help differentiate early cardiac pathology from physiological remodeling in athletes (Tsarouhas et al., 2022).

Metabolism

Marathon running induces a wide range of metabolic adaptations that differ from the well-established physiological and immunological health effects observed in shorter running races (<5 km). Marathon runners tend to have higher levels of high-density lipoprotein (HDL) cholesterol and lower levels of triglycerides and serum low-density lipoprotein (LDL) cholesterol compared to age-matched controls (Braschler et al., 2025). Key metabolic adaptations to endurance running primarily involve fuel substrate catabolism, including lipolysis, ketogenesis, elevated glycolysis, amino acid oxidation, and tricarboxylate cycle (TCA) intermediates (Braschler et al., 2025). Furthermore, some studies suggest the activation of alternative energy-producing pathways, such as ω- and/or α-oxidation of fatty acids and increased autophagy of cellular membranes, as evidenced by elevations in dicarboxylic acids, hydroxy acids, and odd-chain fatty acids, coupled with reduced phospholipid levels (Stander et al., 2021). Additionally, fluctuations in purine and pyrimidine metabolism, the urea cycle, and reactive oxygen intermediates have been observed. These findings emphasize the high energetic demands of endurance running and highlight the metabolic flexibility of athletes to utilize multiple fuel substrates during endurance races to sustain performance and complete the event (Stander et al., 2021).

Following endurance exercise, the recovery of metabolic adaptations to pre-exercise levels may take between 3 and 72 hours, depending on the duration, intensity, and distance of the running race. Cessation of running activates anabolic pathways required for recovery, such as nucleotide salvage pathways, glycogenesis, lipogenesis, and protein synthesis, while simultaneously inhibiting catabolic pathways involved in energy production during endurance events (Stander et al., 2021). Marathons and ultramarathons are gaining popularity worldwide as recreational activities, despite their potential adverse effects on health. Therefore, both runners and researchers seek strategies that may expedite the recovery process in a cost-effective manner and enhance athletic performance.

There is ongoing debate regarding the use of supplements containing functional foods before and after workouts. Besides their nutritional value, functional foods are, by definition, supplements rich in bioactive compounds that provide health benefits (Stander et al., 2021). Antioxidant, anti-inflammatory, antimicrobial properties, and radical-scavenging activity are well-documented benefits of phytonutrient-rich fruits and vegetables, including blueberries, beetroot, pears, cherries, bananas, pomegranates, carrots, and blackcurrants. These plant-based foods may enhance athletic performance and support physiological recovery during or after exercise. Moreover, due to their high content of phytochemicals such as polyphenols, vitamin C, rutin, and epicatechin—which inhibit cyclooxygenase activity and disrupt the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway—and the abundance of betalains, beetroot (Beta vulgaris L.) has been proposed as one of the most potent antioxidant and anti-inflammatory functional foods, potentially surpassing the others listed above (Stander et al., 2021). The Australian Institute of Sport has classified beetroot as a Class A performance-enhancing supplement, based on scientific evidence—primarily due to the presence of bioactive pigments such as betalains, which have nitrate-donating properties. Nitrates are believed to enhance nitric oxide bioavailability, which supports the regulation of cellular respiration, vasodilation, and neurotransmission via the nitrate–nitrite–nitric oxide pathway (Stander et al., 2021). Studies, including those by the Australian Institute of Sport, have successfully applied beetroot juice as a performance-enhancing supplement. Notwithstanding, evidence regarding its ability to expedite the physiological recovery process after exercise indicates that beetroot ingestion does not accelerate metabolic recovery (Stander et al., 2021).

In a related study, researchers investigated post-marathon alterations across key energy-producing pathways, including the phosphagen system, ketogenesis, the tricarboxylic acid (TCA) cycle, anaerobic and aerobic glycolysis, and amino acid oxidation (Bester et al., 2021). A central feature of anaerobic glycolysis is the conversion of pyruvate to lactate via lactate dehydrogenase (LDH), which regenerates NAD^+ from NADH, thereby sustaining glycolysis under hypoxic conditions. This mechanism was supported by observed post-marathon elevations in both lactic acid and pyruvic acid concentrations (Bester et al., 2021). Although anaerobic glycolysis facilitates rapid NAD^+ regeneration and short-term ATP production, it is inherently limited by lactic acidosis, necessitating a subsequent shift toward aerobic glycolysis and alternative fuel pathways. During endurance exercise, carbohydrates serve as the predominant oxidative substrate, with glycogen and glucose reserves typically depleting after approximately 90 minutes of continuous effort at intensities exceeding 75% of maximal oxygen uptake (Bester et al., 2021). Paradoxically, serum glucose concentrations were elevated immediately after the marathon, as previously reported by Stander et al. (2018). This unexpected hyperglycemia is likely driven by increased gluconeogenesis, reduced insulin secretion, and an elevated glucagon-to-insulin ratio—responses triggered by depleted glycogen stores in muscle and liver. Furthermore, elevated cortisol levels, induced by the physiological stress of prolonged exertion, contribute to this metabolic shift by promoting gluconeogenesis and inhibiting cellular glucose uptake through limited translocation of glucose transporters to the membrane, a mechanism particularly prominent during fasting and intense exercise (Bester et al., 2021).

Highly trained aerobic athletes exhibit specific skeletal muscle adaptations in response to prolonged endurance exercise, including an upregulation of lipid metabolism and a slower utilization of carbohydrate stores (Bester et al., 2021). These metabolic changes facilitate sustained energy production during prolonged activity. Interestingly, a cohort study that included both amateur and well-trained marathon runners found no significant differences in metabolic profiles when comparing participants based on prior endurance training history (Bester et al., 2021).

During extended endurance efforts—particularly beyond 60–90 minutes—lipids become the predominant energy substrate. Fatty acids undergo β-oxidation, producing acetyl-CoA, which is subsequently funneled into the TCA cycle. This pathway is evidenced by elevated post-marathon serum concentrations of citric acid observed in both the current and earlier studies (Bester et al., 2021). In response to heightened energy demands and a disturbed cellular redox balance, enzymes such as citric acid synthase and pyruvate dehydrogenase are upregulated to enhance the generation of NADH and $FADH_2$, which feed into the electron transport chain for ATP synthesis (Bester et al., 2021). However, when the rate of acetyl-CoA production exceeds mitochondrial oxidative capacity—especially under conditions of NAD^+/NADH imbalance—there is a metabolic shift toward ketogenesis. The formation of ketone bodies under such conditions serves as a compensatory energy mechanism, ensuring continued ATP production when traditional oxidative pathways become saturated or inefficient.

During prolonged endurance running, branched-chain amino acids (BCAAs) become preferentially oxidized in response to acidosis, a lowered ATP:ADP ratio, and the depletion of muscle glycogen stores; nevertheless, BCAAs provide only a small fraction of the total energy required to complete a marathon (Bester et al., 2021). When serum leucine concentrations fall, autophagy can be triggered as a last-resort mechanism to meet the event's substantial energy demands. This process involves reduced glutamine transport into cells, leading to inhibition of mechanistic target of rapamycin complex 1 (mTORC1) (Bester et al., 2021). In the present study, elevated serum creatine and creatinine levels were also observed, findings that most likely reflect skeletal muscle damage, possible myocardial injury, or transient reductions in renal function (Bester et al., 2021).

Using an untargeted Proton Nuclear Magnetic Resonance spectroscopy (^{1}H-NMR) metabolomics approach, this study investigated metabolite shifts induced by marathon running. The observed metabolic adaptations to meet the substantial energy demands required for marathon completion involved key pathways, including aerobic and anaerobic glycolysis, amino acid catabolism (particularly of BCAAs), ketogenesis, and the TCA cycle (Bester et al., 2021). Notably, decreases in all three BCAAs, along with concurrent increases in all three endogenous ketone bodies, underscore their essential role in sustaining energy production during prolonged endurance exercise (Bester et al., 2021). These findings may offer potential targets for developing strategies aimed at enhancing athletic performance. Additionally, the observed post-marathon decrease in histamine concentrations—an observation not previously reported—may suggest a novel, alternative pathway contributing to energy metabolism under extreme physical stress (Bester et al., 2021).

Carbohydrate loading and appropriate caloric intake before, during, and after endurance training have been shown to prevent decreases in monocyte phagocytic activity, reduce circulating granulocyte and cytokine levels, and attenuate inflammatory responses such as monocytosis and neutrophilia—effects that are even more pronounced following high-intensity exercise (Sardeli et al., 2024). These benefits are likely mediated by the stabilization of blood glucose levels, which in turn helps regulate stress hormones such as epinephrine and cortisol. As noted above, these hormones influence cellular metabolism and enhance immune function. In contrast, training under glycogen-depleted conditions has been associated with impaired training adaptations (Sardeli et al., 2024). Furthermore, a recent meta-analysis reported an 18% increased risk of upper respiratory tract infections (URTI) within 7–21 days post-marathon (Sardeli et al., 2024), although the exact pathophysiological mechanisms underlying this association remain unclear.

To improve performance, many runners adopt a high-carbohydrate diet—providing approximately 70% of total dietary energy—during the two weeks prior to a marathon. This strategy has been shown to increase the expression of sodium-dependent glucose transporter 1 (SGLT1) in the intestinal mucosa, potentially doubling its activity and enabling more efficient carbohydrate absorption during the race (Braschler et al., 2025). Another scientifically proven approach that enhances the ability to maintain a steady pace during long-distance events (>30 km) is carbohydrate loading, typically involving an intake of 10 g of carbohydrates per kilogram of body mass per day for 24–36 hours before the race. Exercise-induced gastrointestinal symptoms have been reported to improve when certain dietary components—such as fat and protein—are restricted in the days leading up to competition. The most commonly excluded food products to reduce GI distress include dairy, caffeine, chocolate, high-protein, and high-fiber foods (Braschler et al., 2025). A recent study conducted after the Boston Marathon showed that proper post-race hydration significantly reduced both gastrointestinal symptoms and markers of intestinal cell injury within 24 hours of race completion (Braschler et al., 2025).

Basic physiological demands combined with intensive aerobic training often result in insufficient energy intake and the development of Relative Energy Deficiency in Sport (RED-S). This issue is particularly prevalent among endurance athletes, such as marathon runners, due to the mismatch between daily energy expenditure and caloric consumption. Female runners are especially at risk of low energy availability and RED-S, possibly due to a combination of environmental and socio-economic factors; however, current data on prevalence and risk factors remain limited. A general lack of awareness regarding appropriate energy intake is frequently observed among amateur athletes undergoing high-intensity training. RED-S, much like overtraining syndrome, can lead to long-term disruptions in cardiovascular health, metabolism, and reproductive function. Common consequences include chronic fatigue, decreased bone mineral density, menstrual irregularities in women, weakened immune function, and diminished exercise performance. **Due to similarities in pathophysiology and symptomatology, some researchers have proposed the concept of an 'overlap syndrome' between REDs and overtraining syndrome** (Braschler et al., 2025)**.**

Musculoskeletal system

Running—especially long-duration aerobic training such as marathon preparation—has a significant positive impact on the musculoskeletal system, including a 2–3% increase in bone mass achieved through regular exercise (Braschler et al., 2025). This effect is explained by the influence of running on bone metabolism through the activity of two key cytokines: soluble receptor activator of nuclear factor kappa-B ligand (sRANKL) and osteoprotegerin. Osteoprotegerin competitively binds to sRANKL, thereby inhibiting its ability to stimulate osteoclast activity. This mechanism reduces bone resorption and promotes bone formation. Research on blood plasma samples has shown higher levels of osteoprotegerin and significantly reduced sRANKL activation after a marathon compared to baseline levels on a normal day, indicating an inhibition of bone resorption and ultimately contributing to increased bone mass (Braschler et al., 2025).

While regular high-volume running may increase the risk of stress fractures, osteopenia, and decreased foot bone strength, recreational, well-balanced running generally has a positive effect on bone strength (Braschler et al., 2025; Scheer et al., 2022). Stress fractures typically develop due to overuse strain on otherwise healthy bone and require medical treatment and a period of absence from sporting activities. These injuries are relatively common, with incidences reported between 5.5% and 22% among ultra-endurance runners. Among female ultra-endurance runners, approximately 21% develop stress fractures, attributed to increased energy expenditure combined with inadequate nutritional intake (Scheer et al., 2022).

The use of MRI has enhanced understanding of musculoskeletal changes before and after ultra-endurance running. For example, athletes with pre-existing tendinopathies showed deterioration on MRI following races, although no acute changes were observed in patellofemoral or tibiofibular joint structures post-race (Scheer et al., 2022). Most tendon injuries, such as patellar or Achilles tendinopathy, are minor and relatively common; however, some cases may lead to inflammation and chronic conditions, potentially resulting in prolonged absence from sport.

Trabecular bone, due to its high metabolic activity, is considered a good indicator of overall bone health. The calcaneus is often assessed since approximately 90% of its composition is trabecular bone. Ultrasonographic studies in marathon runners have demonstrated increased bone stiffness in the calcaneus, with even more pronounced effects observed in runners over 40 compared to non-runners (Braschler et al., 2025).

During marathon training and competition, skeletal muscles and tendons are subjected to considerable mechanical stress and must undergo adaptive changes to withstand such loads. The most significant adaptations are metabolic and driven by well-structured, consistent endurance training. One study demonstrated a 48% increase in muscle oxygen uptake ($\dot{V}O_2$) following marathon training, even without changes in maximal oxygen uptake ($\dot{V}O_2max$). Additional adaptations include enzymatic remodeling and shifts in muscle fiber composition. Muscle biopsies from trained marathon runners revealed higher concentrations of myoglobin, an increased number of mitochondria, and improved oxygen extraction evidenced by greater capillary density. These changes contribute to more efficient energy metabolism supported by enhanced adenosine triphosphate (ATP) production via oxidative phosphorylation (Braschler et al., 2025).

Moreover, endurance training leads to remodeling of muscle fiber composition, with a greater proportion of type I (slow-twitch) fibers compared to type II (fast-twitch) fibers, enhancing the efficiency of the aerobic energy pathway and providing a performance advantage in long-duration events. In addition to fiber type remodeling, endurance training induces architectural

changes at the microscopic level, such as shorter muscle fascicles and larger pennation angles, which reduce muscular fatigue and improve metabolic efficiency. Notably, these changes do not decrease muscle echogenicity and appear to enhance performance by promoting more efficient transmission of muscular force to the ground during running (Braschler et al., 2025).

There is ongoing debate regarding the potential link between marathon training and increased prevalence of degenerative joint diseases such as osteoarthritis. MRI imaging of the knee has shown a temporary decrease in cartilage thickness following acute bouts of exercise; however, the long-term effects of endurance running on joint health remain inconclusive. One MRI-based study found no harmful long-term effects of marathon training, with knee joint parameters returning to baseline eight weeks after the race. Nonetheless, some recreational marathon runners exhibited transient meniscal signal alterations. Additionally, a study of former professional athletes with a lifetime mileage of 142,000 km revealed no increased incidence of knee osteoarthritis compared to age-matched sedentary controls (Braschler et al., 2025).

Another study found no increased prevalence of osteoarthritis in the lower extremity joints of endurance athletes when experienced marathon runners were compared to age- and BMI-matched sedentary controls. The primary risk factors for degenerative joint changes leading to osteoarthritis include the accumulation of micro-damage, often resulting from pre-existing high-grade meniscal lesions or malalignment of the lower extremities. These conditions can be exacerbated by overtraining and mechanical overload (Braschler et al., 2025). Therefore, adequately structured training programs combined with sufficient recovery—particularly quality sleep—are unlikely to increase the risk of osteoarthritis in endurance runners. Supporting this, a recent study reported a prevalence of hip or knee osteoarthritis of 17.9% in the general population, whereas endurance runners demonstrated a significantly lower prevalence of 8.8%, suggesting a protective effect of marathon training on joint health (Braschler et al., 2025).

Additionally, another study demonstrated a favorable effect of marathon training in the prevention of osteoarthritis by protecting chondrocyte progenitor cells through modulation of the vitamin B6 salvage pathway; however, as this finding is based on an in vitro model, further research is needed to confirm its relevance in vivo (Braschler et al., 2025).

Nevertheless, several harmful consequences to the musculoskeletal system have been observed during endurance running. Performance limitations in marathon training are largely attributable to running-related musculoskeletal injuries, reported by 18.2% to 92.4% of runners. Of particular concern, 56% to 90% of marathon trainees experience at least one running-related injury annually—most commonly affecting the lower extremities, with approximately 70% of

all injuries occurring at or below the knee. These injuries are primarily caused by overtraining and overuse (Braschler et al., 2025). The wide variation in reported incidence rates can be attributed to differences in study methodology, injury definitions, and data collection approaches.

A recent systematic review identified the following prevalence ranges for specific injuries among endurance runners: patellofemoral pain syndrome (5.5%–22.7%), medial tibial stress syndrome (13.6%–20.0%), Achilles tendinopathy (9.1%–10.9%), plantar fasciitis (4.5%–10.0%), ankle sprain (10.9%–15.0%), and iliotibial band syndrome (1.8%–9.1%) (Braschler et al., 2025). An increase in radiological damage scores is commonly observed when comparing pre- and post-race MRI scans of the knee joint, with changes frequently noted in structures such as the lateral patellar cartilage, iliotibial band, prepatellar bursa, and semimembranosus tendon (Braschler et al., 2025).

Bone stress injuries—particularly affecting the medial tibia (9.1%), femoral neck, and metatarsals—are relatively common among endurance and marathon runners. These injuries are typically linked to chronic overload and are influenced by both intrinsic and extrinsic risk factors, including a history of prior injury and poor nutritional status (e.g., low body weight, inadequate caloric intake, or vitamin D deficiency), all of which increase the risk of stress fractures and new injuries (Braschler et al., 2025).

First-time marathon participants represent a particularly vulnerable group: 9.5% sustain major injuries (such as bone stress injuries), while 49.2% experience minor injuries (e.g., medial tibial stress syndrome) during preparation or the event itself (Braschler et al., 2025). To reduce injury risk, it is recommended that runners complete at least one long-distance training run within the month preceding the marathon (Braschler et al., 2025). Although less prevalent than ligamentous or muscular injuries, bone stress injuries should not be underestimated due to their potential to impair long-term training continuity and performance.

Respiratory System

The most crucial aspects of respiratory performance for marathon and ultra-marathon athletes are efficient blood oxygenation and sufficient ventilation. Ultra-endurance running places the respiratory system under abnormal physiological conditions. At rest, the proximal airways humidify, warm, and filter inspired air before it reaches the lung parenchyma. However, during exercise, minute ventilation (VE) can increase dramatically—from 35–62 $L \cdot min^{-1}$ in recreational athletes to over 115 $L \cdot min^{-1}$ in elites—representing up to a 15-fold increase over baseline levels. At these rates, the airway conditioning capacity may be exceeded (Braschler et

al., 2025; Scheer et al., 2022). As a result, unconditioned air reaches the distal airways, which may contribute to epithelial damage and impaired mucosal defense. This exposure is thought to trigger exercise-induced bronchoconstriction through smooth muscle contraction and inflammation, ultimately narrowing the airways (Braschler et al., 2025; Scheer et al., 2022).

Inhalation of cold, dry air further exacerbates this phenomenon by repeatedly stressing bronchial smooth muscle, promoting airway remodeling and dysfunction. Consequently, endurance athletes exhibit a higher prevalence of asthma compared to the general population, with rates ranging from 4.3% to 24.8% (Braschler et al., 2025). Despite this risk, marathon training offers significant health benefits to the respiratory system across all age groups. Older runners (aged 40–75) may slow or prevent age-related declines in pulmonary function, while younger runners often experience improvements in forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) (Braschler et al., 2025). In bronchoprovocation tests, recreational marathoners show smaller reductions in lung volumes after methacholine challenge compared to sedentary controls, suggesting enhanced baseline lung capacity and reduced airway reactivity (Braschler et al., 2025). This observation also supports aerobic training as a potential adjunct therapy in diseases such as cystic fibrosis.

Respiratory muscle fatigue is another frequently observed phenomenon in endurance runners. After exhaustive efforts such as marathons or ultra-marathons, both inspiratory and expiratory muscles demonstrate reduced force-generating capacity—mirroring the fatigue observed in skeletal muscles post-race (Braschler et al., 2025). Mouth-pressure maneuvers are commonly used to evaluate respiratory muscle strength, but findings are inconsistent. Some studies report no change in expiratory function, while others show a decrease in maximum expiratory pressure (MEP) without significant change in peak expiratory flow (PEF), or vice versa. Similarly, studies on inspiratory fatigue report either unchanged maximum inspiratory pressure (MIP) or a concurrent decline in both MIP and peak inspiratory flow (PIF) (Braschler et al., 2025). These conflicting results likely reflect the multifactorial nature of respiratory limitations—including airway obstruction, muscle fatigue, and dynamic restriction.

In summary, marathon training can enhance respiratory health and capacity, though not without potential drawbacks. While it may prevent pulmonary decline and improve ventilatory efficiency, temporary impairments in lung function have been observed following races, largely due to muscle fatigue, airway narrowing, and restrictive dynamics. Additionally, there is evidence of elevated risk for asthma, allergic, and atopic conditions among marathon runners (Braschler et al., 2025).

Despite the high adaptability of the respiratory system, certain performance-limiting mechanisms can still emerge. These include respiratory muscle fatigue, airflow restriction, exercise-induced arterial hypoxemia due to widened alveolar-arterial oxygen gradients, and upper airway narrowing or collapse (Tiller et al., 2020). Radiographic studies have shown that up to 17% of marathon runners experience exercise-induced pulmonary edema, characterized by accumulation of extravascular lung water (EVLW). Interestingly, this condition does not typically impair performance or cause lasting functional changes (Tiller et al., 2020).

However, a subset of runners appears particularly susceptible to pulmonary edema. In these individuals, EVLW is more pronounced, along with a greater reduction in alveolar-capillary diffusion capacity, suggesting the influence of individual predispositions. Additionally, some runners exhibit signs of right ventricular (RV) dysfunction that exceed left ventricular (LV) impairment, potentially increasing pulmonary vascular pressure and reducing lung diffusing capacity (Tiller et al., 2020). Respiratory muscle fatigue may further contribute to decreased ventilatory capacity and initiate a metaboreflex, which redirects blood away from peripheral muscles, intensifying sensations of dyspnea (Tiller et al., 2020).

Post-race periods are also associated with elevated prevalence of upper respiratory tract infections (URTIs), particularly following high-intensity or high-volume marathons (Sardeli et al., 2024). While the precise mechanisms remain unclear, elevated levels of stress hormones, such as norepinephrine and cortisol, are believed to suppress immune function. Initially, acute increases in norepinephrine may stimulate immunity, but prolonged exposure appears to dampen immunosurveillance and reduce effector cell activity. Cortisol, due to its potent anti-inflammatory properties, may further disrupt immune regulation during prolonged endurance activity. Seasonal variation also plays a role, with approximately 70% of URTIs occurring in autumn and winter and only 30% during spring and summer. Nonetheless, even when environmental conditions are controlled, younger athletes have shown a higher incidence of URTIs post-marathon than older athletes—an inverse pattern compared to pre-race susceptibility (Sardeli et al., 2024).

Supporting this observation, a study by Nieman et al. found that younger male and female runners (<30 years) experienced significantly more post-marathon URTIs compared to runners who remained asymptomatic before the race. This suggests that both immune suppression and demographic factors contribute to post-race infection risk in endurance athletes.

Renal System

Marathon running imposes transient cardiorenal dysfunction due to significant physiological stress, as evidenced by elevated levels of catecholamines and neurohormones such as aldosterone, vasopressin, and atrial natriuretic

peptide (ANP). These changes, along with the elevation of cardiac biomarkers, may be associated with reduced kidney function or the development of acute kidney injury (AKI) (Braschler et al., 2025).

To maintain blood pressure, regulate fluid balance, and meet the increased cardiac demands during long-distance running, the body activates the renin–angiotensin–aldosterone system (RAAS). However, this adaptive response may contribute to AKI by inducing tubular injury secondary to renal hypoperfusion, as blood flow is preferentially redistributed toward active skeletal muscles during exertion (Braschler et al., 2025). Simultaneously, the kidneys attempt to compensate for dehydration by conserving sodium and water, which may impose further stress on the cardiorenal axis and contribute to the development of acute cardiorenal syndrome.

Fortunately, these renal and cardiac alterations are typically transient, with biomarker levels returning to baseline within 24 to 72 hours post-exercise (Braschler et al., 2025). Nonetheless, proper post-race recovery is critical, particularly after repeated high-intensity efforts, to prevent cumulative cardiorenal damage that could have long-term consequences.

In the context of chronic kidney disease (CKD), regular physical activity—including moderate endurance exercise such as marathon training—has demonstrated therapeutic benefits. Inactive individuals with CKD tend to exhibit faster disease progression compared to active patients. One study reported a 1.5-fold slower weekly decline in estimated glomerular filtration rate (eGFR) among those engaging in over 150 minutes of physical activity per week (Braschler et al., 2025).

Despite these benefits, data on AKI prevalence in marathon runners are striking. According to the Acute Kidney Injury Network (AKIN) criteria, serum creatinine (sCr) elevations indicative of AKI are observed in approximately 40% to 82% of marathon participants (Braschler et al., 2025). Acute tubular injury, diagnosed in about 75% of runners via urine microscopy, appears to be the primary underlying mechanism. In addition, microscopic hematuria has been found in one-third of finishers, further confirming renal stress (Braschler et al., 2025).

The pathophysiology of AKI in endurance runners remains under debate. One widely accepted hypothesis is pre-renal AKI resulting from extensive fluid loss combined with inadequate rehydration. A strong correlation has been shown between greater sweat losses and increased AKI risk, underscoring the importance of effective volume regulation during competition (Braschler et al., 2025). Moreover, significant redistribution of blood volume away from internal organs toward working muscles during prolonged exertion can exacerbate renal hypoperfusion. Under such conditions, cardiac output may drop by up to 25%, and since the kidneys normally receive 20% of resting cardiac output, this reduction may lead to ischemic tubular damage and temporary kidney dysfunction (Braschler et al., 2025).

Additionally, exertional rhabdomyolysis may release large amounts of myoglobin, which can cause pigment-induced nephropathy and contribute to AKI. Interestingly, post-race recovery involving light-intensity continuous running, initiated around 48 hours after a marathon, has been associated with the most favorable renal outcomes (Braschler et al., 2025).

Environmental conditions on race day—such as temperature, humidity, and elevation—also influence the incidence and severity of AKI. Under typical conditions (15.6 °C, 50% humidity, flat terrain), average body fluid loss is estimated at 3% (Hernando et al., 2022). Nevertheless, signs of renal stress remain common at the finish line. In one study assessing sCr and GFR, 48.68% of runners met AKI criteria immediately post-race, with 97%

of these cases categorized as Grade I. These changes were consistent across age groups, and most values normalized within 24 hours, indicating transient renal dysfunction (Hernando et al., 2022). Hematuria was detected in 36.85% of participants, further supporting evidence of renal involvement.

It is important to note that traditional renal markers such as sCr may be influenced by exercise-induced muscle injury, including elevations in lactate dehydrogenase (LDH), which confound GFR estimates. To address this, several novel biomarkers have been proposed—such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and cystatin C—which may more specifically reflect glomerular and tubular stress by indicating intracellular damage, and are less affected by muscle breakdown (Hernando et al., 2022). However, their clinical use remains limited due to high cost, restricted availability, and lack of widespread validation in athletic populations. Further research is needed to confirm their diagnostic utility under exercise-induced stress conditions.

Post-race hydration appears to influence renal recovery dynamics significantly. Increased fluid intake following marathon completion promotes glomerular filtration and may explain the biphasic pattern of GFR changes observed after the race. One study noted that hydration normalization typically occurs within 48 hours and aligns with GFR stabilization (Hernando et al., 2022). In some cases, a temporary improvement in GFR at 24 hours may reflect overhydration and enhanced renal perfusion. Notably, studies have also shown that light-intensity running in the days following a marathon supports recovery by helping resolve exercise-induced renal and muscular stress (Hernando et al., 2022).

Sleep, Libido and Brain Functions

Lower libido scores have been observed in men engaged in marathon-specific training compared to those not participating in such activity (Hackney et al., 2022). Although completing more marathons was associated with a further reduction in libido, the effect was modest within this population. Among men of similar age, the most influential factors impacting libido were the number of years spent in training and the proportion of high-intensity workouts, both demonstrating an inverse relationship with libido levels (Hackney et al., 2022). Notably, neither marathon training itself nor the number of completed races were the primary determinants. These findings indicate that cumulative training load and intensity are more significant contributors to reduced libido than marathon participation alone. Furthermore, the potential role of Relative Energy Deficiency in Sport (RED-S)—a syndrome previously identified in both male and female athletes—is hypothesized to influence physiological mechanisms underlying decreased libido. In this context, reduced frequency of morning erections was associated with lower libido scores, supporting a possible link between RED-S and endocrine suppression in endurance-trained men (Hackney et al., 2022).

Although few studies have examined the neurological effects of marathon training in amateur runners, growing evidence suggests benefits for brain health. Among the brain regions affected, the hippocampus appears particularly responsive to physical activity, likely due to its high neuroplasticity and sensitivity to age-related degeneration (Ao et al., 2023). As a critical structure involved in spatial navigation, memory processing, emotional regulation, sensorimotor integration, and broader cognitive functions—including sleep and stress responses—the hippocampus serves as a central target of exercise-induced neuroadaptations.

Compared to sedentary controls, amateur marathon runners have demonstrated significantly greater volumes in both the left and right hippocampus, including specific subfields such as CA1, CA4, the granule cell and molecular layer of the dentate gyrus (GC–DG), the molecular layer, left CA2–3, and the hippocampus–amygdala transition area (HATA) (Ao et al., 2023). These anatomical enhancements were accompanied by better subjective sleep quality, as assessed by the Pittsburgh Sleep Quality Index (PSQI), although no significant differences in sleep duration were found between groups. Importantly, no direct associations were observed between hippocampal volumes and either PSQI scores or total sleep time, suggesting that structural brain adaptations and sleep quality may operate through distinct mechanisms (Ao et al., 2023). These results highlight the potential of endurance exercise as a non-pharmacological strategy to preserve hippocampal function, although further longitudinal research is needed to clarify causality and underlying pathways.

During the early phase of the COVID-19 lockdown, research into sleep patterns among athletes revealed heterogeneous outcomes: approximately half reported improved or worsened sleep, while the remaining athletes experienced no significant change, characterizing their sleep as normal (Nikolaidis et al., 2023). An important contributor to these variations may be the Sleep Regularity Index (SRI), which measures consistency in sleep onset and offset. Studies tracking SRI over five to seven days observed higher regularity among women, athletes in individual sports, and those competing at elite levels. Additionally, athletes with more regular sleep patterns showed higher sleep efficiency, lower variability in total sleep time and sleep onset, and overall improved sleep behavior (Nikolaidis et al., 2023; Driller et al., 2022).

Adequate sleep is essential for both performance and health, particularly in long-distance runners. Susceptibility to infection poses a considerable challenge for marathon athletes, as illness can interrupt training and reduce performance gains. As emphasized in earlier literature, sufficient sleep—along with proper nutrition, strategic rest periods, and avoiding contact with infectious individuals—can reduce the risk of upper respiratory tract infections (URTIs) (Sparling et al., 1993). Furthermore, good sleep efficiency has been associated with a lower incidence of musculoskeletal injuries among distance runners (Nikolaidis et al., 2023). Research into post-marathon sleep patterns revealed that marathon races can lead to suppression of rapid eye movement (REM) sleep and reductions in overall sleep duration—effects not seen after typical 90-minute training sessions (Nikolaidis et al., 2023).

Nocturnal heart rate (HR) variability serves as a reliable marker of sleep efficiency and autonomic recovery. In one study, physically active men were assessed under three different conditions: on a rest day, following a marathon, and after a moderate-intensity endurance session. The RR interval—the time between heartbeats—increased by 109% after the training session and by 130% after the marathon, relative to the rest day. Conversely, the standard deviation of RR intervals, a key index of HR variability, decreased to 90% following the training session and to 64% after the marathon, indicating diminished autonomic nervous system modulation and impaired sleep efficiency after more strenuous efforts (Nikolaidis et al., 2023). These findings underscore the substantial physiological burden imposed by high-intensity endurance events. However, the long-term implications of these alterations remain uncertain and warrant further investigation.

In a separate study comparing sleep-related HR responses following a marathon and a typical training session (separated by a two-week washout), no significant differences were observed in sleep-time heart rate, despite higher HR during waking hours on the marathon day. The authors interpreted this result as evidence of decreased

adrenergic activity during sleep, potentially serving as a protective mechanism to support recovery (Nikolaidis et al., 2023).

Taken together, these findings suggest that well-structured sleep strategies may reduce the risk of infection, prevent injury, and enhance overall recovery in endurance athletes. At the same time, marathon events may temporarily impair sleep efficiency through altered autonomic control. In ultramarathon events, sleep becomes an even more strategic variable. For races exceeding 200 kilometers, maintaining regular sleep is critical to sustaining performance. By contrast, in shorter ultramarathons, planned sleep restriction—applied over several days—may paradoxically enhance performance and lead to faster finish times (Nikolaidis et al., 2023).

Water-Electrolyte Balance

During long-distance running competitions, fluid and electrolyte imbalances are common. Electrolyte disturbances can vary widely due to numerous environmental factors, including heat and humidity. Among these imbalances, the most frequently affected electrolyte is sodium, with exercise-associated hyponatremia (EAH) occurring in approximately 1% to 20% of marathon athletes (Braschler et al., 2025).

The primary factor contributing to EAH is excessive fluid intake during the race, often accompanied by minimal or no decrease in body mass index (BMI). Moreover, the intense physical exertion experienced during competition induces physiological stress and may lead to exertional rhabdomyolysis, which stimulates the release of antidiuretic hormone (ADH) and proinflammatory cytokines. These responses, in turn, may result in the syndrome of inappropriate antidiuretic hormone secretion (SIADH), further promoting fluid retention (Braschler et al., 2025).

Additional contributing factors include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), female sex, body weight gain during the event, and environmental conditions such as high ambient temperatures. To mitigate these risks, it is recommended that runners consume electrolyte-containing fluids at a rate of approximately 500–1000 ml per hour, along with sodium supplementation of around 1–2 grams per hour. Importantly, hydration strategies should be individually implemented and tailored to each athlete's marathon plan (Braschler et al., 2025).

In the past, marathon guidelines often emphasized drinking as much as possible to avoid dehydration. However, more recent research has shown that over 10% of runners may develop some degree of EAH, which is primarily caused by excessive fluid consumption during prolonged endurance activity (Namineni et al., 2023). EAH is defined as a serum sodium concentration below 135 mmol/L measured during or after physical activity. Mild cases may manifest as dizziness, nausea, confusion, or seizures, while severe cases can progress to encephalopathy, pulmonary edema, or even death (Namineni et al., 2023).

The pathogenesis of EAH involves a complex interplay of overlapping factors: excessive fluid intake, inappropriate ADH secretion leading to water retention, and abnormal shifts of sodium into osmotically inactive compartments (Namineni et al., 2023; Braschler et al., 2025).

Numerous risk factors have been associated with EAH, including weight gain during the race, prolonged race duration, female sex, use of NSAIDs, extreme BMI values, and fluid intake exceeding 3–3.5 liters during the event (Namineni et al., 2023). Survey data from marathon participants revealed that slower runners tend to hydrate more frequently and are more likely to rely on unverified information sources. In contrast, faster runners generally base their hydration strategies on scientific evidence, while first-time marathoners commonly obtain advice from non-

specialist online platforms (Namineni et al., 2023). Despite these differences, both experienced and inexperienced runners showed an overall inadequate understanding of hyponatremia. However, a greater awareness of EAH was noted among faster and more experienced participants (Namineni et al., 2023).

In light of the rising incidence of EAH, the Third International Exercise-Associated Hyponatremia Consensus Development Conference (2015) and the Wilderness Medical Society guidelines (2019) both advocated for a "drink to thirst" approach as the optimal strategy to prevent both dehydration and overhydration. Alarmingly, more than 95% of runners in the referenced study did not follow this guideline, highlighting a significant gap in the practical application of preventive strategies (Namineni et al., 2023).

Gastrointestinal System and Liver Health

The gastrointestinal (GI) system benefits significantly from marathon training and regular moderate exercise. Physical activity enhances gut motility and accelerates intestinal transit, thereby preventing the accumulation of fecal residues and excess intraluminal gas. Furthermore, physically active individuals show a markedly reduced risk of cholelithiasis—by up to 3.3- and 2.3-fold—particularly when other risk factors, such as obesity, are excluded (Braschler et al., 2025). Moreover, epidemiological data demonstrate a 1.2- to 3.6-fold lower risk of colorectal cancer among runners compared to sedentary individuals (Braschler et al., 2025).

Despite these positive effects, some negative gastrointestinal outcomes have been observed, particularly during high-intensity or long-duration endurance efforts. GI symptoms are among the most frequently reported issues during marathon races, affecting between 20–57% of participants—especially younger runners and females (Braschler et al., 2025). Common complaints include nausea, vomiting, heartburn, abdominal cramps, flatulence, loss of appetite, urgency to defecate, bloating, and (bloody) diarrhea (Braschler et al., 2025).

Several mechanisms have been proposed to explain these symptoms. One major factor is splanchnic hypoperfusion: during intense exercise, blood is redirected from the gastrointestinal tract to working muscles, with intestinal blood flow reduced by up to 80%. This can lead to mucosal ischemia, increased gut permeability, and translocation of microbiota, potentially triggering endotoxin release and diarrhea (Braschler et al., 2025). In parallel, mechanical vibrations and repetitive motion of the intestines while running may further irritate the gut and contribute to GI discomfort.

Moreover, endurance races have been associated with elevated levels of gastrointestinal hormones. For instance, glucagon-like peptide-1 (GLP-1) has been shown to rise to concentrations comparable to those observed in pancreatic tumors. Increases in other hormones—such as gastrin, secretin, and vasoactive intestinal polypeptide (VIP)—have also been documented during marathon events (Braschler et al., 2025).

Dehydration is another key contributor to GI symptoms. In particular, abdominal cramps have been reported in up to 80% of runners who lost more than 4% of their body weight during a race. Additionally, impaired nutrient absorption—especially of carbohydrates—may exacerbate these issues. The sodium-dependent glucose transporter 1 (SGLT1), responsible for glucose absorption in the gut, is limited to ~60 g/h under sedentary conditions. However, optimal marathon fueling strategies typically involve carbohydrate intake near 90 g/h. Without proper gastrointestinal adaptation through training, this discrepancy can lead to bloating and discomfort (Braschler et al., 2025).

In parallel with these gastrointestinal considerations, endurance exercise also affects iron metabolism at both systemic and cellular levels. Hepcidin (Hpc), the central regulator of iron homeostasis, inhibits duodenal iron absorption and promotes iron mobilization from intracellular stores. Multiple studies have documented post-exercise increases in hepcidin, indicating that physical activity alters iron regulation (Tomczyk et al., 2020). Conversely, inactivity may lead to excessive iron accumulation in organs such as the liver, heart, skeletal muscle, and endocrine glands.

Notably, athletes—including recreationally active elderly individuals—consistently show lower body iron stores. This is likely due in part to hepcidin elevation induced by training, which may reduce iron absorption over time (Tomczyk et al., 2020). Genetic predispositions also play a role. For example, hereditary hemochromatosis, especially common in Northern Europeans, may confound observations related to exercise-induced iron regulation.

Exercise also stimulates erythropoiesis, drawing on iron stores. Ferritin, the main intracellular iron storage protein, is utilized for hemoglobin synthesis during red blood cell production. This process is regulated by erythropoietin (EPO) and erythroferrone (ERFE), the latter of which suppresses hepcidin to increase iron availability. In the referenced study, all athletes maintained normal ferritin and transferrin levels, except for two individuals who exhibited reduced serum iron and transferrin (Tomczyk et al., 2020). Genetic analysis revealed that 11 of 29 runners were heterozygous for the H63D HFE mutation, while 18 were wild-type. Importantly, no significant differences in iron markers were found between these groups immediately post-marathon (Tomczyk et al., 2020).

Interestingly, one week post-race, ERFE levels slightly increased in wild-type runners. At the same time, markers of inflammation and muscle damage—such as creatine kinase (CK), leukocytes, neutrophils, and pentraxin 3—also rose, although high-mobility group box 1 protein (HMGB1) did not (Tomczyk et al., 2020). The observed increase in transferrin, total iron-binding capacity (TIBC), and EPO is likely part of an adaptive response to restore iron homeostasis and support erythropoiesis (Tomczyk et al., 2020).

Post-race levels of EPO, ERFE, and hepcidin appear to depend on baseline iron and ferritin concentrations. While many runners showed an increase in hepcidin after the marathon, others did not. Importantly, HFE heterozygosity did not consistently predict hepcidin response. Similarly, post-race EPO levels varied among participants but were generally higher in those with lower baseline iron—indicating a compensatory response to pre-existing deficiency (Tomczyk et al., 2020).

In addition to the gastrointestinal and hematologic effects, running also has a notable impact on liver health. Nonalcoholic fatty liver disease (NAFLD) is highly prevalent and can progress to fibrosis, nonalcoholic steatohepatitis (NASH), and ultimately cirrhosis. Its pathophysiology involves systemic insulin resistance. Encouragingly, endurance training has been shown to reduce intrahepatic fat by approximately 3.5%, improve insulin sensitivity, lower fasting free fatty acid levels, and enhance both lipid and glucose metabolism—thereby improving overall liver function (Braschler et al., 2025).

Furthermore, improved cardiorespiratory fitness from marathon training may help delay fibrosis and reduce inflammation in NAFLD patients. These benefits are thought to result from a reduction in oxidative stress affecting both the liver and vascular endothelium. However, certain studies have also reported transient increases in liver enzymes, such as AST and ALT, peaking roughly 48 hours after marathon completion. Additionally, markers of

cholestasis—gamma-glutamyltransferase (GGT), bilirubin, and alkaline phosphatase (ALP)—may rise post-race, though they typically return to baseline within 24 hours (Braschler et al., 2025).

The etiology of these elevations remains debated. For instance, increased bilirubin levels may reflect exercise-induced hemolysis rather than impaired biliary excretion. Likewise, AST and GGT—enzymes also found in skeletal muscle—may reflect muscle damage rather than direct hepatocellular injury. Meanwhile, metabolic demands during prolonged endurance activity, particularly increased fatty acid oxidation and gluconeogenesis, may transiently alter hepatocyte membrane permeability, contributing to biomarker fluctuations (Braschler et al., 2025).

Nonetheless, liver injury cannot be ruled out entirely, particularly as ALP and ALT are more liver-specific. Some researchers have proposed that oxidative stress from intense muscle activity could induce hepatic ischemia. Interestingly, short cycles of leg ischemia—known as remote ischemic preconditioning (RIPC)—have been investigated as a potential method to mitigate post-race liver stress (Braschler et al., 2025).

In rare but severe cases, acute liver failure has been reported during or shortly after marathon events. Approximately 30% of these cases required liver transplantation and were typically associated with multiple organ failure, triggered by exertional heat stroke or severe rhabdomyolysis and systemic inflammation (Braschler et al., 2025).

Training Methods

The evolution of our understanding of how to train for long-distance running is owed primarily to coaches and athletes, rather than to sports scientists. Historically, scientific research focused more on explaining why elite athletes train the way they do, rather than on driving innovation in how training should be structured. As a result, over the past two decades, an increasing number of scientific publications have sought to describe the training characteristics of world-leading distance runners (Haugen et al., 2022).

Furthermore, peripheral adaptations—such as increased mitochondrial biogenesis and capillary density in skeletal muscle—are crucial for improving long-distance running performance. Scientifically, the most effective way to achieve these adaptations is through the accumulation of high-frequency, high-volume, low-intensity training (LIT) (Haugen et al., 2022). Continuous running serves as one of the most effective stimuli for endurance-specific adaptations. Runners with better running economy tend to accumulate higher volumes of low-intensity training, from which they derive the greatest benefit. Reduced energetic cost of movement, decreased movement variability, and improved neural entrainment are among the key benefits of high volumes of LIT (Haugen et al., 2022).

Previously, it was believed that high-intensity training (HIT) more effectively stimulated central adaptations—such as increased stroke volume—than high-frequency LIT. However, increases in VO_2max are not consistently observed following periods of intensified HIT in well-trained athletes. Nevertheless, HIT, via an adenosine monophosphate (AMP)-activated signaling pathway, appears to more effectively stimulate peripheral adaptations in fast-twitch motor units (Haugen et al., 2022).

Taken together, a complex set of overlapping and complementary adaptations can be achieved through a combination of HIT and LIT, which supports the judicious application of varied training intensities in the development of endurance performance (Haugen et al., 2022). To improve understanding, it is worth adding the

context of accumulated duration of LIT or HIT, as it plays a crucial role in enhancing adaptive signaling and stress responses.

Although somewhat simplistic, the training philosophy of Frank Shorter—gold medalist in the marathon at the 1972 Olympics in Munich—remains highly influential. His coach, Bill Bowerman, co-founder of Nike and a leading U.S. coach, summarized Shorter's training as follows: 2–3 weekly interval sessions, one weekly long run, and "fill the rest with as much LIT as you can handle." This approach continues to be recognized as one of the most successful training models to this day (Haugen et al., 2022).

Moreover, the training structure for marathoners is predominantly centered around weekly long runs rather than high-intensity interval sessions (Haugen et al., 2022). Cross-training with alternative locomotion modalities—including swimming, cycling, and elliptical workouts—is often used to supplement training beyond long runs and is commonly practiced by many long-distance runners with success. The main argument for this approach is that running, compared to other cross-training options, involves a shorter total training duration and a higher mechanical and ballistic load—which may contribute to injury prevention—while simultaneously helping to reduce training monotony.

In addition to performance enhancement, marathon training provides important health benefits. Regular physical activity, such as marathon preparation, is a key component in the prevention of coronary artery disease (CAD). Several studies have shown that endurance athletes possess lower risk factors for CAD compared to sedentary control groups (Braschler et al., 2025).

However, it should be noted that the long-term effects of previously unhealthy lifestyles, such as atherosclerosis and cardiovascular disease, may not be fully reversed—even through marathon running or intense training. Nonetheless, preparing for a marathon still provides measurable improvements in cardiovascular health (Braschler et al., 2025).

Interestingly, potential myocardial damage has been indicated by elevations in cardiac biomarkers such as cardiac troponin I, creatine kinase (CK), creatine kinase myocardial band (CK-MB), myoglobin, atrial natriuretic peptide (ANP), and N-terminal prohormone of brain natriuretic peptide (NT-proBNP), which have been observed during and after the completion of a marathon (Braschler et al., 2025). High-sensitivity cardiac troponin T (hs-cTnT), NT-proBNP, tumor necrosis factor alpha (TNF-α), cystatin C, interleukin (IL)-6, and IL-10 reached peak levels 24 hours post-race and returned to baseline within 72 hours (Braschler et al., 2025). These biomarker changes may result from ischemia, cardiomyocyte necrosis, or altered cardiomyocyte metabolism. However, based on hs-cTnT kinetics, it is most likely that these changes reflect transient cellular strain or altered myocyte metabolism rather than irreversible damage (Braschler et al., 2025).

Moreover, when comparing ultramarathoners to marathoners, significantly higher levels of biomarkers associated with myocyte necrosis and cardiac congestion are observed in the former, suggesting that the duration of exercise plays a critical role in biomarker elevation (Braschler et al., 2025). Recreational athletes who trained less than 35 miles per week before a marathon were more likely to experience post-race diastolic dysfunction, as indicated by elevated troponins and NT-proBNP. These findings point to a correlation between insufficient training volume and increased cardiac biomarker release (Braschler et al., 2025). Nonetheless, in most marathon participants, cardiac biomarkers were only transiently elevated.

Additionally, several studies have reported adverse effects on the right ventricle (RV), such as impaired diastolic function. In contrast, Vitiello et al. found negligible effects of marathon running on biventricular systolic function (Braschler et al., 2025). Echocardiographic and cardiac MRI studies have shown that prolonged relaxation times may indicate post-race RV enlargement and diastolic dysfunction, potentially leading to elevated pulmonary pressures and right atrial (RA) enlargement (Braschler et al., 2025). Encouragingly, these changes generally returned to baseline within 24 hours. Furthermore, a strong correlation was found between the degree of RV dysfunction and levels of inflammatory cytokines such as TNF-α and IL-12p70 (Braschler et al., 2025).

However, MRI studies on cardiac alterations remain inconclusive. Some have shown delayed gadolinium enhancement in 12.9% of athletes, primarily in the interventricular septum and affecting the RV (Braschler et al., 2025). This finding, along with RV dysfunction, has raised concerns about potential triggers for arrhythmias and the possible need for implantable cardioverter-defibrillators (ICDs) in rare cases (Braschler et al., 2025). Conversely, other studies found no evidence of myocardial necrosis or structural abnormalities despite elevated biomarkers and signs of dysfunction (Braschler et al., 2025). Therefore, possible long-term adverse remodeling, especially of the RV, remains uncertain and warrants further study.

Beyond cardiovascular implications, training methods also influence performance outcomes and injury risk. A study investigating training volume, longest endurance run, and injury incidence in recreational runners found that longer runs, higher volume, and faster pace correlated with better finishing times in both half-marathon and marathon events (Fokkema et al., 2020). Notably, none of these variables were associated with an increased incidence of running-related injuries. For half-marathon runners, runs exceeding 21 km were especially beneficial, while marathon runners showed improved outcomes with training volumes of at least 40 km per week. Interestingly, runs longer than 35 km did not provide additional performance benefits (Fokkema et al., 2020).

Finally, nutritional strategies also play a key role in training efficacy and recovery. A recent study examined the effects of varying carbohydrate intakes—60 g/h, 90 g/h, and 120 g/h—on muscle damage during a mountain marathon. Results showed that the 120 g/h group had significantly lower levels of muscle damage markers such as CK, LDH, and GOT (Viribay et al., 2020). These findings suggest that higher carbohydrate intake during prolonged endurance events may reduce muscle damage and perceived exertion, and could help refine fueling strategies in long-distance athletes (Viribay et al., 2020).

Elite athletes

The main goal in long-distance running is the sustained ability to produce adenosine triphosphate (ATP) aerobically and to convert muscular work into power and speed. Three key variables must be optimized to achieve this: maximal oxygen uptake (VO_2max – the highest rate at which the body can take in and utilize oxygen during intense exercise), running economy (VO_2 at a given sub-maximal running velocity), and fractional utilization (the ability to sustain a high percentage of VO_2max while running) (Haugen et al., 2022). Moreover, some research highlights a fourth variable—neuromuscular power or anaerobic capacity—which plays an important role in the final phase of races (Haugen et al., 2022). Additionally, there are observations of specific adaptations that delay muscular deterioration and fatigue—often referred to as “fatigue resistance,” considered by some as a fifth key variable—which enable athletes to maintain race pace during the final 7–10 km of an elite marathon (Haugen et al., 2022). To achieve a high international standard in these physiological determinants, a long-distance runner

typically requires 8–10 years of systematic training (Haugen et al., 2022). Depending on the runner's background or ethnicity, the distribution of these variables may vary, and a sub-optimal score in one parameter can often be compensated for by a higher value in another. A notable example is a case study by Jones AM ("The Physiology of the World Record Holder for the Women's Marathon", 2006), which showed that Paula Radcliffe's $\dot{V}O_2max$ remained essentially stable at approximately 70 $ml \cdot kg^{-1} \cdot min^{-1}$, while her running economy improved by about 15 % between 1991 and 2003. This supports the idea that different performance determinants may develop at different rates over time (Haugen et al., 2022).

Building on these physiological insights, Nike's "Breaking2" project—an initiative aimed at breaking the two-hour marathon barrier—subjected the world's top male distance runners to a series of assessments to determine the specific requirements needed to achieve this feat. One primary focus was the oxygen (O_2) cost of running at the critical pace of approximately 21 $km \cdot h^{-1}$, the minimum average speed required to complete a marathon in under two hours. Notably, the O_2 cost of over-ground running at this velocity had not been accurately measured before this study. The project found that the average O_2 cost at 21 $km \cdot h^{-1}$ was 191 ± 19 $mL \cdot kg^{-1} \cdot km^{-1}$, corresponding to a VO_2 of roughly 4.0 $L \cdot min^{-1}$—or 67 $mL \cdot kg^{-1} \cdot min^{-1}$ for a 59 kg athlete (Jones et al., 2021). Despite the elite status of the participants, only 7 of 18 runners were able to sustain a steady-state VO_2 at this pace, underscoring the exceptional physiological demands of running at such high speeds for extended durations (Jones et al., 2021).

Consequently, although the absolute VO_2 required to run at 21 $km \cdot h^{-1}$ varies with body mass, the relative oxygen uptake remains approximately 67 $mL \cdot kg^{-1} \cdot min^{-1}$ (Jones et al., 2021). Crucially, this metabolic rate must stay below the athlete's critical metabolic rate—closely linked to their critical speed—in order to be sustained over the time needed for a sub-two-hour marathon. This necessitates a high VO_2peak so that the steady-state VO_2 at race pace (e.g., 4.0 $L \cdot min^{-1}$ in a 59 kg runner) constitutes a manageable fraction of the athlete's maximal capacity (Jones et al., 2021). For instance, a VO_2peak of ~80 $mL \cdot kg^{-1} \cdot min^{-1}$ would correspond to a fractional utilization of around 85 %, which is considered physiologically attainable for elite endurance athletes (Jones et al., 2021). It is important to emphasize that the physiological variables assessed in the study should be interpreted holistically rather than in isolation, as they interact to determine overall performance potential.

Taken together, the findings indicate that translating metabolic output into over-ground speed—via the oxygen cost of running at race pace and its resistance to fatigue—is instrumental in defining the absolute VO_2 that can be sustainably maintained for two hours, a key metabolic determinant (Jones et al., 2021). While long-term training adaptations and genetic predispositions have already been optimized by elite athletes, future progress will likely depend on scientific innovations and strategic interventions that further increase the mean sustainable oxidative metabolic rate and/or enhance running economy (Jones et al., 2021).

Parallel to such physiological advances, running shoes equipped with advanced technologies now play a crucial role in marathon performance. A retrospective observational analysis of real-world data demonstrated that female runners benefit more than male runners from Nike's modern racing models—including Vaporfly 4 %, NEXT %, Alphafly, and related prototypes (Senefeld et al., 2021). Although the analysis centered on Nike products, technological similarities across brands suggest the results can be generalized to other modern racing shoes. The dataset showed that athletes wearing these shoes achieved faster marathon times than those in earlier models: on average, male runners improved by 2.8 minutes (2.0 %), and female runners by 4.3 minutes (2.6 %) (Senefeld et

al., 2021). Furthermore, the 2019 introduction of these shoes coincided with marked improvements in average finishing times across both sexes, suggesting a broader population-level impact (Senefeld et al., 2021).

Overall, subgroup analyses of elite athletes revealed meaningful gains after switching to the latest models: male elites improved by 1.2 minutes (0.8 %), whereas female elites achieved a larger relative gain of 3.7 minutes (1.6 %) (Senefeld et al., 2021). Although percentage improvements were similar, the absolute time reduction was numerically greater in females because males already ran faster baseline times—a critical distinction given that marathon success is ultimately determined by finishing time rather than percentage change. These observations—confirmed by full-cohort and case-control analyses—underscore that shoe technology has become an important performance-enhancing factor in distance running, with particularly pronounced benefits for female and elite-level athletes (Senefeld et al., 2021).

These results reinforce earlier laboratory-based assessments and are further supported by crowdsourced data from recreational runners and additional real-world performance analyses, illustrating that even a seemingly modest 2.3 % improvement can be decisive for podium positions, qualification standards, or record-breaking achievements at the elite level (Senefeld et al., 2021).

4.Conclusions

Endurance running and prolonged physical exertion induce a wide range of physiological adaptations and temporary stresses across multiple organ systems, reflecting the body's complex response to sustained high-intensity exercise. Cardiovascular changes include transient elevations in cardiac biomarkers and mild myocardial remodeling, characterized by increased ventricular mass and chamber size, primarily progressing from concentric to eccentric hypertrophy with continued training. While systolic and diastolic functions generally remain preserved, right ventricular function may be more vulnerable to transient dysfunction and volume overload during and after endurance events, with potential cumulative effects over time. The inflammatory response triggered by endurance activities extends beyond the cardiovascular system, involving muscle microdamage and systemic activation of immune mediators such as cytokines and acute-phase proteins. This systemic inflammation impacts vascular endothelial function and interacts with oxidative stress and hormonal fluctuations, influencing recovery and adaptation.

Metabolically, endurance training enhances energy utilization efficiency, optimizing aerobic pathways and mitochondrial function. However, prolonged exertion challenges energy stores and can induce glycogen depletion, electrolyte imbalances, and oxidative stress, which collectively affect muscle performance and recovery.

Renal function may be transiently impaired during and after endurance events due to dehydration, altered renal perfusion, and increased metabolic waste, necessitating careful

hydration and electrolyte management. Similarly, the gastrointestinal and liver systems can experience transient disturbances, including increased intestinal permeability, inflammation, and liver enzyme fluctuations, potentially compromising nutrient absorption and metabolic regulation during intense training and competition.

Respiratory adaptations improve oxygen uptake and delivery, supporting increased aerobic capacity, yet the respiratory system is also subject to mechanical stress and inflammation, which can transiently impair function.

Endurance training influences neuroendocrine regulation, impacting sleep quality, libido, and cognitive function. Adequate sleep is crucial for recovery and hormonal balance, while excessive training or insufficient rest can disrupt reproductive hormones, reducing libido and potentially impairing long-term health. Cognitive function is supported by improved cerebral blood flow and neurotrophic factors, though overtraining and systemic inflammation may temporarily affect mood and mental performance.

Overall, the physiological changes observed in endurance athletes represent a balance between beneficial adaptations and transient stress responses. While many alterations are reversible and contribute to enhanced performance, there remains concern about the long-term effects of repeated strenuous exercise, particularly in aging athletes or those with underlying cardiovascular risk. Continued research integrating multi-system biomarkers, advanced imaging, and individualized risk assessment is essential to optimize training methods, enhance recovery, and safeguard athlete health across all systems involved in endurance exercise.

Disclosure

Author Contributions - Konceptualizacja, Jan Bindas; metodologia, Jan Bindas; oprogramowanie Jan Bindas; sprawdź, Jan Bindas, Wiktor Doroszuk i Jakub Hamouta; analiza formalna, Jan Bindas; dochodzenie, Marika Jerzak; zasoby, Patrycja Długosz; przechowywanie danych, Marika Jerzak; pismo - przygotowanie zgrubne, Patrycja Długosz; pisanie - recenzja i redakcja, Jan Bindas; wizualizacja, Wiktor Doroszuk; nadzór, Jan Bindas; administracja projektami, Jakub Hamouta; Wszyscy autorzy przeczytali i zgodzili się z opublikowaną wersją manuskryptu.

Funding Statement - Research did not receive special funding.

Conflict of Interest Statement – Authors do not have any conflict of interest.

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