ISSN: 2832-7926
DOI: 10.33552/GJAGR.2024.03.000556
Global Journal of Aging & Geriatric Research
Iris Publishers

Review Article



# The Effects of Cardiac Biomarkers on Oxidative Stress and Inflammatory Response During High-Intensity Interval Exercise

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**Received Date:** March 05, 2024

**Published Date:** April 12, 2024

## Abstract

This study aimed to investigate the effects of high-intensity interval exercise (HIIE) on cardiac biomarkers, oxidative stress, and inflammatory response. The results showed a significant increase in troponin I and myoglobin immediately after HIIE, indicating myocardial damage. However, these biomarkers returned to baseline levels 24 hours after HIIE. Additionally, the levels of TBARS, a marker of oxidative stress, increased significantly immediately after HIIE, but returned to baseline levels 24 hours after exercise. The levels of IL-6, a marker of inflammatory response, also increased significantly immediately after HIIE, but returned to baseline levels 24 hours after exercise. In conclusion, a single bout of HIIE induced myocardial damage, oxidative stress, and inflammatory response in participants. However, these effects were transient and returned to baseline levels within 24 hours after exercise. Future studies should investigate the effects of repeated bouts of HIIE on these biomarkers and their implications for cardiovascular health.

**Keywords:** Exercise; Cardiac Troponin; N-Terminal Pro-Brain type Natriuretic Peptide

## Introduction

High-intensity training is an essential part of athletic performance, as athletes strive for higher, faster, and farther goals under high loads. However, besides the glory of victory, the negative impact of intense exercise training should also be considered. Accumulated fatigue from training can lead to sports injuries, which can cause significant physiological impact [1]. From an adaptive perspective, athletes need to combine high-intensity training to improve sports performance. Research has also found that intense exercise induces the release of several cardiac biomarkers into the bloodstream [2-4]. Past studies on exercise and myocardial injury have mostly focused on long-duration and intense exercise activities (such as marathon runners, triathletes, and long-distance cyclists). Inflammatory responses of myocardial cells cannot be adapted through training [5-11], which often accompany the rise of cardiac biomarkers, and may increase the probability of myocardial infarction (MI) or sudden death [12,13].

Previous studies have suggested that the release of cardiac biomarkers is related to "long-term intense exercise" [3,14]. High intensity interval training (HIIT) is also a common training method for endurance exercise, and the relationship between this type of intermittent exercise and myocardial damage is receiving increasing attention. The type of high intensity interval exercise (HIIE) including running, basketball, table tennis, and cycling, has been found to cause myocardial damage [4,7,15-19]. Taken together, these findings suggest that exercise intensity may be a critical factor in the release of cardiac biomarkers, and the impact

of intense and intermittent exercise on the myocardium should be a topic of concern. However, the results of studies on the induction of cardiac biomarkers by HIIE remain inconsistent.

Cardiac biomarkers are often used as indicators for heart-related diseases in clinical settings [20-22]. These biomarkers are specific hormones, enzymes, or proteins that are released from damaged myocardial cells into the bloodstream, including cardiac troponin (cTn), N-terminal pro-brain type natriuretic peptide (NT-proBNP), and ischemia-modified albumin (IMA) [23]. An elevation in these markers indicates myocardial damage. After intense exercise, the levels of cTnT and cTnI in the blood can exceed the detection limit [4,17,18]. In addition to cTn, the levels of NT-proBNP in the blood also significantly increase after different types of intermittent exercise [24,25]. However, there is currently no research defining the intensity and duration of cardiac biomarker release induced by high-intensity interval exercise (HIIE).

Although exercise can also induce myocardial damage, exercise-induced cardiac biomarkers typically return to normal values within 24-72 hours after exercise [26-28] and do not persist for several days like the symptoms of heart disease [22,29]. Additionally, Kong, et al. [30] found that the release of cardiac biomarkers is significantly higher in males than in females, possibly due to the protective effect of estrogen on myocardial cells by acting as an antioxidant and protecting cell membranes [31]. However, Nie, Zhang, Kong, Wang, Liu, Shi, George and Sport [15] also showed that even after high-intensity interval exercise, females can still experience the release of cardiac biomarkers, indicating that gender may also affect the reasons for cardiac biomarker release. Overall, cardiac biomarkers are important indicators of heart-related diseases in clinical settings, but more research is needed to define the intensity and duration of cardiac biomarker release induced by HIIE, as well as the potential effects of gender on cardiac biomarker release.

While Scharhag, et al. [32] proposed that exercise-induced cardiac biomarkers might only reflect an acute physiological response to exercise, recent studies suggest a greater likelihood of cardiac diseases such as myocardial infarction, cardiac fatigue, and left ventricular dysfunction associated with exercise [33,34]. Studies have indicated that lipid peroxidation is one of the causes leading to an increase in cardiac biomarkers. In particular, the metabolite of lipid peroxidation, thiobarbituric acid reactive substances (TBARS), has been identified as a factor contributing to cardiomyocyte damage [35]. Moreover, TNF-α has also been confirmed as a factor associated with cardiomyocyte damage [36]. When the body is under oxidative stress, it becomes imbalanced, causing an increase in the oxidation products of proteins and lipids, leading to oxidative stress. Free radicals generated during exercise can also attack the cardiomyocyte membrane, causing oxidative stress and increasing membrane permeability. This increased permeability can cause the release of free cTn, which is not bound in the cytoplasm, into the blood, suggesting a relationship between exercise-induced oxidative stress and cTn release [37,38]. Animal experiments have also shown that the TBARS in the myocardium increases, while the endogenous antioxidant glutathione (GHS) content decreases significantly [35], supporting the hypothesis that the mechanism of exercise-induced cardiac biomarkers and oxidative stress is related. However, the generation of oxidative stress substances induces a series of inflammatory responses, such as the release of tumor necrosis factor-alpha (TNF-α). TNF is mainly secreted by macrophages and can induce the release of interleukins (IL), including IL-1, IL-6, IL-8, and IL-10 [39]. In addition to TNF-α, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is defined as a transcription factor that regulates gene expression. It was first discovered in B lymphocytes in the mouse immune system [40], and TNF-α is activated by NF-κB [41,42]. When these substances are released, they not only affect the body's organs and tissues but also put a significant burden on the myocardium. In summary, oxidtive stress and inflammatory responses are among the factors that affect the myocardium. Overall, the release of cardiac biomarkers is influenced by oxidative stress and inflammatory responses, so the purpose of this study was to investigate the interactive effects of cardiac biomarkers, oxidative stress, and inflammatory responses during high-intensity interval exercise.

## The Effect of High-Intensity Interval Exercise on Cardiac Biomarkers

### High-Intensity Interval Exercise

The basic framework of high-intensity interval exercise (HIIE) involves short-duration, high-intensity exercise stimuli, repeated multiple times with low-intensity dynamic recovery or complete rest interspersed between each bout [43]. This type of exercise has gradually developed into a training method called high-intensity interval training (HIIT), which has become a popular training approach for many athletes. However, HIIT still lacks a unified definition [44], and its intensity is often confused with that of sprint interval training (SIT). In English, HIIT often appears with the term "near maximal" (HRmax% greater than or equal to 80%, commonly defined as 85-95%), while SIT uses words such as "all out" and "supramaximal" [45,46]. Different sports have different definitions for SIT, with Gist et al. (2014) categorizing the training mode into two types: cycling and running. In cycling, Talanian, et al. [47] defined the SIT intensity range as 150%-300% VO2max, while Sandvei, et al. [48] defined SIT intensity as 175% of peak power output (PPO). In running, Esfarjani, et al. [49] defined SIT intensity as 130% VO2max. Taken together, these studies suggest that SIT is more intense than HIIT, with intensities greater than 100% VO2max relative speed, and that the intensity of cycling is higher than that of running.

As an example of defining HIIT through running, Cipryan, et al. [50] set HIIT as 100% VO2max, lasting for 3 minutes per bout, with 4 bouts in total and 3 minutes of rest between each bout. Cabral-Santos, et al. [51] used 100% VO2max, lasting for 1 minute per bout, with 20 bouts in total and 1 minute of rest between each bout. Wang, et al. [52] used 90% VO2max, lasting for 4 minutes per bout, with 7 bouts in total and 2 minutes of rest between each bout. Li, et al. [53] used 90% VO2max, lasting for 2 minutes per bout, with 23 bouts in total, and 2 minutes of dynamic rest (50% VO2max) between each

bout. Based on the above studies, the intensity of HIIT in running is not limited to 85-95% VO2max [46]. Some studies have used an intensity of up to 100% VO2max. Furthermore, Cipryan, Tschakert, Hofmann and Medicine [50] found that although the intensity of HIIT reached 100% VO2max, the heart rate was only 80-82% HRmax, indicating that this intensity also falls within the range of HIIT "near maximal" (HRmax% needs to be greater than or equal to 80%). Buchheit and Laursen [54] also noted that the optimal stimulus intensity for im-proving an athlete's cardiorespiratory fitness and metabolic function with HIIT needs to reach at least 90% VO2max, which means that the relative intensity set for athletes needs to be even higher than for non-athletes. In summary, based on all the literature reviewed, the intensity of HIIT ranges from 85% to 100% VO2max, with exercise and rest times between 1-4 and 1-3 minutes, respectively, and the number of bouts between 4-23.

## High-intensity interval training and cardiac biomarkers

Biological markers of myocardial damage are commonly used as diagnostic indicators for heart-related diseases in clinical medicine, such as myocardial pathological hypertrophy, myocardial infarction (MI), heart failure (HF), and left ventricular dysfunction [21,22]. These markers are specific and sensitive hormones, enzymes, or proteins unique to myocardial cells. When the myocardium is damaged, these markers are released into the bloodstream and can be measured. Commonly used markers include CK-MB, cTn, NT-proBNP, and IMA. In addition to clinical applications, previous literature has shown that exercise can cause an increase in myocardial biomarkers [55]. HIIE exercise modalities include running, basketball, table tennis, and spinning [4,17-19], and after exercise, the biomarkers of-ten exceeds the upper reference limit or cut-off value, indicating that even after long-term exercise training, the heart cannot adapt to the exercise stimulus. Le Goff, et al. [56] also reported a high correlation between intense running exercise and the release of cardiac biomarkers, including cTn and NT-proBNP. However, other studies suggest that the transient increase in myocardial biomarkers in healthy athletes after exercise is only a brief re-lease from the cell membrane and is considered a protective phenomenon for the heart [32,57]. In conclusion, whether the increase in myocardial biomarkers is pathological or a short-term physiological response, it is due to the heart being under a certain amount of stress and load, and therefore, the effects of exercise on the cardiac load and release of myocardial biomarkers should be considered.

In studies related to exercise and cardiac biomarkers, cTn, IMA, and NT-proBNP are often used as diagnostic indicators for monitoring myocardial performance after training [14]. Initially, it was believed that cardiac biomarkers would not be induced by high-intensity interval exercise (HIIE). The earliest study by Bianco, et al. [58] examined changes in serum cTnT levels before and after 80-90 minutes of rugby and soccer games. The results showed that cTnT levels were negative after the game and the next day. This result was similar to the results of two other studies on amateur boxers (Bianco et al., 2005) and indoor soccer players [25], which showed negative cTnI and cTnT values after exercise. However, different results have been found in other intermittent exercise modalities, including studies on basketball [17] and table tennis [4] players, which show a temporary increase in blood cTnI or cTnT values after exercise. Nie, Tong, Shi, Lin, Zhao and Tian [17] studied adolescent basketball players and found that the cTnT levels of some players were higher than the URL at 2 and 4 hours after the game. The study also tested cTnI and found that the changes in cTnI and cTnT were very similar and significantly positively correlated (r = .951). Ma, Liu and Liu [4] studied young table tennis players and observed their serum cTn response after 6 x 10 minutes of forehand training. The results showed that the cTnI levels of the players immediately after exercise were significantly higher than before exercise and returned to pre-exercise levels 48 hours after exercise. In summary, the literature shows that the observation of HIIE and cardiac biomarker responses is mainly based on competition or specific training.

In recent years, there has been increasing emphasis on the release of cardiac biomarkers in response to high-intensity interval exercise (HIIE), leading to research into specific exercise intensities, durations, and rest ratios. Duttaroy, Thorell, Karlsson and Börjesson [19] found that adults with exercise habits who engaged in 43 minutes of intermittent cycling at an intensity of about 85% HRmax would induce the release of hs-cTnT, but it would return to resting values the next day. Li, Nie, Lu, Tong, Yi, Yan, Fu and Ma [53] observed the response of elite marathon runners to high-intensity interval training in low or normal oxygen environments. The study involved 23 intervals of running at 90% VO2max for 2 minutes, interspersed with 2 minutes of walking at 50% VO2max, and showed that hs-cTnT was significantly higher immediately after exercise and at 2- and 4-hours post-exercise, while cTnI was significantly higher at 2- and 4-hours post-exercise compared to before exercise (no difference between low and normal oxygen environments). These two studies suggest that high-intensity interval exercise with intensities above 85% VO2max and heart rates above 85% HRmax may induce the release of cardiac biomarkers, and this type of high-intensity interval exercise includes basketball, soccer, table tennis, boxing, and American football, among others. In addition, there may be differences in the response between males and females, although males have significantly higher levels of cardiac biomarker release, possibly because estrogen has a protective effect on cardiac cells similar to that of antioxidants [31], females still experience cardiac biomarker release after HIIE [15].

Although individuals vary in their response to cardiac biomarkers, most show an upward trend after high-intensity interval exercise. The mechanisms underlying the increase in cardiac biomarkers after high-intensity interval exercise remain unclear, and past studies have suggested that it may be due to an excessive production of free radicals, myocardial stretch, changes in core temperature, or changes in pH [59]. These responses can also cause subacute myocardial cell apoptosis and necrosis in clinical settings [60,61]. However, compared to clinical reactions, exercise-induced responses generally increase myocardial cell membrane permeability and secretion of non-cytosolic myocardial troponin. In contrast, the increase in troponin in MI is due to myocardial cell death and the release of myofilament-bound troponin, so the exercise-induced biomarker increase usually recovers to baseline

levels quickly and does not exhibit the sustained pathological response seen in MI [26,62].

Regarding NT-proBNP, Banfi, D'Eril, Barassi and Lippi [24] found that after 90 minutes of rugby training, athletes had a significant increase in their blood NT-proBNP levels. Simi-larly, Carranza-García, George, Serrano-Ostáriz, Casado-Arroyo, Caballero-Navarro and Legaz-Arrese [25] showed that indoor soccer games caused a significant increase in serum NT-proBNP levels in male and female players, which remained elevated for 3-6 hours post-game before returning to baseline. Thus, NT-proBNP in serum is significantly induced after HIIE. Regarding IMA, Çolak, et al. [63] measured serum IMA levels in wrestlers before and after 90 minutes of training and found that IMA levels significantly increased after exercise. Falkensammer, et al. [64] suggested that IMA has poor specificity for myocardial damage and may be influenced by intestinal or skeletal muscle ischemia. Therefore, IMA is often used in combination with other biomarkers in clinical settings.

## The Impact of High-Intensity Interval Exercise on Myocardium and Oxidative Stress

During exercise, free radicals generated can attack the myocardial cell membrane, leading to lipid peroxidation and increased membrane permeability. As a result, free cTn that was previously unbound in the cytoplasm can penetrate the cell membrane and enter the bloodstream. Therefore, the oxidative stress experienced by the myocardium is believed to be related to cTn release after exercise [37,38]. In animal experiments, it was found that while myocardial TBARS levels increased, the endogenous antioxidant glutathione (GHS) content significantly decreased [35]. This experiment also supports the mechanism by which exercise induces myocardial biomarkers and oxidative stress. The main cause of oxidative stress is the rate of reactive oxygen and nitrogen species (RONS) generation in the body [65]. The imbalance between RONS generation and antioxidant defense systems leads to the phenomenon of oxidative stress. The rate of RONS generation is influenced by the intensity and duration of a single exercise session [66]. During intense exercise, increased oxygen consumption leads to cell equilibrium disruption. In the process of oxidative phosphorylation by mitochondria to produce ATP, more RONS with unpaired electrons may be generated through the electron transport chain [67]. The massive production of RONS within a short period of time may induce acute oxidative stress, leading to muscle fatigue and a decrease in physical activity [68,69]. These oxidative stress products induced by exercise are called biomarkers of oxidative stress [70].

The related biological markers of oxidative stress include lipid peroxidation products such as lipid hydroperoxide (LOOH), TBARS, malondialdehyde (MDA), and F2-isoprostanes, as well as protein oxidation products such as protein carbonyls (PC) and 8-hydroxy-2'-deoxyguanosine (8-OHdG) [71]. When the body is exposed to an increase in reactive oxygen and nitrogen species (RONS) due to exercise, the endogenous antioxidants such as glutathione (GSH) and oxidized glutathione (GSSG) are stimulated to increase [67,72]. This provides a self-regulatory mechanism to protect the body during subsequent exercise bouts [70]. Nie, Close, George, Tong and Shi [35] found that rats subjected to 3 hours of swimming exercise at 5% of their body weight showed significantly higher levels of cTnT in their blood immediately and 2 hours after exercise compared to the control group. The TBARS content in the rat myocardium was also significantly increased, while the endogenous antioxidant GSH content was significantly decreased. This animal study supports the involvement of oxidative stress in exercise-induced myocardial biomarkers.

In previous studies, Djordjevic, et al. [73] compared the level of oxidative stress in athletes and non-athletes after exercise. The results showed that the oxidative stress produced by exercise was lower in athletes, and the concentration of TBARS in the blood before exercise was significantly higher in non-athletes than in athletes, while GSH was significantly lower in non-athletes than in athletes. This indicates that regular exercise training can not only improve the degree of oxidative stress but also increase the concentration of GSH in the body. The study also suggested that regular exercise can increase the level of GSH in the body [74,75], and GSH can directly or indirectly eliminate free radicals [76], which can maintain the stability of the redox system under oxidative stress [77].

Different exercise regimens have varying requirements for training intensity, time, methods, and rest periods, and physiological responses also differ depending on the type of exercise. HIIE, for example, has been shown to induce an increase in TBARS and affect GSH regulation [78]. Wang, Chan, Hsu, Ho and Lee [52] studied healthy university students and found that after seven sessions of four-minute HIIE at 90% VO2max with two minutes of complete rest intervals, TBARS concentration in the blood was significantly induced immediately after exercise and after one hour. Fisher, Schwartz, Quindry, Barberio, Foster, Jones and Pascoe [78] studied eight males and found that after four sets of 30-second cycling at 90% maximum anaerobic power (Max-AP) with four minutes of 15% Max-AP recovery intervals, TBARS and GSSG were significantly higher immediately after exercise than before exercise. Bogdanis, et al. [79] studied recreational male athletes and found that after four sets of 30-second Wingate cycling sprints (resistance = 7.5% body weight) with four minutes of rest intervals, TBARS were significantly higher immediately after exercise, 24 hours, and 48 hours later than before exercise, and Glutathione peroxidase (GPx) was significantly higher 24 and 48 hours after exercise than before exercise and immediately after exercise. Li, Nie, Lu, Tong, Yi, Yan, Fu and Ma [53] studied elite marathon runners and found that after 23 sessions of two-minute running at 90% VO2max speed with two-minute 50% VO2max speed recovery intervals in normoxia or hypoxia conditions, GSH was significantly higher immediately after exercise in normoxia, but MDA did not show significant differences. In contrast, Lu, et al. [80] studied basketball players and found that there was no difference in TBARS concentration in the blood after seven sessions of two-minute HIIE at 90% VO2max with one minute of complete rest intervals. These five studies suggest that HIIE may induce an increase in TBARS, indicating a temporary oxidative imbalance due to exercise stimulation, although exercise training may improve this imbalance. However, most studies indicate that

there is a temporary oxidative imbalance reaction after exercise [81], and this reaction varies depending on exercise intensity and duration. Therefore, this study investigates whether HIIE-induced myocardial biomarkers are affected by TBARS and GSH.

## The Impact of High-Intensity Interval Exercise on Myocardium and Inflammatory Response

In previous studies, Frangogiannis, Mendoza, Lindsey, Ballantyne, Michael, Smith and Entman [36] confirmed that TNF-α is one of the factors that causes damage to cardiomyocytes. Inflammation is an essential immune response for the body when it is infected or injured, as it promotes tissue repair [82] and maintains tissue homeostasis [83]. The initial stage of the inflammatory response is triggered by macrophages and neutrophils [84], and inflammatory cytokines and chemokines are activated in the spleen, including TNF-α and NF-κB [85,86]. NF-κB is not only a critical transcription factor but also an important pro-inflammatory mediator [87] that regulates the function of TNF-α and leukocytosis [88]. When the inflammatory response occurs, NF-κB is activated, which increases the concentration of pro-inflammatory cytokines such as TNF-α and IL-1β in the blood and stimulates the inflammatory cascade [89]. Therefore, NF-κB and TNF-α are critical indicators of the early stage of inflammation.

Additionally, the chemokines involved in inflammation also include interleukin-8 (IL-8), which induces neutrophilia and lymphocytopenia when pro-inflammatory cytokines are activated [90]. IL-8 also upregulates the activation of more pro-inflammatory cytokines through infiltration [91]. When exercise induces an inflammatory response, the body not only releases pro-inflammatory cytokines into the bloodstream but also releases anti-inflammatory cytokines such as IL-4 and IL-10, which inhibit the function of pro-inflammatory cytokines [92]. Therefore, these substances are also used as biological markers of the inflammatory response. Moreover, past studies on inflammation often used interleukin-6 (IL-6) as an observation indicator [93,94]. Literature has indicated that IL-6 is secreted by contracting skeletal fibers [95], and the concentration of IL-6 in the blood also increases when muscles are damaged [96,97].

Exercise training is composed of different intensities, durations, modes, and rest times, and the choice of mode varies depending on the specific needs of the individual. The HIIE exercise mode often affects the constant state of physiological stress in the body [98]. Lira, et al. [99] studied leisure athletes and conducted a 5-kilometer interval run, with one minute of 100% VO2max intensity running followed by one minute of complete rest. The results showed that TNF-α was significantly higher after the run than before. Cabral-Santos, Gerosa-Neto, Inoue, Panissa, Gobbo, Zagatto, Campos, Lira and medicine [51] studied recreational male athletes and conducted 20 rounds of one minute of 100% VO2max intensity interval running, with one minute of complete rest in between. The results showed that TNF-α and IL-6 were significantly elevated immediately after exercise. Cipryan, Tschakert, Hofmann and Medicine [50] studied track and field athletes and conducted four rounds of three-minute interval running at 100% VO2max intensity, with three minutes of complete rest in between. The results showed that IL-6 in the blood was significantly induced immediately after exercise. The above studies found that HIIE significantly induced the release of TNF-α and IL-6, and both athletes and non-athletes may experience a temporary increase in these inflammatory markers. Although inflammation is a necessary mechanism in the body to maintain tissue homeostasis and immune response, high-intensity exercise can produce too many free radicals, leading to oxidative stress, which can impair tissue or organ function, resulting in disease or reduced athletic performance. Prolonged inflammation in the body can also have negative effects, and TNF-α has been proven to be one of the factors that cause myocardial cell damage [36].

In addition to causing myocardial damage, TNF-α has been commonly associated with the diagnosis of cardiovascular disease using myocardial biomarkers. Murthy, et al. [100] conducted a study on 60 HF patients and investigated the relationship between BNP, TNF-α, cTnI, CK-MB and the severity of symptoms. The results showed that an elevated TNF-α concentration accounted for 40% of HF patient deaths. The study also suggested that using BNP in conjunction with TNF-α for diagnosis would be an excellent predictive indicator for HF mortality and incidence. Kowalewski, et al. [101] conducted a study on 55 patients with ventricular arrhythmias and found that ventricular arrhythmias were caused by myocardial ischemia or cell death. The study observed changes in cTnI, IL-6, and TNF-α and showed that while cTnI and IL-9 remained unchanged, the concentration of TNF-α significantly increased, suggesting that inflammation may be one of the underlying causes of ventricular arrhythmias. From the studies, it can be concluded that TNF-α, in addition to causing myocardial damage, is also a commonly used diagnostic indicator for cardiac abnormality. Therefore, this study found that myocardial biomarkers induced by HIIE may be affected by TNF-α and IL-6.

## Conclusions

In conclusion, HIIE can induce oxidative stress and inflammatory response in the myocardium, as evidenced by changes in biomarkers such as TBARS and GSH. The extent of these effects may vary depending on the specific HIIE protocol, including the intensity, duration, and rest intervals used. While HIIE can lead to short-term oxidative imbalance, regular exercise training may help improve the body's ability to counteract these effects. Further research is needed to fully understand the relationship between HIIE and oxidative stress/inflammatory response in the myocardium, and to identify strategies for optimizing exercise-induced benefits while minimizing potential negative effects.

## Acknowledgement

None.

## Conflict of Interest

No Conflict of Interest.

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