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Review Article

Physiological and performance characteristics in the *Spartathlon*: A narrative review of scientific findings[1]

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A R T I C L E I N F O

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A B S T R A C T

Background: The *Spartathlon* is a 246-km ultra-endurance running race, considered as one of the most iconic and physically demanding ultra-marathons in the world. In this narrative review, we aimed to synthesize the available current evidence on the physiological responses, performance trends, and health implications associated with participation in the *Spartathlon*.

Methods: A systematic literature search was conducted to identify high-quality scientific studies on the *Spartathlon*. The databases Cochrane, EMBASE, PubMed, Scopus, and Web of Science were used to retrieve articles published up to December 2025. We found a total of 33 publications in Web of Science, 25 in Embase, 24 in Scopus, 23 in PubMed, and 1 in Cochrane. After removing duplicates and applying the eligibility criteria, a final selection of studies was included for analysis in this narrative review.

Results: The findings on the cardiac system showed reversible changes in echocardiography and cardiac biomarkers. Running the *Spartathlon* leads to specific effects on the locomotor system, such as an increase in peak pressure in the forefoot area, an increase in biochemical markers of muscle damage and changes in bone metabolism markers. Notably, the use of oral proton pump inhibitors was associated with a lower incidence of gastrointestinal bleeding. The *Spartathlon* also showed the highest prevalence of exercise-associated hyponatremia (EAH) of up to 65% as reported in the literature on ultra-marathon running. In addition, running *Spartathlon* leads to an inflammatory response and an increase in oxidative stress.

Conclusions: Participation in the *Spartathlon* leads to several well-documented post-race physiological alterations, particularly affecting the cardiovascular and musculoskeletal systems. Overall, the *Spartathlon* represents a unique model for studying human physiological resilience and adaptation under extreme conditions.

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Introduction

Ultra-marathons are running events that exceed the classical marathon distance of 42.195 km, typically ranging from 50 km to >5000 km, and may be completed in a single stage or over multiple days (Scheer et al., 2020; Fariod et al., 2023). Among these events, the *Spartathlon* is one of the most iconic and historically significant ultra-marathons (Christou et al., 2023; Knechtle et al., 2022). Its origin traces back to the account of the Greek messenger Pheidippides, who, according to Herodotus, was dispatched from Athens to Sparta in 490 BCE to request military support during the Persian Wars. It is believed that he covered the ~246- km route on foot, departing in the morning and arriving by the evening of the following day (www.spartathlon.gr/en/home/).

In 1982, British Royal Air Force commander and long-distance runner John Foden sought to reconstruct this legendary journey. Together with two colleagues, he ran from Athens to Sparta along the presumed historical route, completing the distance in ~36–39h (Scoltens 34:30 h:min, Foden 37:37 h:min, McCarthy 39:00 h:min). This successful reenactment marked the birth of the modern *Spartathlon*, which has since been held annually on the last Friday of September. Today, athletes must complete the historic route within a strict 36-hour time limit.

The *Spartathlon* is widely regarded as one of the most demanding and prestigious ultra-marathons in the world (Christou et al., 2023; Knechtle et al., 2022). The race begins at the Acropolis in Athens at 07:00 and concludes in Sparta before the statue of King Leonidas by 19:00 the following day. Participants traverse challenging terrain, including muddy roads and a mountain pass reaching 1200 m of elevation, without opportunities for rest or sleep (Dimitra et al., 2021). These extreme conditions induce substantial metabolic, cardiovascular, and biochemical responses (Stergioulas, Tripolitsioti & Nicolaou, 2008; Pagourelias et al., 2022; Pagourelias et al., 2020). For example, participation in *Spartathlon* has been associated with marked alterations in lipid metabolism and prostaglandin ratios, reflecting acute metabolic stress (Stergioulas, Tripolitsioti & Nicolaou, 2008). Cardiovascular studies have documented structural cardiac changes and elevated cardiac stress markers in the immediate post-race period (Pagourelias et al., 2022; Pagourelias et al., 2020).

Beyond physiological responses, demographic analyses of ultra-marathon events—including the *Spartathlon*—have consistently shown performance differences between male and female athletes, indicating a stable sex-related performance gap in ultra-endurance running (Da Fonseca-Engelhardt et al., 2013). The *Spartathlon* has also attracted scientific interest due to its extreme environmental and physiological demands, similar to research conducted in other iconic events such as the *Badwater Ultramarathon* in the United States of America (Brown & Connolly, 2015).

Given the race's unique characteristics, limited participant pool, and the growing scientific interest in extreme endurance physiology, a comprehensive review of the available *Spartathlon* literature is warranted. Such an overview can help contextualize *Spartathlon* findings within the broader field of ultra-marathon research and provide practical insights for future athletes, coaches, and medical professionals.

The aim of this narrative review is to compile and critically discuss the current scientific evidence on the *Spartathlon* and to situate these findings within the wider context of ultra-endurance research. The insights gained may support future participants and their coaches in developing race-specific preparation and performance strategies.

Methods

Search strategy and eligibility criteria

This is a narrative review (Sukhera, 2022) that searches for scientific evidence on the *Spartathlon* in Cochrane, EMBASE, PubMed, Scopus, and Web of Science, published up to December 2025. These databases were selected due to their broad coverage of biomedical, sports science, and interdisciplinary research, ensuring comprehensive retrieval of relevant literature. The search was conducted and completed in December 2025. The selected articles were related to *Spartathlon* and were published until December 2025 with no language restrictions. The following search terms were used: ((Spartathlon) OR (Spartathlon ultra marathon) OR (Spartathlon race) OR (246-km ultra marathon) OR (246 km running race)). Data extraction was performed by two authors (BK, MT) for all selected studies, considering: (Scheer et al., 2020) authors; (Fariod et al., 2023) year of publication; (Christou et al., 2023) study design; (Knechtle et al., 2022) sample characteristics; (Dimitra et al., 2021) running/race characteristics; (Stergioulas, Tripolitsioti & Nicolaou, 2008) variables assessed; (Pagourelias et al., 2022) main results; and (Pagourelias et al., 2020) health associated factors. Furthermore, reference lists were checked for further references.

The identification and screening processes were conducted by the lead author (BK) in collaboration with co-authors (SD and MT). All records retrieved through the search strategy were initially compiled by the lead author, and duplicate entries were subsequently removed independently by two authors (BK and MT). Following the removal of duplicates, the remaining records underwent screening based on titles and abstracts. Studies considered potentially eligible were then assessed through full-text reading. Regarding the eligibility criteria, the population included human participants of both biological sexes, while animal and in vitro studies were excluded. The intervention of interest comprised ultra-marathoners competing in the *Spartathlon*, with studies involving other populations being excluded. For the comparator, studies were required to include assessments conducted pre-race, during the race, or post-race. Studies lacking clearly defined assessment time points were excluded. The outcomes considered eligible included variables related to participation, performance, age of peak performance, changes in body mass, and aspects of the cardiovascular and musculoskeletal systems, as well as nutrition, fluid metabolism, oxidative stress, and immune system responses. Studies addressing outcomes not related to physiological, performance, or participation aspects were excluded. Finally, regarding study design, only original research articles and case reports published in peer-reviewed journals were included, whereas reviews, systematic reviews, meta-analyses, editorials, letters to the editor, conference abstracts, theses, dissertations, study protocols, and non–peer-reviewed publications were excluded.

Study appraisal and synthesis of evidence

Given the narrative nature of this review, no formal risk of bias assessment or standardized methodological quality appraisal of the included studies was performed. Instead, the objective was to provide a comprehensive and integrative overview of the existing literature on the *Spartathlon*, organizing findings into key thematic domains such as participation, performance, and physiological responses. The synthesis of the evidence was conducted using a descriptive and thematic approach, without a pre-defined qualitative or quantitative synthesis protocol. Studies were grouped according to their primary focus, and findings were interpreted in light of the broader context of ultra-endurance research.

Results

Literature search

We found a total of 106 publications with 33 publications in Web of Science, 25 in Embase, 24 in Scopus, 23 in PubMed, and 1 in Cochrane. Duplicates, animal studies, in vitro studies, and articles not related to the topic were excluded after the initial screening of search results (title and abstract screening). A total of 19 studies were finally included in this review, investigating only *Spartathlon*. The PRISMA flowchart of search and selection strategies is presented in Fig. 1.

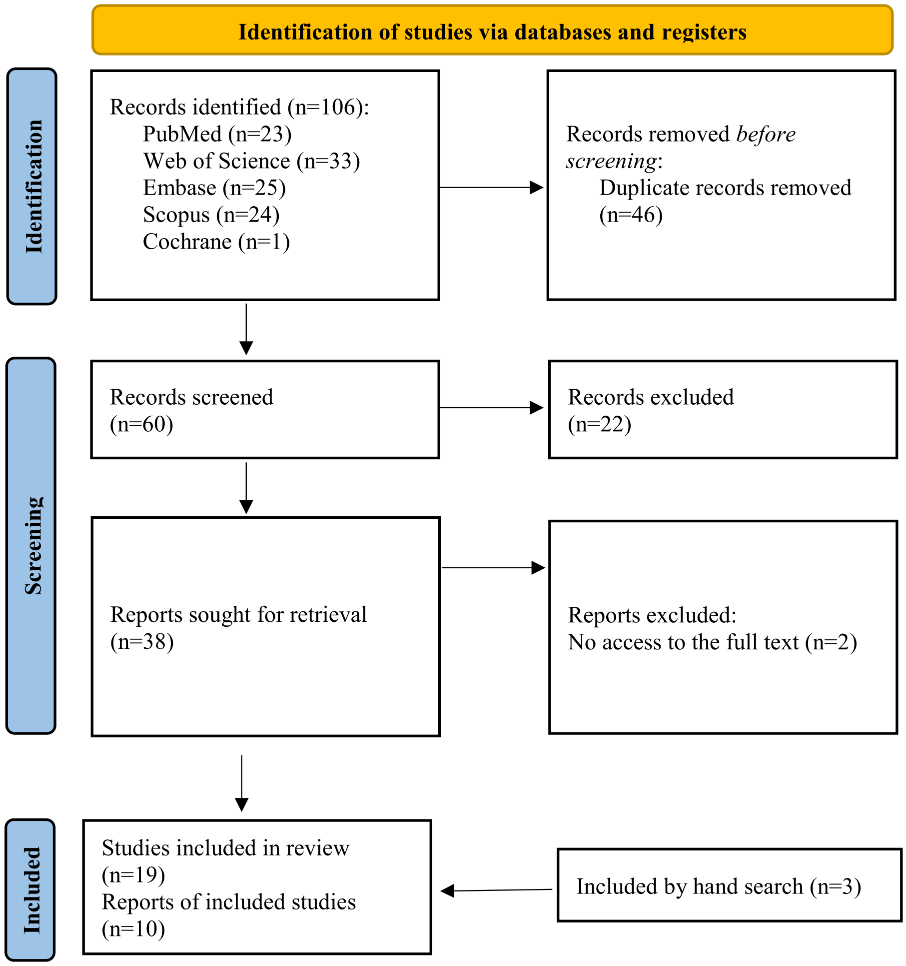

Fig. 1. PRISMA flow diagram of the screening process.

Sample and study characteristics

The included studies can be grouped into several thematic domains. Non-physiological aspects comprised participation trends (Da Fonseca-Engelhardt et al., 2013; Zingg et al., 2013; Knechtle et al., 2021), performance trends (Da Fonseca-Engelhardt et al., 2013; Zingg et al., 2013; Knechtle et al., 2021), the age of peak performance (Da Fonseca-Engelhardt et al., 2013; Zingg et al., 2013; Knechtle et al., 2021), and pacing strategies during the race (Knechtle et al., 2022).

Physiological investigations covered a broad range of systems. Hydration and body mass changes during the race were examined in several studies (Seal et al., 2019; Christou et al., 2020; Koutlianos et al., 2021). Cardiovascular responses were assessed using echocardiography (Christou et al., 2023; Pagourelias et al., 2022; Christou et al., 2020; Koutlianos et al., 2021) and through analyses of cardiac biomarkers (Dimitra et al., 2021; Christou et al., 2020). Effects on the musculoskeletal system, including skeletal muscle and bone responses, were reported across multiple studies (Koutlianos et al., 2021; Kerschan-Schindl et al., 2015; Karagounis et al., 2009; Skenderi et al., 2006; Kerschan-Schindl et al., 2009; Kerschan-Schindl et al., 2021). The gastrointestinal system was addressed in selected investigations (Skenderi et al., 2006; Thalmann et al., 2006).

A substantial body of work focused on the post-race inflammatory response (Margeli et al., 2005; Bartzeliotou et al., 2007; Papassotiriou et al., 2008; Goussetis et al., 2009; Papassotiriou et al., 2007), including increases in specific inflammatory biomarkers (Dimitra et al., 2021; Margeli et al., 2005; Bartzeliotou et al., 2007; Papassotiriou et al., 2008; Goussetis et al., 2009; Papassotiriou et al., 2007). Further metabolic topics included exercise-associated hyponatremia (EAH) (Dimitra et al., 2021; Stergioulas, Tripolitsioti & Nicolaou, 2008; Seal et al., 2019; Margeli et al., 2005) and changes in endocrine-related metabolites (Margeli et al., 2005). Finally, several studies evaluated oxidative stress responses to the race (Stergioulas, Tripolitsioti & Nicolaou, 2008; Schulpis et al., 2008; Skenderi et al., 2008).

Participation trends

Participation trends in the *Spartathlon* have been examined in three key studies (Da Fonseca-Engelhardt et al., 2013; Zingg et al., 2013; Knechtle et al., 2021). Across the years, the total number of successful finishers has steadily increased (Da Fonseca-Engelhardt et al., 2013; Zingg et al., 2013; Knechtle et al., 2021), accompanied by a notable rise in the proportion of successful female finishers (Da Fonseca-Engelhardt et al., 2013). Between 2000 and 2012, the percentage of women participants increased slightly from 11.9% to 12.5% (Da Fonseca-Engelhardt et al., 2013). An analysis of the geographical origin of successful finishers showed that athletes from Japan represented the largest group, followed by runners from Germany, Greece, and France (Knechtle et al., 2021). When focusing on the top five annual performers, the most frequently represented nations were Japan, followed by Germany and Great Britain Knechtle et al., 2021.

Performance trends

Performance trends in the *Spartathlon* were examined in three studies (Da Fonseca-Engelhardt et al., 2013; Zingg et al., 2013; Knechtle et al., 2021). Successful finishers typically require ~33:34:27 h:min:s to complete the race, with reported ranges between 28:50:38 h:min:s and 35:07:07 h:min:s (Stergioulas, Tripolitsioti & Nicolaou, 2008; Pagourelias et al., 2022). Regarding nationality, men from the United States of America were identified as the fastest overall, whereas women from the United Kingdom achieved the fastest performances among female competitors (Knechtle et al., 2021). Both female and male runners demonstrated performance improvements over recent decades (Zingg et al., 2013; Knechtle et al., 2021). Depending on the study, either a progressive improvement was observed among the annual top five men and women (Knechtle et al., 2021), or their running speed remained stable over time at approximately 10.8 ± 0.7 km/h for men and 8.7 ± 0.5 km/h for women (Da Fonseca-Engelhardt et al., 2013). Across all years, men consistently outperformed women, with an average sex difference of ~20% (Da Fonseca-Engelhardt et al., 2013).

Age of peak performance

The age of peak performance in the *Spartathlon* was examined in three studies (Da Fonseca-Engelhardt et al., 2013; Zingg et al., 2013; Knechtle et al., 2021). Across these investigations, the overall peak age for optimal performance was consistently identified at ~40–45 years (Da Fonseca-Engelhardt et al., 2013; Zingg et al., 2013). Sex-specific analyses showed that the fastest men typically achieved their best performances between 20 and 39 years, whereas the fastest women tended to peak later, between 30 and 49 years (Da Fonseca-Engelhardt et al., 2013; Knechtle et al., 2021). Nationality-specific analyses further indicated that runners aged 30–39 years were the fastest across most countries. An exception was observed among Greek athletes, whose peak performance occurred in a younger age group, reported as 20–29 years (Knechtle et al., 2021).

Pacing during the spartathlon

Pacing in the *Spartathlon* has been examined in a single study that analyzed 2598 finishers (2255 men and 343 women) from 2011 to 2019 (Knechtle et al., 2022). Successful runners demonstrated a characteristic reverse J-shaped pacing pattern, with running speed progressively declining from the start to the 7th checkpoint, followed by an increase in the final race segments (Knechtle et al., 2022). Sex-specific analyses revealed subtle differences: men exhibited more pronounced changes in running speed at the first two checkpoints, whereas women showed greater variation at the final checkpoint (Knechtle et al., 2022). Despite these differences, neither sex nor age significantly influenced the average running speed between checkpoints (Knechtle et al., 2022). Instead, the pacing strategy was primarily determined by performance level. Both the fastest and slowest runners maintained more consistent running speeds across checkpoints, whereas mid-level performers displayed a greater variability (Knechtle et al., 2022).

Effect on body mass

Changes in body mass during participation in the *Spartathlon* were examined in three studies (Seal et al., 2019; Christou et al., 2020; Koutlianos et al., 2021). Across all investigations, running the *Spartathlon* resulted in a measurable decrease in body mass (Seal et al., 2019; Christou et al., 2020; Koutlianos et al., 2021). Reported losses ranged from –3.35% (Koutlianos et al., 2021) to –3.6 ± 2.7%, corresponding to –2.5 ± 1.9 kg (Seal et al., 2019). Importantly, these studies assessed only absolute changes in total body mass; no analyses of body fat mass, lean mass, or skeletal muscle mass were conducted.

Effects on the cardiovascular system

A total of four studies investigated the cardiac effects of participating in the *Spartathlon* (Christou et al., 2023; Pagourelias et al., 2022; Christou et al., 2020; Koutlianos et al., 2021). Ultra-marathon running imposes substantial acute stress on the cardiovascular system, as demonstrated by consistent echocardiographic and hemodynamic alterations across all studies. Completion of the *Spartathlon* elicited a broad spectrum of acute cardiac changes, including modifications in chamber geometry, systolic and diastolic function, myocardial strain patterns, and the release of cardiac biomarkers. These responses appear to reflect a characteristic pattern of transient, exercise-induced cardiac stress, driven by the combined effects of hypovolemia, altered preload and afterload, myocardial fatigue, and short-term inflammatory and neurohormonal activation. Despite the magnitude of these acute alterations, the available studies consistently describe them as functional and reversible, aligning with observations from other prolonged ultra-endurance events.

Structural remodeling and loading conditions

Completion of the *Spartathlon* resulted in marked shifts in cardiac loading. Body weight loss of 3–4% indicated substantial dehydration, which reduced venous return and left ventricular (LV) end-diastolic dimensions (Christou et al., 2020). This preload reduction was clearly illustrated in an elite finisher who experienced non-cardiac syncope and collapsed intravascular volume immediately after the race (Christou et al., 2023). Intravenous administration of 3 L of fluids restored chamber volumes and normalized inferior vena cava dynamics, demonstrating the strong dependence of post-race cardiac geometry on circulating volume status (Christou et al., 2023).

In a cohort of 27 finishers, LV wall thickness increased significantly, and right ventricular (RV) end-diastolic area also increased (Christou et al., 2020). These changes likely reflect a combination of myocardial edema, increased sympathetic tone, and acute shifts in transmural pressure. The negative correlation between the sum of LV wall thicknesses and percentage change in body weight supports the interpretation that dehydration and hemoconcentration contributed to the apparent wall thickening (Christou et al., 2020).

Ventricular systolic function and myocardial strain

Both ventricles demonstrated mild but significant reductions in global longitudinal strain (GLS). LV GLS decreased from −20.9 ± 2.3% to −18.8 ± 2.0%, and RV GLS decreased from −22.9 ± 3.6% to −21.2 ± 3.0% (Pagourelias et al., 2022; Christou et al., 2020). Importantly, strain impairment was regionally heterogeneous: basal and mid-ventricular segments were affected, whereas apical strain was preserved (Pagourelias et al., 2022). This pattern is consistent with the known susceptibility of basal RV and LV segments to increased wall stress during prolonged exercise.

The elite finisher exhibited a similar pattern, with LV strain improving after rehydration while RV strain continued to deteriorate, suggesting that RV function is more sensitive to sustained afterload and may recover more slowly (Christou et al., 2023). The significant reduction in tricuspid annular plane systolic excursion (TAPSE) further supports the presence of transient RV systolic dysfunction (Christou et al., 2020).

Diastolic function and cardiac cycle timing

Running the *Spartathlon* significantly altered the temporal characteristics of the cardiac cycle. Systole was significantly prolonged and diastole significantly shortened across all strain curves (Pagourelias et al., 2022). A reduced diastolic duration limits ventricular filling, particularly under conditions of tachycardia and hypovolemia. This mechanism likely contributed to the observed reductions in LV end-diastolic dimensions and may have amplified the functional impact of dehydration.

Biomarker responses and their determinants

N-terminal pro-B-type natriuretic peptide (NT-proBNP) increased significantly after *Spartathlon* (Dimitra et al., 2021; Christou et al., 2020) and showed strong associations with hemodynamic and structural parameters. Pulmonary artery systolic pressure was the only independent determinant of post-race NT-proBNP (Christou et al., 2020), indicating that increased RV afterload was a major driver of myocardial wall stress. NT-proBNP also correlated positively with RV basal and mid-cavity dilation and negatively with TAPSE (Christou et al., 2020), reinforcing the central role of RV strain in biomarker elevation.

High-sensitivity troponin I increased significantly (Dimitra et al., 2021; Christou et al., 2020) and correlated negatively with body-weight loss, suggesting that dehydration and hemoconcentration may influence post-race troponin kinetics (Christou et al., 2020). However, the rise in troponin I did not correlate with any echocardiographic parameter, supporting the interpretation that post-race troponin release reflects physiological membrane leakage rather than structural myocardial injury.

Effects on the kidney function

Renal function was assessed in one study that measured serum creatinine concentrations before and after the race (Christou et al., 2020). Creatinine increased from 0.84±0.17 mg/dL pre-race to 0.97 ±0.16 mg/dL post-race, indicating a significant rise consistent with an acute, exercise-induced reduction in kidney function (Christou et al., 2020). Although the increase remained within a mild range, it reflects the transient functional renal stress commonly observed after prolonged ultra-endurance exercise.

Effects on the musculoskeletal system

Running the *Spartathlon* imposes substantial mechanical and biochemical stress on the musculoskeletal system. Biomechanical analyses demonstrated marked alterations in foot-loading characteristics, particularly increases in peak pressure and impulse values under the forefoot (Karagounis et al., 2009). These changes likely reflect compensatory loading patterns associated with progressive fatigue of intrinsic foot muscles and altered gait mechanics during prolonged ultra-endurance running. In contrast, impulse values under the toes decreased, suggesting reduced toe-flexor engagement immediately after the race (Karagounis et al., 2009). Notably, measurements obtained 24h post-race showed a return toward baseline values, indicating that these alterations were functional and reversible, most likely due to the restoration of local neuromuscular activity (Karagounis et al., 2009).

The *Spartathlon* also induces profound skeletal muscle damage, as evidenced by consistent elevations in biochemical markers across studies (Koutlianos et al., 2021; Skenderi et al., 2006). Post-race concentrations of creatine kinase (CK) and lactate dehydrogenase (LDH) reached levels characteristic of extreme muscular stress, with one study reporting CK 43,763±6,764 IU/L and LDH 2,300±285 IU/L (Skenderi et al., 2006). These values rank among the highest documented in ultra-endurance events and reflect extensive sarcolemmal disruption, muscle-fiber necrosis, and inflammatory infiltration. Additional biomarkers, such as myostatin, an inhibitor of myogenic differentiation, were also elevated after the race (Kerschan-Schindl et al., 2015), suggesting a temporary suppression of muscle-regeneration pathways in response to extreme exertional load.

Beyond muscle tissue, the *Spartathlon* exerts measurable effects on bone metabolism (Kerschan-Schindl et al., 2009; Kerschan-Schindl et al., 2021; Kerschan-Schindl et al., 2015). The phosphaturic hormone fibroblast growth factor-23 (FGF23) increased 6.5-fold from pre- to post-race (Kerschan-Schindl et al., 2021), indicating substantial osteocytic activation and altered phosphate regulation. Markers of Wnt-signaling inhibition showed a differentiated response: sclerostin remained unchanged, whereas dickkopf-1 (DKK1) decreased after the race (Kerschan-Schindl et al., 2015), suggesting a complex and potentially compensatory modulation of bone-formation pathways.

Markers of bone turnover exhibited a distinct temporal pattern. Cross-linked C-telopeptide of type I collagen (CTX)—a marker of bone resorption—was significantly elevated immediately after the race and remained increased three days later (Kerschan-Schindl et al., 2009). Conversely, osteocalcin (Oc), a marker of bone formation, was transiently suppressed, indicating a short-term imbalance favoring bone resorption (Kerschan-Schindl et al., 2009). Furthermore, both RANKL and OPG increased three days after race start compared with pre-race values (Kerschan-Schindl et al., 2009), reflecting activation of the RANKL–OPG axis, a central regulatory pathway in bone remodeling. Across studies, sclerostin levels showed no significant pre- to post-race differences, reinforcing the notion that bone responses to ultra-endurance exercise are multifaceted and marker-specific.

Effect on the gastrointestinal system

Three studies investigated the effects of the *Spartathlon* on the gastrointestinal system (Skenderi et al., 2006; Kerschan-Schindl et al., 2021; Thalmann et al., 2006). Ultra-endurance exercise imposes substantial physiological stress on the gastrointestinal tract, primarily through splanchnic hypoperfusion, neuroendocrine activation, and mechanical strain, all of which can impair gastrointestinal integrity and function. One study reported marked alterations in gastrin regulation, demonstrating a 35% decrease in gastrin among non-finishers and a 46% increase among finishers (Kerschan-Schindl et al., 2021). Despite this rise, post-race gastrin levels in finishers were 56% lower than those of non-finishers, suggesting that finishers may experience a more pronounced suppression of gastric secretory activity during extreme endurance stress (Kerschan-Schindl et al., 2021). These divergent responses likely reflect differences in exercise duration, gastrointestinal perfusion, and neurohormonal feedback between finishers and non-finishers.

Hepatic responses were also assessed. One study measured liver enzymes before and after the race and found a dramatic post-race increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), whereas gamma-glutamyl transferase (γ-GT) remained unchanged (Kerschan-Schindl et al., 2021). Post-race values reached AST 1,182±165 IU/L and ALT 264±37 IU/L (Kerschan-Schindl et al., 2021). These elevations likely reflect a combination of exercise-induced hepatocellular stress, increased muscle breakdown, and altered hepatic blood flow, all of which are well documented in prolonged ultra-endurance events.

Another study examined whether prophylactic proton pump inhibitor (PPI) therapy could reduce gastrointestinal complications during the race. The authors reported that a short pre-race regimen of pantoprazole 20 mg effectively reduced the incidence of gastrointestinal bleeding among *Spartathlon* participants (Thalmann et al., 2006). While these findings are observational and should not be interpreted as prescriptive, they highlight a potentially relevant strategy for mitigating gastrointestinal bleeding risk in extreme endurance conditions.

Inflammatory responses

Several studies have examined the inflammatory effects of the *Spartathlon* on participating athletes (Margeli et al., 2005; Bartzeliotou et al., 2007; Papassotiriou et al., 2008; Goussetis et al., 2009; Balfoussia et al., 2014). Ultra-endurance exercise of this magnitude induces a profound acute-phase response, characterized by coordinated activation of cytokines, chemokines, adhesion molecules, and endothelial mediators.

A proteomic analysis demonstrated that 52 proteins were differentially expressed across three time points—pre-race, immediately post-race, and two days post-race—of which 30 proteins were directly involved in inflammatory pathways (Balfoussia et al., 2014). This broad proteomic shift underscores the systemic nature of the inflammatory response elicited by the race.

Consistent with these findings, several studies reported marked post-race increases in C-reactive protein (CRP), interleukin-6 (IL-6), serum amyloid A (SAA), monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8), soluble vascular cell adhesion molecule-1 (sVCAM-1), soluble intercellular adhesion molecule-1 (sICAM-1), and soluble thrombomodulin (sTM) (Dimitra et al., 2021; Margeli et al., 2005; Goussetis et al., 2009). These elevations reflect acute systemic inflammation, endothelial activation, and exercise-induced tissue damage. Importantly, procalcitonin levels remained unchanged (Margeli et al., 2005; Papassotiriou et al., 2008), indicating that the inflammatory response was aseptic and not suggestive of bacterial infection despite its severity.

The race also triggered a pronounced bone marrow–derived regenerative response. One study demonstrated a rapid mobilization of endothelial progenitor cells (EPCs), with circulating EPCs increasing nearly ten-fold by the end of the race (Papassotiriou et al., 2007). This surge likely represents a compensatory mechanism aimed at repairing endothelial microdamage induced by prolonged exertion (Goussetis et al., 2009).

Markers of endothelial activation and cell adhesion showed a characteristic temporal pattern. Molecules such as E-selectin, ICAM-1, VCAM-1, lipocalin-2, MCP-1, and thrombomodulin peaked immediately after the race and returned to baseline within ∼48h (Bartzeliotou et al., 2007; Papassotiriou et al., 2007). In contrast, L-selectin and P-selectin remained unchanged at the end of the race and exhibited a similar decline at 48h post-race (Papassotiriou et al., 2007), suggesting selective activation of endothelial pathways.

Overall, the *Spartathlon* induces a robust, multifaceted inflammatory response, involving cytokine release, endothelial activation, acute-phase protein synthesis, and bone-marrow mobilization. These responses are transient, resolving within days, but reflect the substantial physiological stress imposed by this extreme ultra-endurance event.

Exercise-associated hyponatremia (EAH)

Participation in the *Spartathlon* appears to carry a substantial risk of developing exercise-associated hyponatremia (EAH). In a study of 63 successful finishers, 41 athletes (65%) developed hyponatremia, with 27 runners (43%) presenting with mild and 14 runners (22%) with severe EAH (Seal et al., 2019). This represents one of the highest documented EAH prevalences in ultra-endurance sport.

The exceptionally high rate of EAH in the *Spartathlon* is likely attributable to the extreme duration of the race, the challenging environmental conditions, and the substantial terrain undulations, all of which promote prolonged exposure to thermoregulatory stress, variable pacing, and opportunities for excessive fluid intake (Seal et al., 2019). These factors collectively increase the risk of dilutional hyponatremia, particularly when athletes consume fluids beyond their physiological needs. Overall, the available evidence indicates that the *Spartathlon* represents a high-risk environment for EAH, underscoring the importance of appropriate hydration strategies, athlete education, and on-course medical monitoring.

Metabolic effects

Running the *Spartathlon* induced substantial alterations in lipid metabolism and endocrine function. Some studies reported significant changes in circulating metabolites, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and the TC:HDL-C ratio (Stergioulas, Tripolitsioti & Nicolaou, 2008; Margeli et al., 2005). In one study, mean concentrations of TC, TG, and LDL-C decreased markedly within 20min after finishing the race, reaching their lowest values shortly after completion, with a tendency to return toward baseline 24h post-race (Stergioulas, Tripolitsioti & Nicolaou, 2008). In contrast, HDL-C increased significantly within 20min after *Spartathlon* compared with pre-race values and remained elevated both immediately post-race and at 24h. The combined decrease in TC and increase in HDL-C resulted in a significant reduction in the TC:HDL-C ratio, indicating a transient shift toward a more favorable lipid profile (Stergioulas, Tripolitsioti & Nicolaou, 2008).

Another study confirmed these findings, reporting that TC, TG, LDL-C, and apolipoprotein B decreased to their lowest values at the end of the race and remained suppressed 48h post-race (Margeli et al., 2005). HDL-C showed a mild increase immediately after the race but returned to baseline by 48h. Apolipoprotein AI, however, decreased significantly during *Spartathlon* and remained low at 48h, suggesting a short-term perturbation in lipoprotein transport and reverse-cholesterol pathways (Margeli et al., 2005).

Endocrine responses were also evaluated. Thyroid hormone levels increased during the race but remained within the normal physiological range (Dimitra et al., 2021), indicating a mild activation of metabolic rate without overt thyroid dysfunction. The most pronounced hormonal change was observed in cortisol, which tripled immediately after the race and declined by 48h, although the decrease did not reach statistical significance (Dimitra et al., 2021). This pattern reflects intense hypothalamic–pituitary–adrenal (HPA) axis activation, characteristic of extreme endurance exercise.

Leptin, a marker of energy availability and adipose-tissue signaling, decreased during the race, consistent with prolonged energy deficit and high metabolic demand. By 48h post-race, leptin levels had increased significantly from immediate post-race values and approached pre-race concentrations, indicating early recovery of energy-regulatory pathways (Dimitra et al., 2021).

Overall, these findings demonstrate that the *Spartathlon* induces a robust but transient metabolic shift, characterized by reductions in atherogenic lipids, elevations in HDL-C, activation of stress-related endocrine pathways, and dynamic changes in energy-regulatory hormones.

Oxidative stress

Prolonged and exhaustive exercise such as running the *Spartathlon* has been strongly implicated in the generation of reactive oxygen species (ROS), leading to measurable oxidative stress (Stergioulas, Tripolitsioti & Nicolaou, 2008; Schulpis et al., 2008; Skenderi et al., 2008). Several studies demonstrated that *Spartathlon* induces both oxidative damage and compensatory antioxidant responses, reflecting the extreme metabolic and mechanical demands placed on athletes (Stergioulas, Tripolitsioti & Nicolaou, 2008; Schulpis et al., 2008; Skenderi et al., 2008).

One study reported a significant increase in 8-iso-prostaglandin $F_2\alpha$, a reliable biomarker of lipid peroxidation and oxidative injury. Levels rose markedly at the end of *Spartathlon* and remained 2.5-fold higher than baseline even 48h post-race, indicating sustained oxidative stress beyond the immediate recovery period (Skenderi et al., 2008). In parallel, athletes exhibited an increase in total antioxidant capacity (TAC) immediately after *Spartathlon*, which also remained elevated at 48h (Skenderi et al., 2008), suggesting a coordinated upregulation of endogenous antioxidant defenses in response to the heightened oxidative load.

Additional evidence of redox imbalance was observed in erythrocytes. Glucose-6-phosphate dehydrogenase (G6PD) activity—critical for maintaining NADPH availability and supporting glutathione recycling—was reduced in *Spartathlon* finishers after the race (Schulpis et al., 2008). This reduction was accompanied by an increase in oxidized glutathione (GSSG) and an elevated GSSG/GSH ratio, indicating a shift toward a more oxidized intracellular environment (Schulpis et al., 2008). These findings highlight the vulnerability of red blood cells to oxidative stress during extreme endurance exercise, likely due to repeated mechanical deformation, hemolysis, and high metabolic turnover.

Overall, the available evidence demonstrates that the *Spartathlon* elicits a robust oxidative challenge, characterized by increased lipid peroxidation, impaired redox homeostasis, and compensatory antioxidant activation. These responses are consistent with the extreme duration and intensity of the event and align with observations from other ultra-endurance competitions.

Discussion

This narrative review aimed to summarize the current body of scientific knowledge derived from studies involving *Spartathlon* participants or data on their performance and physiological responses.

While several findings from the *Spartathlon* were unique to this race and offer practical relevance for athletes and coaches, many results also reinforce observations from other ultra-marathon investigations (Knechtle & Nikolaidis, 2018). The *Spartathlon* represents a distinctive model of extreme ultra-endurance exercise, characterized by continuous, prolonged, moderate-intensity running under strict cut-off times, substantial elevation changes, and challenging environmental conditions. This combination elicits a cascade of physiological responses across multiple organ systems. The sustained mechanical and metabolic load is associated with marked increases in immunological markers, tissue-damage biomarkers, and stress-related endocrine signals. Although transient cardiac strain, skeletal muscle damage, and inflammatory activation mirror findings from other ultra-endurance events (Lee et al., 2017; Graziano et al., 2022), the magnitude, duration, and systemic integration of these responses appear particularly pronounced in the *Spartathlon* due to its exceptional demands.

A central theme emerging from the available evidence is the interdependence of hydration status, cardiovascular strain, and renal stress. The exceptionally high prevalence of EAH suggests that fluid–electrolyte imbalance is not merely a coincidental finding but may represent a key physiological stressor in this race. EAH may contribute to or exacerbate cardiac biomarker elevations, transient renal impairment, and inflammatory signaling, highlighting the physiological vulnerability that arises under extreme endurance conditions (Jacoby, 2020). The limited data on renal function underscore the need for more comprehensive investigations into kidney responses during this event.

The musculoskeletal and skeletal systems also exhibit coordinated stress responses. Substantial elevations in CK, LDH, and myostatin indicate extensive skeletal muscle breakdown, while alterations in bone-turnover markers—such as FGF23, CTX, and the RANKL/OPG axis—suggest that both mechanical loading and metabolic strain influence bone remodeling during and after the race. Concurrent changes in plantar pressure distribution may reflect adaptive gait modifications that help maintain forward propulsion but may also increase localized musculoskeletal loading, potentially contributing to cumulative fatigue or overuse injury.

Importantly, these physiological perturbations do not occur in isolation. Inflammation, oxidative stress, and metabolic shifts interact dynamically, creating a complex internal environment that shapes performance and recovery. Elevated cytokines, lipid peroxidation markers, and hormonal fluctuations likely contribute to systemic fatigue, influencing how athletes regulate effort across the race. The characteristic reverse J-shaped pacing pattern observed in successful finishers may represent an adaptive behavioral strategy designed to balance performance optimization with the management of accumulating physiological strain (Biswas, 2016; Abbiss & Laursen, 2008). This interplay between internal physiological stress and external pacing behavior underscores the value of *Spartathlon* as a model for studying integrated human endurance physiology.

Participation trends

Participation in the *Spartathlon* has shown a clear upward trend in the number of successful finishers over time. This development is particularly noteworthy given the race's strict qualification criteria and an even more stringent system of checkpoint-based eliminations, which remove runners who fail to meet intermediate time limits (Knechtle et al., 2021; Knechtle et al., 2022). Despite these demanding conditions, both male and female finisher numbers have increased, mirroring trends observed in other ultra-endurance events of comparable distance, such as the *Badwater Ultramarathon* in the United States (Da Fonseca-Engelhardt et al., 2013; Zingg et al., 2013).

However, this global rise in ultra-marathon participation is not universal. While substantial growth has been documented in iconic events such as the *Comrades Marathon* in South Africa (Nikolaidis et al., 2021), similar increases have not been observed in more traditional 100-km races. For example, participation in the long-standing *100 km Lauf Biel* in Switzerland has not followed the same upward trajectory (Knechtle, Scheer, Nikolaidis & Sousa, 2020). These contrasting patterns suggest that participation growth may be influenced by race-specific characteristics—such as prestige, difficulty, historical significance, and qualification requirements—rather than representing a uniform global trend across all ultra-endurance formats.

The age of peak performance

The age at which athletic performance peaks varies considerably across sports, and identifying this peak is important for long-term training and career planning. Assessing the age of peak performance typically requires comparing outcomes across multiple age groups or tracking athletes longitudinally. In ultra-endurance events, age-related performance trends consistently indicate that peak performance occurs later than in shorter endurance disciplines.

In the *Spartathlon*, finishers are composed almost entirely of master athletes (Da Fonseca-Engelhardt et al., 2013; Zingg et al., 2013), and the age of peak performance has been consistently identified at ~40–45 years—roughly a decade beyond the conventional master-athlete threshold of ~35 years (Reaburn & Dascombe, 2008). This pattern aligns with findings across various ultra-marathon distances and reflects the endurance-specific physiological and psychological adaptations that tend to favor older athletes (Knechtle & Nikolaidis, 2018). These adaptations include enhanced fatigue resistance, superior pacing regulation, greater psychological resilience, and long-term aerobic conditioning, all of which contribute to the delayed performance peak observed in ultra-endurance sport (Knechtle & Nikolaidis, 2018).

Pacing during the spartathlon

Pacing refers to the strategic distribution of effort across an endurance event and, in ultra-marathons, is commonly evaluated by examining changes in running speed or the time required to cover standardized segments (e.g., 1- km splits). To date, only one study has specifically investigated pacing during the *Spartathlon*. The authors identified a characteristic reverse J-shaped pacing profile, marked by an initial decline in running speed, followed by a period of relative stabilization, and concluding with a final deceleration phase (Knechtle et al., 2022).

This pacing pattern may be specific to ultra-endurance events of extreme duration, as similar reverse J-shaped curves have been observed in 24-hour ultra-marathoners (Inoue et al., 2019; Bossi et al., 2017), who often cover distances comparable to those achieved by *Spartathlon* participants. The resemblance suggests that athletes competing over ~200–250 km may adopt a common pacing strategy shaped by the need to balance energy expenditure, manage cumulative fatigue, and respond to the progressive physiological strain inherent to such prolonged efforts.

Effect on body mass

Three studies have examined changes in body mass among *Spartathlon* participants, consistently reporting a decrease in body mass after the race (Seal et al., 2019; Christou et al., 2020; Koutlianos et al., 2021). However, these studies did not determine whether this reduction was primarily attributable to dehydration, loss of fat mass, or loss of skeletal muscle mass (Knechtle et al., 2012). This distinction is important, as endurance exercise is known to influence adipose-tissue metabolic activity, including increased lipolysis and altered lipid mobilization (Savard et al., 1987).

Further insights can be drawn from multi-stage ultra-endurance events, where changes in body composition have been studied in greater detail. For example, during the 7-day *Marathon des Sables*, athletes demonstrated significant reductions in total body mass, fat-free mass, and fat mass (Zouhal et al., 2009). These findings suggest that prolonged ultra-endurance exercise—especially when performed over multiple days or under extreme environmental conditions—can lead to substantial shifts in body composition, not merely acute fluid loss (Knechtle & Nikolaidis, 2018).

Although comparable body composition data are lacking for the *Spartathlon*, the observed post-race reductions in body mass likely reflect a combination of fluid deficits, glycogen depletion, and substrate oxidation, with potential contributions from muscle catabolism during prolonged exertion (Knechtle & Nikolaidis, 2018). Future studies incorporating bioimpedance, DXA (Dual-Energy X-Ray Absorptiometry), or serial body composition assessments would help clarify the relative contributions of these components in *Spartathlon* athletes.

Effects on the cardiovascular system

Competing in the *Spartathlon* induces a characteristic pattern of transient cardiac stress driven by several interacting mechanisms (Christou et al., 2023; Pagourelias et al., 2022; Christou et al., 2020; Koutlianos et al., 2021). Table 1 shows a summary of the findings.

Hypovolemia and reduced preload lead to diminished LV filling, smaller chamber dimensions, and an apparent increase in wall thickness. RV afterload rises progressively during prolonged exercise due to elevated pulmonary pressures, placing a disproportionate strain on the thin-walled RV and explaining both the RV-dominant reduction in strain and the strong post-race increase in NT-proBNP.

Myocardial fatigue and metabolic stress from sustained sympathetic activation and high cardiac output further contribute to global reductions in longitudinal strain. At the same time, inflammatory and neurohormonal activation—reflected by marked increases in cytokines and cortisol (Dimitra et al., 2021)—can impair myocardial relaxation and alter vascular tone, and influencing cardiac performance. Finally, transient myocardial edema likely contributes to increased wall thickness and reduced strain, consistent with the reversible nature of these findings in the hours following rehydration and recovery (Knechtle & Nikolaidis, 2018).

Table 1
Summary of changes of the cardiovascular system found during *Spartathlon*.

Domain	Parameter	Direction
Vessels	Carotid–femoral pulse wave velocity	↑
	Arterial stiffness (peripheral indices)	=
	Carotid artery intima–media thickness	=
Myocardium	Myocardial wall thickness (global)	↓
	Myocardial wall thicknesses (regional)	↓
	Left ventricular wall thickness	↑
Atria	Atrial strain (global)	=
	Right atrial strain	=
	Left atrial strain	=
Left Ventricle	Left ventricular strain	↓
Ventricles (Global & RV)	Ventricular longitudinal strain	↓
	Right ventricular strain	↓
	Right ventricular systolic function	↓
	Effective diastolic period	↓
	Left ventricular dimensions	↓
	End-diastolic dimensions	↓
Cardiac Biomarkers	Troponin I	↑
	NT-proBNP	↑

Note: = (does not change), ↑ (increase), ↓ (decrease).

The heart and blood vessels of ultra-marathon runners are generally capable of meeting the demands of prolonged exercise to supply skeletal muscles with nutrients and remove metabolic waste products (Knechtle & Nikolaidis, 2018). Several studies have investigated *Spartathlon* participants for potential effects on the heart and cardiac biomarkers, and participation has been associated with minor, transient changes in myocardial structure and function, consistent with findings from other ultra-marathon research (Knechtle & Nikolaidis, 2018). Notably, no case studies have reported cardiac-related deaths during the *Spartathlon*, although such incidents have occurred in shorter endurance events, where the risk of sudden cardiac arrest appears higher (Cunningham, Maghrabi & Sanatani, 2017). Sudden cardiac arrest and death seem more likely to occur during a half-marathon or marathon (Kim et al., 2025) than during an ultra-marathon.

Effects on the locomotor system

The mechanical load imposed on the locomotor system during the *Spartathlon* has been only minimally investigated. To date, one study has examined the effects of the race on the foot, and—remarkably—no comparable analyses exist for other ultra-marathons of similar distance. Only a single study in marathon runners has addressed comparable foot-loading characteristics, underscoring the novelty and relevance of the *Spartathlon* findings (Nagel, Fernholz, Kibele & Rosenbaum, 2008). In *Spartathlon* participants, peak pressure and impulse values in the forefoot increased from pre- to post-race, while values under the toes decreased (Karagounis et al., 2009). This pattern likely reflects a fatigue-related shift in gait mechanics, with reduced toe-flexor engagement and compensatory loading of the forefoot. Such adaptations may help maintain forward propulsion under extreme fatigue but may also increase localized mechanical stress on the metatarsal region.

These findings have practical implications for athletes and coaches, particularly regarding footwear selection. Footwear capable of attenuating forefoot loading or supporting fatigued toe-flexor function may help mitigate mechanical strain during prolonged ultra-endurance running. Recent evidence suggests that advanced footwear technologies—including carbon-fiber plates, optimized midsole geometries, and high-energy-return foams—can enhance running economy and reduce mechanical loading during endurance events (Rodrigo-Carranza et al., 2021). Whether such technologies confer similar benefits in ultra-marathons of extreme duration remains an important avenue for future research.

Overall, the limited evidence indicates that the *Spartathlon* imposes substantial mechanical demands on the locomotor system, with measurable alterations in plantar-pressure distribution. Further biomechanical studies are warranted to better understand how gait, footwear, and fatigue interact over distances exceeding 200 km.

Effects on the skeletal muscles

Participation in the *Spartathlon* is associated with substantial skeletal muscle stress, as reflected by marked elevations in CK and LDH—two well-established biomarkers of muscle injury in ultra-marathon runners (Knechtle & Nikolaidis, 2018). These increases indicate extensive sarcolemmal disruption, muscle-fiber damage, and inflammatory infiltration, consistent with the extreme mechanical and metabolic demands of running >240 km. One study additionally reported a significant post-race increase in myostatin, a negative regulator of muscle growth and a key inhibitor of myogenic differentiation (Kerschan-Schindl et al., 2015). Elevated myostatin suggests a temporary suppression of muscle-regeneration pathways, likely reflecting the acute catabolic environment induced by the race.

Interestingly, this response contrasts with findings from the Trans

Europe Foot Race (TEFR)—a 64-day, 4,486- km multi-stage ultra-marathon—where no change in myostatin levels was observed (Klenk et al., 2021). This discrepancy highlights the importance of race format, intensity, and daily load in shaping muscle-regulatory responses. The absence of myostatin elevation in the TEFR may be attributable to the lower daily physical stress and the distributed workload across many days, which likely allow for partial recovery between stages. In contrast, the condensed, continuous, high-intensity format of the *Spartathlon* produces a more pronounced acute catabolic signal, resulting in measurable increases in myostatin.

Overall, the available evidence suggests that the *Spartathlon* imposes exceptionally high acute muscular stress, distinct from the cumulative but more evenly distributed load observed in multi-stage ultra-endurance events.

Effects on the gastrointestinal system

Ultra-endurance exercise induces a substantial redistribution of blood flow away from relatively inactive tissues, including the gastrointestinal tract, toward the working skeletal muscles. This reduction in splanchnic perfusion can impair gastrointestinal function and has been linked to a range of exercise-associated complications, including gastrointestinal bleeding, which is reported relatively frequently among ultra-endurance athletes (Thalmann et al., 2006; Knechtle & Nikolaidis, 2018; Papantoniou et al., 2023). Participation in the *Spartathlon* has similarly been associated with elevations in liver enzymes (Skenderi et al., 2006) and increases in total bilirubin (Schulpis et al., 2008), responses that are well documented in other ultra-marathon events (Knechtle & Nikolaidis, 2018). These biochemical alterations typically return to baseline within several days post-race (Knechtle & Nikolaidis, 2018).

One observational study reported that pre-race use of PPI was associated with a lower incidence of gastrointestinal bleeding during an ultra-endurance event (Thalmann et al., 2006). While this association is noteworthy, it should remain framed strictly as an *observational finding* rather than interpreted as a prescriptive or clinically actionable recommendation. Given that gastrointestinal bleeding is relatively common among endurance athletes (Papantoniou et al., 2023), such results highlight an area where controlled, prospective research may be warranted. Beyond pharmacological associations, current practical guidelines emphasize non-pharmacological strategies—particularly individualized nutrition planning and systematic "gut training"—as primary approaches to managing or reducing gastrointestinal symptoms during ultra-endurance competition (Costa et al., 2025). These approaches are grounded in accumulated observational evidence, athlete experience, and expert consensus rather than formal therapeutic directives, underscoring the need for individualized strategies tailored to an athlete's tolerance, prior symptoms, and race-specific demands.

Effects on bones

During prolonged exercise such as ultra-marathons, the skeletal system is exposed to sustained mechanical loading due to its continuous role in supporting body mass and facilitating locomotion. Table 2 shows the changes on musculoskeletal biomarkers during the *Spartathlon*.

Biochemical data from the *Spartathlon* indicate increases in circulating fibroblast growth factor-23 (FGF23) (Kerschan-Schindl et al., 2021), decreases in DKK1 levels (Kerschan-Schindl et al., 2015), and alterations in the RANKL/OPG signaling axis (Kerschan-Schindl et al., 2009), all of which are key regulators of bone remodeling. The practical implications of these acute biomarker fluctuations remain uncertain, as FGF23 (Mehreen et al., 2025), DKK1 (Ke, Richards, Li & Ominsky, 2012), and the RANKL/RANK/OPG pathway (Hooshiar, Tobeiha & Jafarnejad, 2022) have been studied primarily in clinical populations with bone pathology rather than in ultra-endurance athletes. Consequently, their relevance for long-term skeletal health in this context is not yet established.

Table 2
Summary of changes of musculoskeletal biomarkers found during *Spartathlon*.

Category	Biomarker	Direction
Muscle Damage / Turnover	CK (creatine kinase)	↑
	LDH (lactate dehydrogenase)	↑
Muscle Growth / Regulation	Follistatin	↑
	Myostatin	↑
Bone Remodeling — RANKL/ OPG Axis	RANKL	↑
	OPG	↑
Bone Remodeling — Other Pathways	FGF23	↑
	CTX (cross-linked C-telopeptide of type I collagen)	↑
	Osteocalcin (Oc)	↓
	Sclerostin	=
	Cathepsin K	=
	DKK1 (Dickkopf-1)	↓↑*

Note: = (does not change), ↑ (increase), ↓ (decrease), * DKK1 shows bidirectional findings across studies (some report decreases, others increases).

More practically oriented research has examined structural and functional aspects of joint and cartilage health in ultra-marathoners. Studies investigating knee integrity during the *Comrades Marathon* (Hagemann, Rijke & Corr, 2008) and cartilage biomarker responses following multi-day ultra-endurance events (Kim, Lee & Kim, 2007; Shin et al., 2012) provide insight into how repeated mechanical loading may influence joint tissues. These investigations offer a more direct perspective on musculoskeletal adaptations and potential vulnerabilities associated with ultra-endurance running, complementing the biochemical findings from the *Spartathlon*.

The aspect of inflammation

Participation in the *Spartathlon* has been associated with a pronounced inflammatory response, reflected by substantial increases in several circulating inflammatory markers. Table 3 presents the inflammatory response after finishing *Spartathlon*.

It is well established that prolonged aerobic exercise, including ultra-marathon running, leads to elevated concentrations of cytokines such as IL-6, interleukin-1 receptor antagonist (IL-1ra), interleukin-1β (IL-1β), IL-8, interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α) (Alves

Table 3
Summary of the inflammatory response found during *Spartathlon.*

Category	Biomarker	Direction
Acute-Phase Reactants	CRP (C-reactive protein)	↑
	SAA (serum amyloid A)	↑
Cytokines / Chemokines	IL-6 (Interleukin-6)	↑
	IL-8 (Interleukin-8)	↑
	MCP-1 (monocyte chemoattractant protein-1)	↑
Endothelial Activation / Adhesion Molecules	ICAM-1 (intercellular adhesion molecule-1)	↑
	sICAM-1 (soluble ICAM-1)	↑
	VCAM-1 (vascular cell adhesion molecule-1)	↑
	sVCAM-1 (soluble VCAM-1)	↑
	E-Selectin	↑
	L-Selectin	=
	P-Selectin	=
Endothelial Injury / Coagulation-Related	sTM (soluble thrombomodulin)	↑
	TM (thrombomodulin)	↑
Innate Immune Activation	Lipocalin-2 (NGAL)	↑
	NGAL (neutrophil gelatinase-associated lipocalin)	↑
Vascular Repair / Regeneration	EPCs (endothelial progenitor cells)	↑

Note: = (does not change), ↑ (increase), ↓ (decrease).

et al., 2022). These cytokines form part of the acute-phase response, which is triggered by mechanical muscle damage, metabolic stress, and immune activation during prolonged endurance exercise. Importantly, these increases are typically transient (Knechtle & Nikolaidis, 2018). Most inflammatory markers return to baseline within hours to several days after the race (Alves et al., 2022; De Sousa et al., 2021), indicating that the inflammatory surge represents a physiological and self-limiting response rather than a pathological process. This temporary elevation reflects the substantial muscle damage, oxidative stress, and metabolic strain induced by ultra-endurance efforts and may contribute to post-exercise tissue repair, immune modulation, and adaptation. The *Spartathlon* elicits a robust but reversible inflammatory response, consistent with the extreme duration and intensity of the event and aligned with findings from other ultra-endurance competitions.

Exercise-Associated hyponatremia (EAH)

Exercise-associated hyponatremia (EAH), defined as an abnormally low blood sodium concentration during or following prolonged physical activity, remains a significant health concern in ultra-endurance sport (Knechtle & Nikolaidis, 2018). The *Spartathlon* has demonstrated exceptionally high EAH prevalence, with incidences of 52% when excluding and 65% when including athletes who were already hyponatremic before the race (Seal et al., 2019). To date, these values represent the highest documented EAH prevalence in the ultra-endurance literature. In contrast, EAH appears far less common in most other ultra-marathon events (Knechtle et al., 2019). No cases were observed in a 24-hour ultra-marathon (Knechtle, Knechtle & Rosemann, 2010), despite athletes covering distances comparable to *Spartathlon* finishers (Inoue et al., 2019; Bossi et al., 2017), and only ~5% prevalence has been reported in a 100- km race (Knechtle, Knechtle & Rosemann, 2011). These observational discrepancies highlight that the *Spartathlon* presents a uniquely high-risk context for EAH.

Given this pattern, heightened awareness of hydration behavior and known EAH risk factors is warranted when preparing for and participating in the *Spartathlon*. Although contemporary evidence and consensus guidelines consistently indicate that sodium supplementation plays a minimal role in preventing EAH, the belief in its necessity remains widespread among ultra-marathon runners (Hoffman & White, 2020). This persistent perception underscores the importance of evidence-based education, while recognizing that hydration strategies should remain framed strictly as observational findings rather than prescriptive recommendations, and must be individualized according to athlete experience, tolerance, and race-specific demands.

Effects on the metabolism

To date, only one study has specifically examined the metabolic effects of participating in the *Spartathlon*, focusing primarily on lipid metabolism. This investigation reported a significant decrease in total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C), accompanied by an increase in high-density lipoprotein cholesterol (HDL-C) after the race (Stergioulas, Tripolitsioti & Nicolaou, 2008). These findings suggest a transient shift toward a more favorable lipid profile, consistent with the metabolic demands of prolonged endurance exercise.

Similar alterations in lipid metabolism have been documented in other ultra-marathon events. For example, Górecka et al. (Górecka et al., 2020) observed changes in lipid profiles and increased plasma levels of angiopoietin-like protein 4, a regulator of lipid mobilization, following a mountain ultra-marathon. Likewise, Jörres et al. (Jörres, Gunga & Steinach, 2021) reported physiological and metabolic changes during a 100- km walking march, including shifts in lipid metabolism that align with the *Spartathlon* findings. Broader reviews of ultra-marathon physiology (Knechtle & Nikolaidis, 2018) further support the notion that prolonged endurance events may induce beneficial metabolic adaptations, particularly in lipid handling and cardiovascular risk markers.

These studies suggest that ultra-endurance exercise such as the *Spartathlon* may exert favorable metabolic effects, although the underlying mechanisms—such as increased lipid oxidation, altered hormonal regulation, and changes in energy-substrate utilization—warrant further investigation. Table 4 presents the changes in metabolic markers during the *Spartathlon*.

Oxidative stress

Participation in the *Spartathlon* has been associated with measurable oxidative stress, reflected by changes in antioxidant capacity and redox-related biomarkers. Table 5 shows a summary of the changes in markers of oxidative stress.

Skenderi et al. reported a significant increase in total antioxidant capacity (TAC) immediately after the race, with elevated levels persisting for up to 48h post-event (Skenderi et al., 2008). This rise represents a compensatory upregulation of endogenous antioxidant defenses in response to the substantial oxidative load generated during prolonged endurance exercise. However, oxidative-stress responses may extend well beyond the immediate recovery period. Turner et al. demonstrated that ultra-endurance exercise can lead to a sustained depletion of antioxidant capacity lasting up to one month (Turner, Hodges, Bosch & Aldred, 2011). This suggests that while acute antioxidant responses may initially rise, longer-term oxidative imbalance or delayed recovery of antioxidant systems may occur following extreme endurance efforts.

Importantly, the nature and duration of oxidative stress appear to vary depending on race distance, elevation profile, and environmental demands. In the *Tor des Géants*, a 330- km mountain ultra-marathon with 24,000 m of elevation gain, Mrakic-Sposta et al. (Mrakic-Sposta et al., 2015) observed a decrease in antioxidant capacity, indicating a different oxidative pattern compared with flatter or shorter events. The extreme altitude variation, prolonged duration, and cumulative fatigue likely impose distinct oxidative challenges compared with the *Spartathlon*.

These findings highlight the complex and heterogeneous oxidative responses elicited by ultra-endurance races (Knechtle & Nikolaidis, 2018). It is likely that race-specific characteristics—including distance, topography, environmental stressors, and pacing demands—shape both the magnitude and direction of oxidative stress (Knechtle & Nikolaidis, 2018). Understanding these differences is essential for developing targeted recovery strategies and optimizing athlete preparation for diverse ultra-endurance events.

Table 4
Summary of changes of metabolic markers found during *Spartathlon*.

Category	Biomarker	Direction
Lipid Metabolism	TC (total cholesterol)	↓
	HDL-C (high-density lipoprotein cholesterol)	↑
	LDL-C (low-density lipoprotein cholesterol)	↓
	TG (triglycerides)	↓
	Apolipoprotein B	↓
	Apolipoprotein AI	↓
Energy-Regulatory Hormones	Leptin	↓
Stress Hormones	Cortisol	↑
Thyroid Axis	TSH (thyroid-stimulating hormone)	=
	T4 (tetraiodothyronine)	=
	FT4 (free T4)	=
	T3 (triiodothyronine)	=
	FT3 (free T3)	=

Note: = (does not change), ↑ (increase), ↓ (decrease).

Table 5
Summary of changes of oxidative markers found during *Spartathlon*.

Category	Biomarker	Direction
Lipid Peroxidation	8-Iso-prostaglandin $F_{2\alpha}$	↑
Antioxidant Capacity	TAC (total antioxidant capacity)	↑
Redox Enzymes / Glutathione System	G6PD (glucose-6-phosphate dehydrogenase)	↓
	GSSG (oxidized glutathione)	↑

Note: ↑ (increase), ↓ (decrease).

Kidney function and spartathlon

To date, only one study has measured renal biomarkers in *Spartathlon* participants, reporting a significant post-race increase in serum creatinine, indicative of an acute reduction in kidney function (Christou et al., 2020). This isolated finding highlights a notable gap in the literature, especially given the extreme physiological demands of the event. Broader ultra-endurance research suggests that prolonged endurance races may lead to acute kidney injury (AKI) incidences ranging from 4% to 85%, with hypohydration identified as a key contributing factor (Juett, James & Mears, 2020). Although typically mild, AKI is a well-documented occurrence in ultra-marathon running (Hoffman & Weiss, 2016).

The *Spartathlon* may present an even higher risk profile due to its exceptionally high prevalence of exercise-associated hyponatremia (EAH)—the highest reported among ultra-marathons. EAH can exacerbate renal stress through fluid overload, electrolyte imbalance, and altered renal perfusion, raising concerns about increased vulnerability to kidney impairment in this event. Ultra-marathon running is increasingly recognized as a potential trigger for AKI, particularly when compounded by dehydration, rhabdomyolysis, or electrolyte disturbances (Knechtle & Nikolaidis, 2018). The prevalence of AKI in ultra-endurance events has been reported to reach ~12% (Poussel et al., 2020), and although most cases resolve without long-term consequences, there is growing concern that even rare episodes of acute renal injury may contribute to progressive renal scarring and increase the risk of chronic kidney disease (CKD) over time. Scheer et al. (Scheer et al., 2022) emphasize this potential in their review of long-term health issues associated with ultra-endurance running.

Given the intensity, duration, and hydration challenges of the *Spartathlon*, further research is needed to clarify the incidence and severity of AKI in this event, the interaction between EAH, dehydration, and renal stress, and the potential long-term implications for kidney health in recurrent participants. A more comprehensive renal assessment—including serial creatinine, cystatin C, urinary AKI biomarkers, and hydration monitoring—would substantially advance understanding of kidney responses in this uniquely demanding ultra-marathon.

Implications and applications for athletes and coaches

The research findings from *Spartathlon* participants provide valuable insights with direct applications for training, competition preparation, and athlete healthcare. The observation that peak performance typically occurs at ~40–45 years of age underscores the importance of long-term endurance development and strategic career planning. This age-related advantage reflects the cumulative benefits of sustained aerobic conditioning, psychological resilience, and extensive pacing experience.

The exceptionally high prevalence of EAH in the *Spartathlon* emphasizes the need for individualized hydration strategies. Athletes must recognize that overhydration can be as harmful as dehydration, and fluid intake should be tailored to personal sweat rates, environmental conditions, and real-time physiological feedback. Coaches and medical teams should prioritize education on electrolyte balance and implement monitoring strategies during training and competition.

Given the documented transient cardiac alterations in ultra-endurance athletes, routine cardiovascular screening and monitoring should be considered, particularly for master athletes. Although most cardiac changes resolve post-race, pre- and post-event assessments may help identify individuals at risk and ensure safe recovery.

Musculoskeletal considerations are equally important. Race-specific changes in plantar-pressure distribution and elevations in muscle-damage biomarkers highlight the relevance of footwear selection, strength training, and biomechanical assessments. Optimizing footwear—potentially incorporating advanced technologies—may help mitigate mechanical strain, while targeted conditioning can reduce injury risk and enhance performance durability.

Gastrointestinal stress remains a critical challenge in ultra-marathon running. Emerging evidence suggests that PPIs may reduce the incidence of GI bleeding, although their use should be carefully evaluated within a medical framework. Nutritional planning must also consider gut tolerance, especially under prolonged exertion and heat stress.

These findings also have implications for race organizers, who can enhance safety protocols by incorporating checkpoint-based medical assessments, hydration and electrolyte monitoring, and early detection systems for EAH, AKI, and heat-related illness. The *Spartathlon* thus serves not only as a model of extreme human endurance but also as a living laboratory for improving athlete health, safety, and performance in ultra-endurance environments.

Limitations and implications for future studies

The present review has several important limitations. A substantial proportion of the available evidence is derived from repeated analyses of similar or overlapping cohorts of *Spartathlon* participants, which may lead to an overrepresentation of certain findings within the literature. This issue is particularly relevant in physiological and biochemical studies, where multiple publications often report different outcomes from the same group of athletes, thereby limiting the independence of results. Another key limitation is the heterogeneity of study designs, methodologies, and outcome measures, which restricts the ability to make direct comparisons across studies. Many investigations are observational and exploratory, frequently lacking control groups, standardized protocols, or longitudinal follow-up. As a result, the strength of causal inference is limited, and several findings must be interpreted with caution.

Although many physiological markers show substantial acute changes following the race, their clinical significance remains uncertain, and elevations do not necessarily indicate pathological conditions. In many cases, these responses likely reflect transient physiological adaptations to extreme endurance exercise rather than adverse health outcomes. Furthermore, the review does not always distinguish between findings supported by multiple independent studies and those based on single investigations. While trends in participation, performance, and age of peak performance are supported by consistent evidence, several physiological outcomes rely on isolated reports, reducing the robustness of conclusions in these domains. Consequently, the current evidence base on the *Spartathlon* should be regarded as exploratory and descriptive rather than definitive.

To strengthen future research, several priorities emerge:

- Standardized study designs employing controlled, longitudinal, and interventional approaches to better elucidate causal relationships in physiological responses to ultra-endurance running.
- Comparative analyses that evaluate the *Spartathlon* alongside other ultra-marathons to differentiate race-specific from generalizable findings.
- Female-specific research, addressing the current underrepresentation of women in ultra-endurance physiology studies.

– Long-term health monitoring, particularly regarding cardiovascular, renal, musculoskeletal, and metabolic outcomes in recurrent participants.
– Footwear and biomechanical investigations, given the unique mechanical demands of the *Spartathlon*.
– Psychological and cognitive assessments, exploring decision-making, fatigue management, and mental resilience in extreme endurance contexts.
– Nutritional and hydration strategies, including individualized approaches to prevent EAH, optimize energy availability, and support gastrointestinal tolerance.

These directions will help build a more comprehensive and methodologically robust understanding of the physiological, biomechanical, and health-related implications of participating in the *Spartathlon*.

Conclusion

In summary, participation in the *Spartathlon* induces a range of well-documented physiological alterations, most notably affecting the cardiovascular, musculoskeletal, metabolic, and immune systems. These responses reflect the extraordinary mechanical, metabolic, and environmental demands of this 246- km ultra-endurance event. Despite the acute perturbations observed across multiple organ systems, many of these changes appear to be transient and reversible, underscoring the remarkable physiological resilience of trained ultra-endurance athletes. The *Spartathlon* thus represents a unique natural model for studying human adaptation under extreme conditions. Its combination of distance, strict cut-off times, and challenging terrain provides an unparalleled opportunity to investigate integrated physiological responses that cannot be replicated in laboratory settings. Continued research—using standardized methodologies, larger and more diverse cohorts, and long-term follow-up—is essential to deepen our understanding of the complex effects of ultra-endurance running. Such efforts will be crucial for enhancing athlete safety, optimizing performance, and informing evidence-based strategies for training, monitoring, and medical support in ultra-endurance sport.

Ethics approval and consent to participate

Not applicable

CRediT authorship contribution statement

Beat Knechtle: Writing – original draft, Conceptualization. **Pedro Forte:** Writing – review & editing. **Volker Scheer:** Writing – review & editing. **Daniela Chlibková:** Writing – review & editing. **Pantelis T. Nikolaidis:** Writing – review & editing. **Luciano Bernardes Leite:** Writing – review & editing. **Katja Weiss:** Writing – review & editing. **Thomas Rosemann:** Writing – review & editing. **Sasa Duric:** Writing – review & editing. **Mabliny Thuany:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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