



Progressive overload in cardiorespiratory exercise training for young and old: Is increasing duration or intensity of exercise more important?

Leo Robert Bell^a, Ryan Worn^a, Mathew William O'Grady^a, Joshua Denham^b, Brendan Joseph O'Brien^{a,*}

^a Institute of Health and Wellbeing, Federation University of Australia, Australia

^b University of Southern Queensland, School of Health and Medical Sciences, Toowoomba, Queensland, Australia

ARTICLE INFO

Keywords:

Cardio-vascular fitness
Progressive
Overload
Exercise intensity
Duration
Running

ABSTRACT

People undertake endurance training to improve their health and cardio-respiratory fitness. Subsequent cardio-respiratory and skeletal muscle aerobic metabolic adaptations are gauged by improvements in maximum or peak oxygen uptake ($\dot{V}O_{2peak}$) and the blood lactate inflection point or threshold during incremental exercise – (LIP). To further improve physiological capability, subsequent homeostatic disturbances from exercise should be progressively greater in succeeding exercise sessions. Therefore, exercise duration, frequency or intensity should be progressively increased during a training regimen to ensure adaptation potential is realized. A progressive increase in training workload is termed “progressive overload”. Despite the universal acknowledgment of the importance of progressive overload, it is unclear if systematically progressing altering either exercise intensity or duration (or distance covered) affect cardio-respiratory gains differently in young and older populations. As running faster results in higher heart rates and greater skeletal muscle metabolic stress than running the same distance at a lower speed, in this hypothesis we postulate that progressively increasing exercise run intensity will result in greater mean and higher incidence of $\dot{V}O_{2peak}$ and LIP gains in young adults (<50 years). However, the mechanisms that initiate improvements in cardio-respiratory fitness and skeletal muscle aerobic function may be different in older adults due to the inevitable aging decline in cardio-vascular function and mechanical and morphological properties of muscle-tendon units. In older adults (>60 years) we hypothesize progressively increasing run distance while maintaining the same speed will just be as effective as to progressively increasing speed to improve $\dot{V}O_{2peak}$ and LIP. To test these hypotheses, we propose a study that compares progressively increasing run intensity to a treatment of progressive matched run distance where speed remains constant in young and old adults.

Background

The health benefits of endurance exercise training are well documented [1]. Previous investigation shows that sedentary people who begin regular endurance exercise training significantly decrease the risk of chronic inactivity diseases such as cardio-vascular disease, diabetes, hypertension, osteoporosis, and obesity [1]. Exercise also reduces the incidence of several cancers [2]. A review of the available evidence from Cochrane systematic reviews on the effectiveness of exercise/physical activity for various health outcomes, shows physical activity reduces pre-mature mortality by 13% and improves quality of life. [3]. Additionally, the health benefits of regular cardio-respiratory training are generally more profound in exercise training regimes of greater intensity

[4,5]. Lavie et al [4] demonstrated that walking reduces deaths from cardio-vascular disease by 33% while running reduces deaths from cardio-vascular by 45%. Maintaining vigorous exercise throughout life reduces aging impact on cardio-vascular function [6]. Trappe et al [6] showed unfit men's peak oxygen uptake ($\dot{V}O_{2peak}$) declined by 15% per decade over two decades, opposed to a 10% decline in $\dot{V}O_{2peak}$ in fitness trained men, and a 6% decline in $\dot{V}O_{2peak}$ per decade in highly trained men. Consequently, the American College of Sports Medicine strongly encourages people to maximise their cardio-respiratory fitness [7].

Two important clinical parameters of cardio-respiratory fitness are the individual's peak oxygen uptake ($\dot{V}O_{2peak}$) and the blood lactate inflection point or threshold – the exercise intensity at which inflections

* Corresponding author.

E-mail address: b.obrien@federation.edu.au (B. Joseph O'Brien).

<https://doi.org/10.1016/j.mehy.2024.111366>

Received 15 April 2024; Received in revised form 4 May 2024; Accepted 8 May 2024

Available online 9 May 2024

0306-9877/Crown Copyright © 2024 Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

in blood lactate are observed [8]. The Heritage Study [9] showed that mean $\dot{V}O_{2peak}$ improved by 17 % after 20 weeks of training in 855 adults. Hickson et al reported gains of 23 % in $\dot{V}O_{2peak}$ after 12 weeks of intense endurance training in men [10]. The blood lactate threshold increases by approximately 17 % after 40 weeks of training [11]. Individuals gradually increase the training workload by manipulating the intensity, frequency, or duration of training sessions to maximise improvements in $\dot{V}O_{2peak}$ and the blood lactate inflection exercise point [12]. The gradual increase in training workload is termed “progressive overload” [12]. The theory for progressive overload is modified from the general adaption syndrome theory proposed by Seyle [13]. The progressive overload theory is based on the theory that adaptation (“supra-compensation”) occurs in response to stress to ultimately improve the individual’s physiological state and capacity for exercise. Exercise disturbs normal homeostatic regulation as cell ATP concentration, glycogen concentration and pH fall, metabolites accumulate and electrolyte concentration, hormone and immune regulation is altered as is blood and oxygen supply [8,12]. These physiological disturbances are more profound with higher exercise intensity and trigger acute genetic and molecular responses to maintain or re-establish homeostasis [8,12]. Adaptations to exercise training result from the cumulative effect of temporary increases in mRNA transcripts that code for specific proteins after each successive exercise bout [12]. In between exercise bouts (during the time of recovery) the molecular responses from exercise result in enhanced gene expression that extends well past contractile activity (up to 24 h after exercise) and tend to reset the homeostatic set-point required for molecular change [12]. These adaptations reduce homeostatic disturbances in succeeding exercise bouts of similar metabolic stress. For example, the key mRNA driving mitochondrial biogenesis, PGC1 α , increases by 10–11-fold 4 h after the first exercise bout. The impact is PGC1 α protein relative abundance increases by 1.2–1.4-fold. However, there is progressive decline in PGC1 α mRNA expression with increasing exercise sessions. By the fourth bout of exercise, changes in mRNA expression fall to 4–5-fold and subsequent protein relative abundance changes decline [12]. Consequently, to extend upon the initial adaptation the exercise stress needs to be greater in succeeding exercise bouts to stimulate a similar relative homeostatic challenge [8,12]. Therefore, succeeding exercise sessions need to be continually more challenging to maintain sufficient stimulus and genetic expression for further physiological adaptation. Appropriate time for rest and recovery is a key tenet of optimizing physiological adaptation to allow sufficient time for the molecular changes to manifest [8,12]. Despite the self-evident nature and anecdotal importance of progressive increments in training workload, scientific evidence supporting *how* this training principle should be implemented in endurance run training to optimize cardio-respiratory fitness and skeletal muscle function is surprisingly limited. It is also unclear if the individual’s age should be a consideration to optimize the impact of progressive overload on cardio-respiratory fitness and aerobic skeletal muscle function.

Hypotheses. *There is sufficient evidence to suggest young and old people respond to exercise differently. We first hypothesize the mean change and frequency of positive responders in cardio-respiratory fitness and skeletal muscle function will be greater in a running regimen that progressively increases run speed compared to a regimen with matched run distance but unchanged run speed in younger people. We also hypothesize the mean change and frequency of positive responders in cardio-respiratory fitness and skeletal muscle function will not be different between a 12-week running regimen that progressively increases run speed compared to a regimen with matched run distance but unchanged run speed in older people.*

Evaluation of the Hypothesis

Studies into the muscle cell molecular changes in response to exercise offer insights into the relevance of progressive increases in training intensity. Booth [14] revealed the mitochondrial protein; cytochrome C increased initially in response to a training regime. However, Booth [14]

also observed that unless the training intensity is increased progressively throughout a training regime, there was no further net gain in cytochrome C concentration, as the stimulus threshold for its activation became progressively higher as the training regime progressed. Booth demonstrated the importance of progressive overload at a molecular level. Studies at a system’s level also support the importance of progressive overload. Hickson and colleagues [10] investigated changes in $\dot{V}O_{2peak}$ over a 10-week training period. In this study nine participants exercised six days per week alternating training between bicycle ergometer and field running. The bicycle ergometer training involved six by five-minute exercise intervals at 90 %-100 % $\dot{V}O_{2peak}$ interspersed with lower intensity work periods (50 %-60 % $\dot{V}O_{2peak}$). The running protocol of the treatment required the participants to run at the maximum velocity that could be sustained for 40 min. To ensure the relative exercise stimulus was maintained, participants were re-tested every week to ensure it was adjusted to 90 %-100 % of $\dot{V}O_{2peak}$ Hickson et al. [10] observed a linear increase in $\dot{V}O_{2max}$ over a 10-week period, resulting in an overall 23 % change after 10 weeks of training. However, Hickson et al. study did not incorporate a control group (where training intensity remained constant for 10 weeks) to allow comparison of the *relative* importance of progressive increments in training intensity. In Hickson’s et al. 1981 study [15] subjects undertook a running/cycling training regime where the initial training intensity and volume was not increased until after the fourth week of training commencement. Hickson et al. [14] showed $\dot{V}O_{2peak}$ increased by 14 % within 3 weeks of initiating training. Despite maintaining the same training regime, $\dot{V}O_{2peak}$ remained unchanged a week later. After the fourth week of training, the relative training intensity was matched to the improved $\dot{V}O_{2peak}$ resulting in a further 8 % increase in $\dot{V}O_{2peak}$. Hickson et al. [15] results showed that unless the training stimulus is increased, further increases in $\dot{V}O_{2peak}$ will not be observed in response to exercise training. McNicol et al. [16] explored the relative importance of progressive overload in 28 previously sedentary participants who undertook 20 min of treadmill running three times a week for six weeks. The study compared the $\dot{V}O_{2peak}$, lactate inflection velocity and 5 km time trial performance in a group that progressively elevated run intensity by 0.1 km·h⁻¹ every treadmill run to a constant-rate treatment who maintained the initial run velocity for the duration of the study. McNicol et al. [16] found a greater increase in $\dot{V}O_{2peak}$ and lactate inflection point in the incremental run intensity intervention. However, it is uncertain if the increase in $\dot{V}O_{2peak}$ and blood lactate inflection point occurred as a response to the rise in run speed or to the concomitant increase in run distance.

More recently Reuter et al. [17] compared changes in cardiovascular performance measures between a group that maintained the same exercise intensity (3 days/week of walking or running for 50 min/session at 55 % heart rate reserve for 26 weeks to a group that switched to higher intensity training after 10 weeks. The higher intensity group completed training at 70 % heart rate reserve for 8 weeks and then undertook a high intensity interval training program (4 × 4-min intervals at 95 % HRmax with 3 × 3-min “breaks” in between at 70 % heart rate maximum) for a further 8 weeks. Reuter et al [17] revealed transfer to high-intensity interval training resulted in greater gains in $\dot{V}O_{2peak}$ than the constant/same intensity training group (3.4 versus 0.4 mL·kg⁻¹·min⁻¹). More recent research has shown increasing exercise intensity after several weeks of low intensity training increases the percentage of positive cardio-respiratory responders to training [18]. Furthermore, gradually progressing running intensity over 6 weeks of running training increased the percentage of positive cardio-respiratory responders to training [19]. Several researchers show higher intensity exercise optimizes improvements $\dot{V}O_{2peak}$ [20,21]. Gormley [20] showed when the volume of exercise training is controlled, higher intensities of exercise improve $\dot{V}O_{2peak}$ greater than lower intensities of exercise in young adults. Helgerud et al. [21] showed 8 weeks of high-

aerobic intensity endurance interval training was more effective than performing the same total work at either lactate threshold or at 70 % heart rate maximum in improving $\dot{V}O_{2peak}$ in moderately trained individuals. It is hypothesized the greater gains in cardio-respiratory fitness from these studies [20,21] is consequential to the higher heart rates, vascular endothelial shear stress and muscle cell metabolic demand of higher intensity exercise [10]. Other researchers have shown higher intensity exercise does not necessarily result in superior gains in cardio-respiratory fitness [22]. Belman and Gaesser [22] showed that training 20 % above and 28 % below the lactate threshold resulted in similar gains in $\dot{V}O_{2peak}$ and lactate threshold in older adults (65–75 years). Badenhop et al [23] also showed in older adults (mean age 67 years) exercising at low intensity (30–45 % heart rate reserve) improved $\dot{V}O_{2peak}$ similarly to a high intensity group (60–75 % heart rate reserve). It is difficult to draw conclusions from the research comparing high versus low intensity exercise as the studies to date have low participant number, and the age of the participants may impact on the experimental outcomes. Appropriately powered studies are clearly required to adequately test hypotheses on training response difference between high and low intensity or longer duration training regimens. It is theoretically possible, that while greater intensity of exercise results in greater physiological stress than lower intensity exercise of similar training duration, sustaining longer durations of exercise in older adults may result in accumulatively similar physiological disturbances (when overall energy expenditure is matched to a higher intensity treatment) that trigger the key molecular responses that enhance cardio-respiratory fitness. It is important to highlight older people respond differently to exercise training with lower absolute gains in VO_{2peak} compared to young people [9]. Although the relative (percent change) gains in $\dot{V}O_{2peak}$ are similar to young people [24]. Unlike young people, improvement in cardio-respiratory fitness and aerobic skeletal muscle function in older adults may be partly attributed to a different mechanism [25]. Gries et al [24] showed lifelong exercise reduces the decline in VO_{2peak} and preserves metabolic phenotype comparable to young exercisers. Gries showed 50 + years of aerobic exercise fully preserved capillarization and aerobic enzymes, regardless of intensity. However, the decline in cardio-vascular capability (a decrease in maximal cardiac output) associated with aging can only be partly attenuated by life-long exercise. Consequently, older people may be more reliant on skeletal muscle adaptations rather than central aspects of cardio- cardiovascular adaptation to improve exercise capacity and VO_{2peak} .

Based on the literature to date we postulate that in young adults (<50 years of age) that progressively increasing run speed will improve cardio-respiratory fitness and skeletal muscle function significantly more than a training regimen of matched progressive run distance with constant run speed. However, we postulate in older adults (>60 years) that progressively increasing distance while maintaining the same run speed will produce similar improvements in cardio-respiratory fitness and skeletal muscle function as progressively increasing run speed (while matching run distance).

Importantly for the untrained individual striving to improve cardio-respiratory fitness and skeletal muscle function, the relative impact of gradual session by session progressions in training intensity or duration needs to be identified, and crucially if the progressive overload emphasis should be different depending on the individual's age. The World Health Organization (WHO) inform global healthy policy and advise all individuals exercise to reduce the incidence of chronic disease and premature mortality. The WHO advocate individuals undertake 150 min of moderate-intensity or 75 min of vigorous intensity exercise a week [3]. However, cardio-respiratory fitness People undertake endurance training to improve their health and cardio-respiratory fitness. Subsequent cardio-respiratory and skeletal muscle aerobic metabolic adaptations are gauged by improvements in maximum or peak oxygen uptake ($\dot{V}O_{2peak}$) and the blood lactate inflection point or threshold during incremental exercise – (LIP). To further improve physiological capability,

subsequent homeostatic disturbances from exercise should be progressively greater in succeeding exercise sessions. Therefore, exercise duration, frequency or intensity should be progressively increased during a training regimen to ensure adaptation potential is realized. A progressive increase in training workload is termed “progressive overload”. Despite the universal acknowledgment of the importance of progressive overload, it is unclear if systematically progressing altering either exercise intensity or duration (or distance covered) affect cardio-respiratory gains differently in young and older populations. As running faster results in higher heart rates and greater skeletal muscle metabolic stress than running the same distance at a lower speed, in this hypothesis we postulate that progressively increasing exercise run intensity will result in greater mean and higher incidence of $\dot{V}O_{2peak}$ and LIP gains in young adults (<50 years). However, the mechanisms that initiate improvements in cardio-respiratory fitness and skeletal muscle aerobic function may be different in older adults due to the inevitable aging decline in cardio-vascular function and mechanical and morphological properties of muscle–tendon units. In older adults (>60 years) we hypothesize progressively increasing run distance while maintaining the same speed will just be as effective as to progressively increasing speed to improve $\dot{V}O_{2peak}$ and LIP. To test these hypotheses, we propose a study that compares progressively increasing run intensity to a treatment of progressive matched run distance where speed remains constant in young and old adults.

and the subsequent health gains will stagnate and not be optimized if exercise sessions are not progressively more physiologically challenging. The current exercise prescription guidelines for the magnitude and timing of progressive overload are vague and not supported by strong evidence or age specific. The American College of Sports Medicine (ACSM) [7] recommend progression from moderate-intense exercise (40–60 % of heart rate reserve), three days week for 15–30 min for 4 weeks to more intense exercise (50–85 % heart rate reserve) training over the next 4–5 months, with duration increased every 2–3 weeks until the individual can sustain 35–40 min of exercise. Whilst the ACSM guidelines provide practical starting exercise recommendations for the apparently healthy individual, the empirical evidence for the advised rate of change in work-rate either in speed or power (watts) is not clear. Weatherwax et al [25] recently showed gains in VO_{2peak} based on training within medically endorsed heart rate training zones result in only 60 % of positive responses. Consequently, exercise prescription based on generic heart rate zones does not optimize the responders to training [25]. Therefore, more evidence is required to determine the rate of exercise intensity in work-rate that can be sustained by the general population. McNicol [16] showed 0.1 km·h⁻¹ increments in run intensity commencing 1.8 km·h⁻¹ below their pre-training lactate inflection point was sustainable for all participants (mean age 20.8 years) over 6 weeks (18 sessions). However, it is not clear if this rate of change in run velocity can be sustained over an additional 6 weeks. Testing of the hypotheses will provide empirical evidence to optimize progression of exercise training work-rate to improve cardio-respiratory fitness in young and old adults.

Hypothesis testing

To evaluate the hypothesis, the study proposes a quasi-experimental independent measures design. Healthy young (18–50-years) and older (60–70 years) male and females who have not participated in running training regimen would serve as participants. Participants would be allocated to one of three running regimen treatment groups: a progressive increase in run intensity treatment (treatment 1), a constant intensity/increased distance treatment (treatment 2) or control. The treatments and control would have two age categories each –young and older. The dependent variables would be assessed before and after a 12-week run training regimen. Participants would be allocated to the treatments using the minimisation technique, to reduce the imbalance in

the starting blood lactate inflection point [26]. 20 participants would be randomly allocated to either of the two experimental and control treatments. An imbalance score is calculated, and further allocation of participants would be selectively placed into the treatments to reduce the imbalance between treatments. The two experimental treatments require the participants to run on a treadmill three times a week with one rest day between each training session to complete 36 overall running sessions. Participants in treatment 2 would be matched to an individual of similar pre-training lactate inflection point in Treatment 1 to inform the distance to be covered Treatment 2. In the control treatment no participants would not engage in exercise training. To determine for significant differences ($p < .05$) in the dependent variables a repeated measures multi variate analysis of variance would be used. The number of participants required to detect a moderate effect size (0.5) in a two tailed test to achieve a power of 80 % ($1-\beta$) would be calculated allowing for a 25 % attrition rate. Responders would be determined as changes exceeding the random or technical error of measure of the dependent variables. The random or technical error of measurement (TEM) would be determined from the differences in control groups dependent variables over the duration of the experiment. TEM is calculated by dividing the standard deviation of the difference score by $\sqrt{2}$ [18].

The participants $\dot{V}O_{2peak}$ would be assessed from a discontinuous incremental running test to volitional exhaustion on a motorised treadmill. Participants would be fitted with a breathing valve which diverts expired air into an online metabolic system. We propose to use a MOXUS Metabolic cart (AEI technologies, USA) incorporated with S-3A/I Oxygen Analyzer, CD-3A Carbon Dioxide Analyzer and Pneumotach Breath Volume Measurement System to determine fraction expired oxygen and carbon dioxide and expired ventilation respectively. Participants commence treadmill running at a sub-maximal run velocity for 6 min before progressively increasing by run velocity every second minute. Sub-maximal heart rate, $\dot{V}O_2$ (running economy) and blood lactate would be recorded every minute during the incremental velocity treadmill test. Blood lactate inflection point would be determined by the first significant change in blood lactate concentration. $\dot{V}O_{2peak}$, final treadmill speed, sub-maximal heart rate, running economy and blood lactate, and lactate inflection point would be assessed one week prior and one week after completion of the 12-week run training treatments and control treatment.

In the Progressive increased run intensity treatment (treatment 1) all run sessions would be 20 min. Participants treadmill speed would progressively increase by $0.1 \text{ km}\cdot\text{h}^{-1}$ from their pre-determined running velocity ($1.8 \text{ km}\cdot\text{h}^{-1}$ below their pre-training lactate inflection point) each run session. In the constant intensity/increased distance treatment (treatment 2) participants treadmill speed would be fixed at $1.8 \text{ km}\cdot\text{h}^{-1}$ below their lactate inflection point for the experimental duration. Distance would be progressively increased by the distance covered in Treatment 1 (approximately 1 % by session). In the control treatment, participants would be requested not to engage in a fitness training regimen for the duration of the experimental protocol. The control group would be used to determine the random error of each dependent variable.

Limitations of the Hypothesis Testing

There are limitations to the proposed hypothesis testing. This hypothesis proposes to deploy a quasi-experimental design in preference to a true random control trial. The rationale for a quasi-experimental design is it allows control over the variable that would most likely determine the percent change in fitness- the initial fitness level. The more unfit a person is, the greater scope for potential improvement. A limitation of our approach that we have chosen to control for the baseline lactate inflection point and not cardio-respiratory fitness ($\dot{V}O_{2peak}$). The percent change in lactate inflection and $\dot{V}O_{2peak}$ from training is

similar McNicol [14]. Other extraneous variables may influence the percent change in $\dot{V}O_{2peak}$ and the lactate inflection point such as diet, individual genetics, motivation, incidental exercise, stress, and socio-economic status.

Consequences of the hypotheses and discussion

The practical outcome of testing the proposed hypothesis is to augment the World Health Organization's exercise prescription guidelines advocating individuals undertake 150 min of moderate-intensity or 75 min of vigorous intensity exercise a week. These fitness guidelines are a core tenet of the most modern countries policies to maintain healthy cardio-respiratory fitness, muscle strength and flexibility. However, cardio-respiratory fitness will stagnate if progressive overload is not implemented in an exercise training regimen as the human body adapts to the initial exercise stimulus. Subsequently the impact of exercise training on reducing chronic disease and mortality risk for the general population is not optimized if subsequent training does not progressively challenge the individual's physiology. Current fitness guidelines do not provide tangible advice to the general population on how progressive overload should be implemented in a training regimen and if it needs to be different for young and old. Progressive overload in training generally focuses on increasing the intensity, duration of training and frequency of exercise sessions. This hypothesis would provide evidence on the relative effectiveness of increasing exercise intensity versus exercise distance to improve cardio-vascular fitness for young and older adults. Guidelines on the most effective work-rate training variables to manipulate, and the rate of work-rate change in run intensity than can be sustained would provide important information to guide health policy to further reduce mortality risk and chronic disease by enabling exercise professionals to design training programs that maximize the individual's cardio-respiratory fitness potential and minimize injury or "burnout" with consideration of their age.

Conclusions

The importance of applying progressive overload in a training regime to maximise the impact of exercise training on cardio-respiratory fitness was initially revealed by the seminal work of Hickson et al. [10,15]. However, there is scope for future research to investigate fundamental questions important for exercise prescription; does progressively increasing run speed or distance covered change cardio-respiratory fitness differently for young and older adults? The proposed investigation aims to test the hypothesis that progressively altering running intensity affects cardio-vascular fitness gains differently to a treatment of matched running distance where speed is unchanged.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AI statement

The authors did not use Artificial Intelligence to compile this thesis.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRedit authorship contribution statement

Leo Robert Bell: Writing – review & editing, Writing – original draft,

Conceptualization. **Ryan Worn**: Writing – review & editing, Writing – original draft. **Mathew William O’Grady**: Writing – review & editing. **Joshua Denham**: Writing – review & editing. **Brendan Joseph O’Brien**: Writing – review & editing, Writing – original draft, Methodology, Conceptualization.

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.

References

- [1] Rueggsegger GN, Booth FW. Health Benefits of Exercise. *Cold Spring Harb Perspect Med* 2018;8:a029694. <https://doi.org/10.1101/cshperspect.a029694>.
- [2] Wang Q, Zhou W. Roles and molecular mechanisms of physical exercise in cancer prevention and treatment. *J Sport Health Sci* 2021;10:201–10. <https://doi.org/10.1016/j.jshs.2020.07.008>.
- [3] Posadzki P, Pieper D, Bajpai R, Makaruk H, Königsen N, Neuhaus AL, et al. Exercise/physical activity and health outcomes: an overview of Cochrane systematic reviews. *BMC Public Health* 2020;20:1724. <https://doi.org/10.1186/s12889-020-09855-3>.
- [4] Lavie CJ, Lee DC, Sui X, Arena R, O’Keefe JH, Church TS, et al. Effects of Running on Chronic Diseases and Cardiovascular and All-Cause Mortality. *Mayo Clin Proc* 2015;90(11):1541–52. <https://doi.org/10.1016/j.mayocp.2015.08.001>.
- [5] Wenger HA, Bell GJ. The interactions of intensity, frequency and duration of exercise training in altering cardiorespiratory fitness. *Sports Med* 1986;3:346–56. <https://doi.org/10.2165/00007256-198603050-00004>.
- [6] Trappe SW, Costill DL, Vukovich MD, Jones J, Melham T. Aging among elite distance runners: a 22-yr longitudinal study. *J Appl Physiol* 1996;80:285–90. <https://doi.org/10.1152/jappl.1996.80.1.285>.
- [7] Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc* 2011;43(13):34–59. <https://doi.org/10.1249/MSS.0b013e318213fefb>.
- [8] Hawley JA, Hargreaves M, Joyner MJ, Zierath JR. Integrative biology of exercise. *Cell* 2014;159:738–49. <https://doi.org/10.1016/j.cell.2014.10.029>.
- [9] Sarzynski MA, Rice TK, Després JP, Pérusse L, Tremblay A, Stanforth PR, Tchernof A, Barber JL, Falciani F, Clish C, Robbins JM, Ghosh S, Gerszten RE, Leon AS, Skinner JS, Rao DC, Bouchard C. The HERITAGE Family Study: A Review of the Effects of Exercise Training on Cardiometabolic Health, with Insights into Molecular Transducers. *Med Sci Sports Exerc* 2022; 54(5S):S1–S43. [10].
- [10] Hickson RC, Bomze HA, Holloszy JO. Linear increase in cardio-respiratory power induced by a strenuous program of endurance exercise. *J Appl Physiol* 1977;42(3): 72–6. <https://doi.org/10.1152/jappl.1977.42.3.372>.
- [11] Denis C, Fouquet R, Poty P, Geysant A, Lacour JR. Effect of 40 weeks of endurance training on the anaerobic threshold. *Int J Sports Med* 1982;3(4):208–14. <https://doi.org/10.1055/s-2008-1026089>.
- [12] Furrer R, Hawley JA, Handschin C. The molecular athlete: exercise physiology from mechanisms to medals. *Physiol Rev* 2023;103:1693–787. <https://doi.org/10.1152/physrev.00017.2022>.
- [13] Cunanan AJ, DeWeese BH, Wagle JP, Carroll KM, Sausaman R, Hornsby 3rd WG, et al. The General Adaptation Syndrome: A Foundation for the Concept of Periodization. *Sports Med* 2018;48(4):787–97.
- [14] Booth F. Effects of endurance exercise on cytochrome C turnover in skeletal muscle. *Ann NY Acad Sci* 1977;301:431–49. <https://doi.org/10.1111/j.1749-6632.1977.tb38219.x>.
- [15] Hickson RC, Hagberg JM, Ehsani AA, et al. Time course of the adaptive responses of cardio-respiratory power and heart-rate to training. *Med Sci Sports Exerc* 1981; 13(1):17–20.
- [16] McNicol AJ, O’Brien BJ, Paton CD, Knez WL. The effects of increased absolute training intensity on adaptations to endurance exercise training. *J Sci Med Sport* 2009;12(4):485–9. <https://doi.org/10.1016/j.jsams.2008.03.001>.
- [17] Reuter M, Rosenberger F, Barz A, Venhorst A, Blanz L, Roecker K, et al. Effects on cardiorespiratory fitness of moderate-intensity training vs. energy-matched training with increasing intensity. *Front Sports Act Living* 2024;4(5):1298877. <https://doi.org/10.3389/fspor.2023.1298877>.
- [18] Reuter M, Rosenberger F, Barz A, Venhorst A, Blanz L, Hecksteden A, et al. Does Higher Intensity Increase the Rate of Responders to Endurance Training When Total Energy Expenditure Remains Constant? A Randomized Controlled Trial. *Sports Med Open* 2023;9:35. <https://doi.org/10.1186/s40798-023-00579-3>.
- [19] Bell LR, McNicol AJ, McNeil E, Van Nguyen H, Hunter JR, O’Brien BJ. The impact of progressive overload on the proportion and frequency of positive cardio-respiratory fitness responders. *J Sci Med Sport* 2023;26:561–3. <https://doi.org/10.1016/j.jsams.2023.08.175>.
- [20] Gormley SE, Swain DP, High R, Spina RJ, Dowling EA, Kotipalli US, et al. Effect of intensity of aerobic training on VO2max. *Med Sci Sports Exerc* 2008;40(7): 1336–43. <https://doi.org/10.1249/MSS.0b013e31816c4839>.
- [21] Helgerud J, Høydal K, Wang E, Karlsen T, Berg P, Bjerkaas M, et al. Aerobic high-intensity intervals improve VO2max more than moderate training. *Med Sci Sports Exerc* 2007;39(4):665–71. <https://doi.org/10.1249/mss.0b013e3180304570>.
- [22] Belman MJ, Gaesser GA. Exercise training below and above the lactate threshold in the elderly. *Med Sci Sports Exerc* 1991;23(5):562–8.
- [23] Badenhop DT, Cleary PA, Schaal SF, Fox EL, Bartels RL. Physiological adjustments to higher- or lower-intensity exercise in elders. *Med Sci Sports Exerc* 1983;15(6): 496–502.
- [24] Gries KJ, Raue U, Perkins RK, Lavin KM, Overstreet BS, D’Acquisto LJ, et al. Cardiovascular and skeletal muscle health with lifelong exercise. *J Appl Physiol* 2018;125(5):1636–45.
- [25] Weatherwax RM, Harris NK, Kilding AE, Dalleck LC. Incidence of O2max Responders to Personalized versus Standardized Exercise Prescription. *Med Sci Sports Exerc* 2019;51(4):681–91. <https://doi.org/10.1249/MSS.0000000000001842>.
- [26] Bland JM, Altman DG. Treatment allocation by minimisation. *BMJ* 2005;330 (7495):843. <https://doi.org/10.1136/bmj.330.7495.843>.