



# Impact of high-intensity interval training on cardio-metabolic health outcomes and mitochondrial function in older adults: a review

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## Abstract

Exercise being a potent stimulator of mitochondrial biogenesis, there is a need to investigate the effects of high-intensity interval training (HIIT) among older adults. This review explores and summarizes the impact of HIIT on mitochondria and various cardio-metabolic health outcomes among older adults, healthy and with comorbid conditions. Electronic databases were scrutinized for literature using permutations of keywords related to (i) Elderly population (ii) HIIT (iii) Mitochondria, cell organelles, and (iv) cardio-metabolic health outcomes. Twenty-one studies that met the inclusion criteria are included in this review. HIIT is an innovative therapeutic modality in preserving mitochondrial quality with age and serves to be a viable, safe, and beneficial exercise alternative in both ill and healthy older adults.

**Keywords:** high-intensity exercise, healthy aging, quality of life, cardiorespiratory fitness

## Introduction

The number of mitochondria in the skeletal muscles varies depending on the fiber type. Type I fibers have the highest mitochondrial content; type IIx fibers, on the other hand, have a lower mitochondrial content. High mitochondrial content increases the oxidative ability and endurance in the muscles [1,2]. Mitochondrial content is the equilibrium between mitochondrial growth (biogenesis) and degradation (mitophagy) [3].

Low cardio-metabolic health (poor physical activity, decreased cardiorespiratory fitness, adiposity, dyslipidemia, insulin resistance, and impaired glucose tolerance) is attributed to a decrease in mitochondrial elements and function as people age. Furthermore, it contributes to a reduction in the skeletal muscle ability to synthesize in response

to factors inducing mitochondrial biogenesis [4,5]. A possible decrease in cardio-metabolic health and a gradual decrease in muscle mass among older adults are closely associated with reduced mitochondrial content [6]. Mitochondrial dysfunction displays declined mRNA expression, protein synthesis, and protein abundance. The main mitochondrial proteome is coded by nuclear DNA, while being unique in that it contains genetic substance and the ability to synthesize protein [7-9]. Protein import machinery (PIM) strictly regulates mitochondrial and nuclear genomes inside the organelle. In contrast, organelle-specific unfolded protein response (UPR<sub>mt</sub>) regulates the homeostasis of proteins inside the mitochondria [10,11]. This UPR<sub>mt</sub> successfully prevents dis-assembly and misfolding of proteins, which can induce proteotoxic stress in mitochondria

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to ensure improper functioning [12]. In addition, the dysfunctional organelles trapped in the mitochondrial network are culled and recycled by mitophagy to maintain the organelles' quality.

Training at high-intensity intervals (HIIT) is a time-efficient strategy that significantly induces biogenesis and serves as a potential remodeling technique [3,12-14]. The exact definition of "HIIT" varies across different studies [15]. Traditionally HIIT is defined as an exercise that includes short, intermittent outbreaks of vigorous activity determined by 85%-95% heart rate reserve (HRR), or maximal heart rate (MHR) or at about 70-90%  $VO_{2\text{peak}}$  (<100%) interspersed with active rest periods [16-18]. These rest periods or intervals between activities contribute in sufficient recovery, allowing for the continuation of many rounds of activity [15].

### Training regimens

HIIT does not have an official well-defined training regimen. [15] However, different permutations have been tested among various studies [19-23] by altering the duration, intensity, the work / rest ratio [24], the exercise modality (especially for the elderly with musculoskeletal conditions and for those at a higher risk of falling) and by using subjective measures to prescribe the exercise intensity (i.e. rating of perceived exertion or dyspnoea on exertion) [25]. Recent exercise trends aim to obtain benefits with the lowest and shortest workload [15]. Matsuo et al. define a "Japanese high-intensity aerobic training (J-HIAT) protocol for sedentary and healthy adults [19]. The regimen constitutes of 3 sets of high-intensity training. The first and the second set are performed at an intensity of 85-90%  $VO_{2\text{max}}$  whereas the intensity reduces to 80-85%  $VO_{2\text{max}}$  in the third set. The duration of the work interval is about 3 minutes per set. Each set is followed by a phase of active rest at 50%  $VO_{2\text{peak}}$  between each set. Cycling was used as the preferred choice of training modality [19]. Similarly, an elderly Japanese high-intensity aerobic training (EJ-HIAT) was developed for sedentary elderly men aging between 60 to 69 years [20]. Participants had to perform 3 sets of work intervals (first set: 85% $VO_{2\text{peak}}$ , second set: 80%  $VO_{2\text{peak}}$ , third set: 75%  $VO_{2\text{peak}}$ ) interspersed with 1-2 minutes of active rest at 50%  $VO_{2\text{peak}}$ . (first set: 2 minutes rest, second set: 1-minute rest) on a cycle. Alvarez et al. [21,22] developed a protocol for overweight and obese women with type 2 diabetes mellitus. The training interval comprised of 8 intervals of jogging or running for approximately 30 seconds interspersed with 120 seconds of low-intensity walking. At the 12th week follow-up, the high-intensity interval duration was increased by 7 to 10% with a 4% decrease in recovery interval duration, every 2 weeks [21,22].

The 4 × 4 min [17,26] or 10 × 1 min protocol has been common in practice. The 4 x 4 min, known as the clinical protocol [23] is the most widely used and can be performed using the cycle ergometer, arm ergometer, or treadmill with handrails and comprises 4 minutes of work duration at 85-85% MHR interspersed with 3 minutes of recovery at 60-70% MHR. The conventional protocol comprises 60 seconds of HIIT at intensity > 90% HRR for 60 seconds followed by 60 seconds of rest or active rest interval. Some of the training modalities commonly used are cycle ergometer, treadmill, track, body weight, or resistance exercises [23]. In addition, the Tabata and Wingate protocol has been classified under sprint interval training (SIT). Tabata is performed at 170%  $VO_{2\text{max}}$  for about 20 seconds followed by 10 seconds of rest or a very low-intensity recovery interval. The Wingate protocol is the most popular comprising of 30 seconds work interval performed at all-out intensity against a constant force with 4 minutes of active recovery at low intensity [23].

Lack of time is the most cited perceived barrier to physical activity. All the above protocols thus stand advantageous to overcome these barriers due to their brief bursts of activity, which aids in reducing the time commitment to exercise, thus increasing participation [23]. A major disadvantage of these protocols may be that they may not be suitable for all population groups, especially the sedentary population [27]. Authors recommend that initial training or familiarization to exercise is necessary as such activities may be perceived as too difficult and extremely demanding by the individual [28]. This may lead to the development of negative feelings towards the activity, aversion towards participation, leading to increased dropouts. Furthermore, it may not be safe, tolerable, or attractive for everybody [18].

### Advantages and disadvantages of HIIT

One of the major advantages of HIIT is that it requires less time compared to traditional continuous training [23]. Thus, it is a highly time-efficient strategy that may aid individuals to adhere to training. HIIT has been shown to effectively improve body composition and, aerobic capacity ( $VO_{2\text{max}}$ ) [29-33]. It has also been shown to improve overall cardiovascular and metabolic health [33] by improving cardio-metabolic markers in older adults, thus improving the health-related Quality of Life (HRQOL) [32,34-37]. Furthermore, studies also report significant improvement in brain function among the elderly [38].

Due to the paucity of data for the elderly population, there is a potential need for medical screening and clearance before participation in HIIT [27]. Pre-participation health screening, as recommended by the American College of Sports Medicine (ACSM), can be

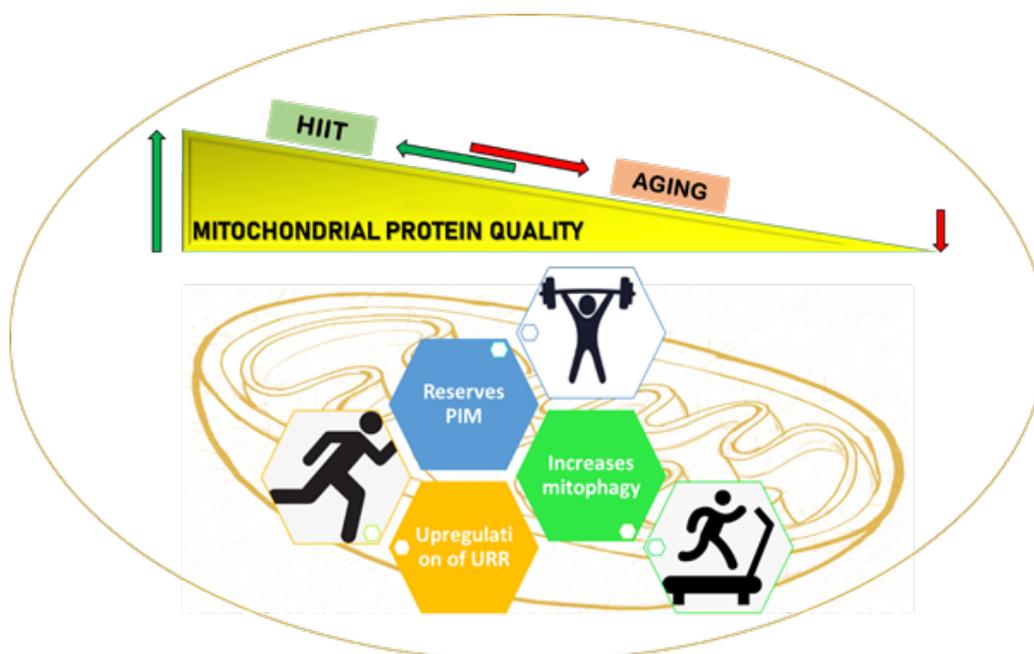
considered before beginning of exercise [25,39]. Secondly, these individuals may be consuming their regular prescribed pharmacotherapy due to multimorbidity which may modulate their heart rate response to exercise. Thus, prescribing the exact exercise intensity may be challenging in these individuals due to over- or underestimation of their  $VO_{2\text{peak}}$  [25,39]. Therefore, the technique of HIIT may need to be modified to adjust to these factors and to facilitate adherence to HIIT among the elderly. The authors also recommend initial supervision for non-trained individuals and assessment of physical activity behavior as it requires a good level of motivation and program adherence [40]. Supervised HIIT programs applied to different populations have been proven safe, with minimal risk [41-44]. Thus, individuals must weigh the pros and cons of training before participation. However, it was noted that the pros outweigh the cons with its established efficacy and cardio-metabolic health benefits.

#### Potential risks involved in training

In terms of its safety and efficacy, HIIT is a well-established training paradigm [27]. However, older individuals may usually appear with numerous comorbidities, frailty, as well as other age-related liabilities such as balance and cognitive impairment [25]. A study reported an increased risk of falls among older adults during their partaking in HIIT [45]. However, a recent study [27] contradicts this finding and reports

a lower number of falls during HIIT sessions. A study evaluating the effect of HIIT in metabolic syndrome adopted the 4 x 4 minute protocol, where the participants performed 4 x 4 min intervals at 90% of maximal heart frequency ( $Hf_{\text{max}}$ ), interspersed with 3-min active recovery at 70% of  $Hf_{\text{max}}$  for a total exercise time of 40 min. They reported two knee injuries in extremely overweight patients.[46]. Additionally, among coronary artery disease patients, Rognmo and colleagues examined the risk of cardiovascular events during planned HIIT and moderate continuous training (MCT). They reported 1 fatal cardiac arrest during moderate-intensity exercise and 2 non-fatal cardiac arrests during HIIT. No incidence of myocardial infarctions was reported [15,25]. Similarly, Levinger et al, in their systematic review, discovered that the incidence of adverse reactions during or 24 hours after HIIT, was about 8% in patients with cardio-metabolic disorders [15]. Thus, these studies conclude that the risk of a cardiovascular event was low with HIIT in a cardiovascular rehabilitation setting [15,25].

HIIT is one of the futuristic therapeutic modalities for maintaining mitochondrial function with age [47]. Therefore, HIIT's role in improving and restoring mitochondrial efficiency through improvements in PIM, UPRmt, and mitophagy is affected by aging and thus, needs to be explored (Figure 1).



**Figure 1.** Reduction in mitochondrial protein quality with age is successfully reversed by HIIT mainly via reserving the protein import machinery (PIM), upregulating unfolded protein response (URR), and increasing mitophagy.

### Protein import machinery

It is a well-acknowledged fact that high-intensity interval training or exercise is a strong stimulus that can induce dynamic adaptations in mitochondria [48]. HIIT in the aged population has effectively induced the expression of key PIM components with increased protein translocation rate in mitochondria [49]. By upregulating PIM components (Tom20, Tom22, and Tom23), cytosolic and mitochondrial chaperones (Hsp90, Hsp60, Hsp70, MSF, Cpn10), HIIT actively induces mitochondrial biogenesis in the elderly [50,51]. This was also proved in a preclinical mice model wherein three days followed by nerve transection; mice deficient in BAX/BAK (pro-apoptotic proteins) showed defective PIM with elevated levels of reactive oxygen species [52]. This impairment was seen to be reversed in mice with high-intensity wheel running training.

### Unfolded protein response in mitochondria

As the longevity or the lifespan of an organism is tightly linked to the maintenance of mitochondrial quality, dysfunctional features in mitochondria are often associated with aging and disorders [53]. Many preclinical studies using drosophila and mice have confirmed that a positive correlation exists between UPR<sub>mt</sub> and longevity [54,55]. Studies using the HIIT program have confirmed the upregulation of UPR<sub>mt</sub> during the early stages of training [56]. Thus, the activation of UPR<sub>mt</sub> is preceded by potential influences on mitochondrial biogenesis and autophagy, which induces positive adaptations [57].

### Mitophagy

An ample amount of evidence suggests that selective degradation of dysfunctional mitochondria (i.e., mitophagy) is a key component of exercise-mediated adaptations [58]. In the muscle, the localization of Parkin to the mitochondrion was increased due to HIIT [59,60]. HIIT also activates AMP-activated protein kinase (AMPK) via ULK1 phosphorylation, resulting in the induction of the autophagy system [60]. The initial increase in mitophagy flux was also encountered after HIIT which was confirmed via the expression of p62, LC3-II, and localization of ubiquitin to a mitochondrial fraction [61]. Based on the studies by Chen et al., the PINK1/Parkin pathway of inducing mitophagy is assumed to play a pivotal part in the mechanisms of mitochondrial remodeling since HIIT induced mitophagy response was blunted in Parkin knockout animals [62]. Activation of mitophagy followed by HIIT remains unclear due to limitations in the studies published. However, available data suggest that HIIT increases mitophagy induction nullifying the need for a more robust mitophagy response. This is due to considerable improvement in the quality of mitochondrial function elevated through the HIIT

paradigm [63].

Hence, in corroboration with established literature, we aimed to explore and summarize the impact of HIIT on mitochondrial biogenesis and its effect on cardio-metabolic health outcomes in older adults.

## Methods

### Data sources and search strategy

The online databases (PubMed, CINAHL, Scopus, Web of Science, ProQuest, Embase) were searched, covering January 2000 to January 2020. Additionally, we reviewed the reference lists of included research. Keywords used were (i) population: elderly, aged, aging, older adults, older person, older people, elder, older, older women, older men, geriatric, senior (ii) HIIT: High-intensity interval training, High-intensity intermittent training, concurrent training, periodic training, interval training, HIIT. (iii) Mitochondria: Mitochondria, Mitochondrial biogenesis, mitochondrial metabolism, molecular, cellular, cell organelles, cellular organelles, organelles. The Boolean operators used were “AND” and “OR” (Figure 2).

### Eligibility criteria

- Older adults, 60 years or older, either gender
- Randomized controlled trials (RCTs), quasi-RCT, and pre-post study design
- Studies including intervention(s) as high-intensity interval training, high-intensity intermittent training, Interval/ intermittent training.
- Published in English.
- Human Subjects
- Published posters or platform presentations were excluded.

### Outcomes of interest

Molecular effects of HIIT on mitochondrial function and aging, cardiorespiratory endurance, adiposity indices, muscle function, lipid profile, HOMA-IR, HRQOL, blood lactate, and glucose metabolism.

### Study selection and quality assessment

The first two authors conducted an independent search and selection of eligible studies. Disputes were resolved by consultation with the third author. The first two authors retrieved the data from the included studies on a data extraction sheet. The information related to the authors, setting, characteristics of the participants (age, gender, body mass index, inclusion criteria, the severity of the disease, sample size), details of interventions (High-intensity interval training- laboratory-based, real-world based, or combination of both), comparison groups, outcomes assessed, follow-up period, and the adverse effects were recorded. Quality assessment of the included studies was performed using the quality index score [64].

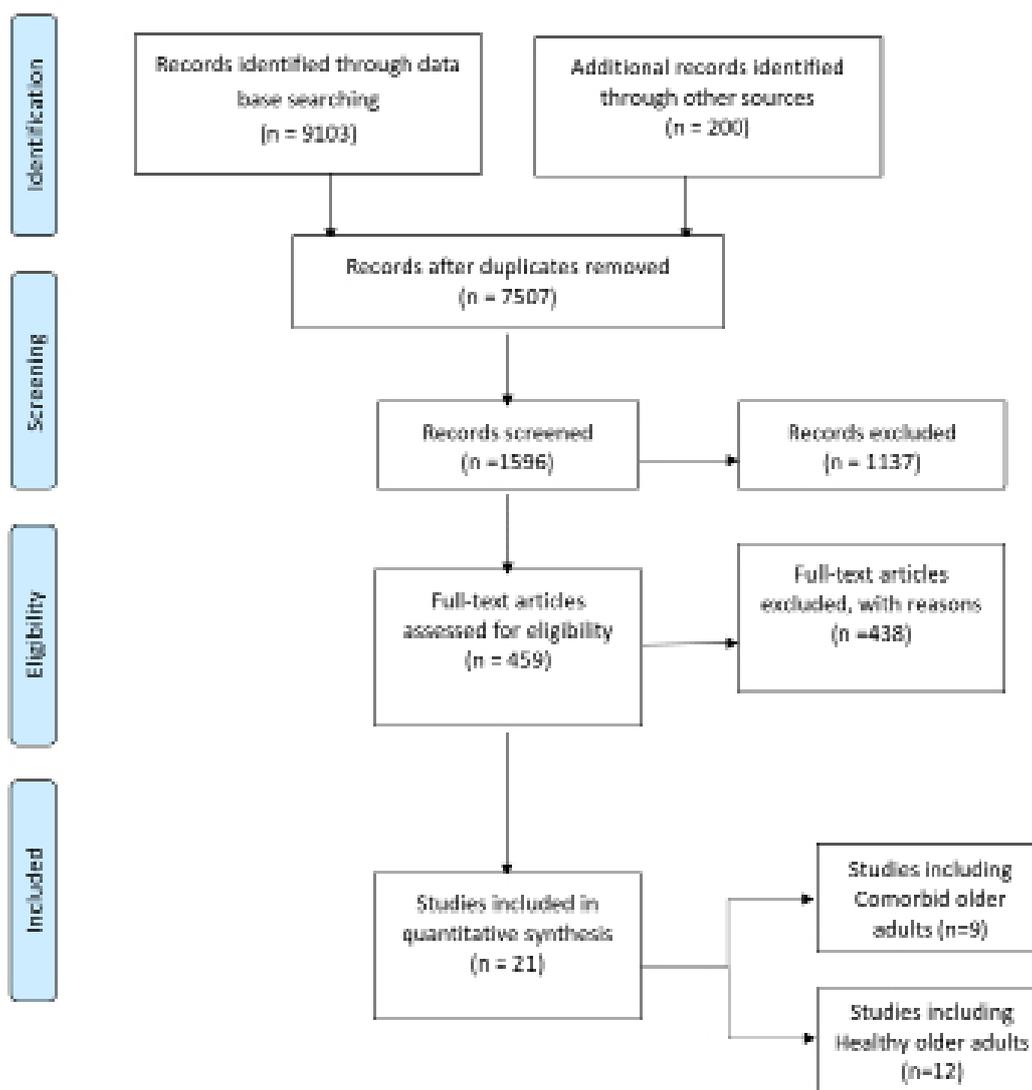


Figure 2. PRISMA Flow Diagram.

## Results and Discussion

A total of 1596 articles were screened after the deletion of duplicates. Of these, 21 studies were included in this review (Table I and Table II) [29-32,34-36,65-78].

HIIT has surfaced as an emergent reservoir of evidence promoting a positive impact on cardio-

metabolic health outcomes in the elderly. This is due to the attention received in preventing age-related decline in mitochondrial biogenesis and improving cardio-metabolic parameters in older adults, particularly body composition, lipid regulation, and insulin sensitivity [79].

**Table I.** Characteristics of included studies: HIIT and Healthy Older Adults.

Author, year	Population	Intervention	Control or comparison group and exercise intensity	Duration (weeks)	No. Of sessions/ week	Outcomes	Results	Quality index score
Nunes et al, 2019 [29]	Post-menopausal obese woman Baseline body fat percentage >40% Occupation: housewives No history of physical training HIIT: n=13 Median (IQR) age: 62.3 (58.2-66.5) Median (IQR) Menopause time(Y): 16.1 (10.0-22.2) CT: n=13 Median (IQR) age: 62.9 (57.6-68.2) Menopause time(Y): 18.3 (12.3-24.2)	<u>HIIT Group</u> Warm-up of 5 minutes walking Cooldown of 3 minutes walking at 60% of MHR Type of exercise: Stair climbing (Step height; 16cm) plus 30 seconds of free bodyweight squats. Total session length: 28 minutes (10 sets of 60 seconds of high-intensity exercises, >80% of MHR, or adapted Borg scale >6 steps) and recovery period of 60 seconds of low-intensity exercise at 60% of MHR or adapted Borg scale at <5. Progression of the intervention: Weekly	<u>Combined training Group</u> Total session length: 60 minutes. 30 minutes of moderate-intensity walking at 70% of MHR and five resistance exercises at 70% of 1RM with three sets of 8 to 12 repetitions and 1.5-minute rest interval between sets and exercises	12 weeks Supervised session	3 Session per week	Bodyweight (KG) BMI Body fat % FM(KG) VAT(KG)	In the HIIT group a reduction in VAT was observed when compared to CT (time vs group effect; P<0.05). No statistical differences between groups were observed for the other body composition and the anthropometric variables	29
Pinillos et al, 2017 [30]	Active Older adults (n=90) EG: (n=47) Mean(SD) age: 73.50 (5.58) Mean BMI (SD): 28.97 (3.53) Male: Female(n)= 13:34 CG: (n=43) Mean(SD) age: 72.09 (5.78) Years Mean BMI (SD): 30.35 (4.07) Male: Female(n)= 13:30	<u>EG</u> High-intensity circuit training with High-intensity interval endurance training. 5-7 min warm-up 4-5 min cooldown Single session volume: ~35-40 min (warm-up and cold down included) Two sets of circuit strength training interspersed with endurance training. Next order of exercise: strength-endurance-strength.	<u>CG</u> Training program as per participant earlier exercise dose 3-4 walking sessions per week Exercise dose: ~150-200 min/week at low-moderate intensity	12week s Supervised session	3 sessions per week on non-consecutive days	Bodyweight (KG) BMI Muscle mass% Fat mass% 30-s Chair test (reps) HS test	The experimental group experienced significant improvements in body mass, fat mass, muscle mass (in kg), and BMI (p < 0.001), whereas the control group did not experience significant changes in any variable (p ≥ 0.05). Within-group comparison (group x time) reported differences in EG (p < 0.001), with significant improvements in both 30-s CST and HS tests), whereas the CG did not experience significant changes in CST and HS test (p ≥ 0.05).	28
Buckinx et al, 2019 [31]	Sedentary obese older adults (n=30) P20- : (n = 15) Male: Female(n)= 7:8 Mean(SD) age: 66.8 ± 3.7 years P20+ : (n = 15) Male: Female(n)= 7:8 Mean(SD) age: 68.1 ± 4.1 years	<u>P20-</u> 5 min warm-up 5 min cool-down A 20-min HIIT of multiples 30-sec sprints at a high intensity (80–85% MHR or Borg' scale > 17) alternating with sprints of 90 s at a moderate-intensity (65% MHR or Borg' scale score 13–16).	<u>P20+</u> 5 min warm-up 5 min cool-down A 20-min HIIT of multiples 30-sec sprints at a high intensity (80–85% MHR or Borg' scale > 17) alternating with sprints of 90 s at a moderate intensity (65% MHR or Borg' scale score 13–16)	12weeks Supervised session	three times per week in non-consecutive days	Body composition: BMI FM (%) Functional capacities: 6MWT, TUG, CST Muscle Function: ULMS Lower Limb: Strain gauge system attached to a chair Muscle composition: pQCT	A 12-week HIIT program improves functional capacities as well as body composition in obese older adults in both P20- and P20 + group (p < 0.05).	29
Garcia B M et al, 2019 [32]	Older women(n=54) HICT: (n=18) Mean (SD) age: 66.3 ± 5.71 years Mean BMI (SD): 30.4 (4.13) MICT: (n=18) Mean (SD) age: 70 ± 8.76 years Mean BMI (SD): 30.1 (3.08) CG: (n=18) Mean (SD) age: 67.4± 5.71 years Mean BMI (SD): 31.2 (4.89)	Warm-up Cool-down The exercise program was divided into a 2-week familiarization period and four 4-week mesocycles period HICT: Exercise intensity: High; 14–18points of RPE MICT: Exercise intensity: moderate; 9–14 points of RPE	Non-exercise control group	18 weeks	Two times per week (1h/session)	BMI and handgrip strength: dynamometer, upper limb strength: arm curl strength, lower limb strength: 30s sit to stand. Cardiorespiratory fitness: 6MWT Gait: TUG Balance: one leg standing	In lower limb strength, gait/dynamic balance, and cardiorespiratory fitness, both HIICT and MICT were statistically better than the CG.	28
Grace F M et al, 2017 [65]	Aging male (n=39) SED (n=22): Mean (SD) age: 62.7±5.2 years LEX (n=17): Mean (SD) age: 61.1±5.4 years	<u>SED</u> (n=22): HIIT (6 x30 s sprint) Block 1: 6 weeks of supervised aerobic pre-conditioning exercise endorsed by ACSM guidelines for older adults. Block 2: HIIT with 6 x 30 s sprints at 50% of peak power output interspersed with intervals of 3 min active recovery against a low (0-50 W) resistance and self-selected cadence	<u>LEX</u> (n=17): Block 1: continued habitual exercise training regimens. Block 2: HIIT with 6 x 30 s sprints at 50% of peak power output interspersed with intervals of 3 min active recovery against a low (0-50 W) resistance and self-selected cadence	6 weeks	5	MET capacity	HIIT accelerates the improvement in MET capacity in both SED and LEX, thus improving cardiovascular health.	25

Author, year	Population	Intervention	Control or comparison group and exercise intensity	Duration (weeks)	No. Of sessions/ week	Outcomes	Results	Quality index score
Hwang C L et al, 2016 [66]	Healthy sedentary older adults (n=51) HIIT (n = 17): Mean (SD) age: 64.8 ± 1.4 years Mean BMI (SD): 28.0 ± 1.1 MICT (n = 18): Mean (SD) age: 65.6 ± 1.8 years Mean BMI (SD): 28.7 ± 1.0 CONT (n = 16): Mean (SD) age: 63.8 ± 1.6 years Mean BMI (SD): 26.7 ± 1.4	<b>HIIT</b> Arm and leg exercise on a non-weight-bearing all-extremity air-braked ergometer. Warm-up: 10 minutes Cool-down: 5 minutes Exercise dose: 4×4 minute intervals at 90% of HRpeak interspersed by 3 × 3-minute active recovery periods at 70% of HRpeak Total duration: 25 min <b>MICT</b> : Arm and leg exercise on a non-weight-bearing all-extremity air-braked ergometer Warm-up: 10 minutes Cool-down: 5 minutes Exercise dose: 70% of HRpeak for 32 min	CONT: no exercise	8 weeks	4 days/week	VO2max BMI Body fat% Blood lipids HOMA-IR Habitual physical activity	VO2peak improved by 11% in HIIT, while no changes were observed in MICT and CONT. Insulin resistance decreased only in HIIT by 26%. Body composition and lipids were unaffected (P ≥ 0.1).	29
Sculthorpe N F et al, 2017 [67]	Sedentary ageing male (n=33) INT (n = 22): Mean (SD) age: 62.3±4.1 years CON (n = 11): Mean (SD) age: 61.6±5.0 years	<b>INT</b> : Supervised "preconditioning" exercise for 6 weeks (training block 1) HIIT (training block 2) 5 minutes of warm-up 6x 30 s sprint at 50% peak power on cycle ergometer each interspersed with 3 min interval of active recovery.	CON: Remained inactive	12 weeks	LHIIT session performed once every 5 days for 6 weeks (9 sessions)	Body fat% PPO rPPO	Following LHIIT, the reduction in body fat accelerated with a concomitant increase in LBM. 6 weeks of LHIIT exercise shows improvements in absolute and relative PPO significantly	27
Robinson M et al, 2017 [68]	Younger and older adults (n=27) HIIT: (n=15, 9 younger, 6 older) Older adults Mean (SD) age: 69 (4) years Older adults Mean BMI (SD): 25.9 (3) SED: Older adults Mean (SD) age: 69 (4) years Older adults Mean BMI (SD): 25.9 (4)	<b>HIIT</b> : The exercise was performed on a cycle ergometer. 3 days per week of 4 x 4-minute intervals at 90% VO2peak with 3 minutes of rest between intervals and 2 days per week of walking on a treadmill at 70% VO2peak for 45 minutes	SED: No structured exercise was given	12 weeks	3+2	HOMA-IR VO2peak Brain glucose metabolism	Brain glucose metabolism was improved. VO2peak was increased for all participants after HIIT and did not change with SED	27
Knowles A M et al, 2015 [34]	Ageing men (n=44) LEX (N=19): Mean (SD) age 61± (5) years SED (N=25): Mean (SD) age 63± (5) years	SED (n=25): Block 1: 6 weeks of supervised aerobic pre-conditioning exercise Block 2: HIIT with 6 x 30 s sprints at 40% of peak power output	LEX (n=19): Positive control group	6 weeks	Once every 5 days	HRQOL Vo2 max	HIIT increases perceptions of HRQL, aerobic capacity in older adults, to varying degrees, in both SED and LEX groups	29
Ballin M et al, 2019 [69]	Community-dwelling old men and women (n=77) Mean (SD) age 70.7 ± (02) years Mean (SD) body mass index (BMI) 29.2 ± 3.3 kg/m <sup>2</sup>	<b>Intervention group</b> : Warm-up and dynamic stretching for 10 min, followed by vigorous interval training work-to-rest ratio - 40/20 s. Progression- Weekly Vigorous-intensity of 7 on Borg CR10 scale	<b>Control group</b> : Participants were asked to maintain their daily living and routines throughout the trial.	10 weeks	3days/week	HRQOL: SF-36 Lipid profile	The intervention resulted in significant effects on the SF-36, total cholesterol, and LDL-cholesterol when compared to the control group.	29
Klonizakis et al, 2014 [70]	Postmenopausal women aged (n=22) HIT (n=12) Mean (SD) age 64 (7) years CT: (n=10) Mean (SD) age 64 (4) years	<b>HIT</b> : The exercise consists of ten 1-minute intervals of cycling exercise at 100% of peak power output separated by 1 minute of active recovery	CT: 40 minutes of continuous cycling at 65% of peak power output	2 weeks	6 sessions in two weeks	Peak oxygen uptake	low-volume HIT can lead to rapid improvements in peak oxygen uptake in postmenopausal women, thus improving cardiopulmonary function	27
Hurst et al, 2019 [71]	Adults aged from 50-81 years (N=36) HIT (n=18) Mean (Range) age: 61.9 (50-81) CON (n=18) Mean (Range) age: 62.8 (50-74)	<b>HIT</b> : Warmup: Combination of upper- (bent over row, shoulder press), lower- (squat, split squat), and full-body (power clean and press, step, and press, pulldown to squat, high pull) 4 reps of each HIT (4sets) each set followed by 3 min passive rest at >90% of MHR	CON: No exercise	12 weeks	2 sessions/ week	HRQOL Leg extensor muscle power Cardiorespiratory fitness	HIT improved Dominant Leg strength, cardiorespiratory fitness, and HRQOL.	29

**Abbreviations:** BMI: Body Mass Index; CT: combined training; CG/ CONT/CON: Control Group; CST: chair stand test; EG: Exercise group; FM (%): Total fat mass; GDF11: Growth differentiation factor 11; HIIT: High intensity interval training; HIT: high intensity training; HIICT: High intensity concurrent training; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; HRQOL: health related quality of life; HS: Handgrip strength test; INT: intervention group; LDL: Low density lipoprotein; LEX: Lifelong exercisers; LHIIT: Low frequency high intensity interval training; LBM: total lean body mass; MICT: Moderate Intensity continuous training; MHR: Maximum Heart rate; PPO: Peak power output; P20+: ≥ 20 g protein in each meal; P20-: < 20 g protein in at least one meal; pQCT: Peripheral Quantitative Computed Tomography, RM: Repetition maximum; SED: Sedentary Ageing; SF-36; short form- 36; TUG: Timed Up and Go Test; ULMs: Maximum voluntary upper limb muscle strength; VAT: visceral adiposity tissue; VO2max: maximal oxygen uptake; VO2peak: peak oxygen consumption; 6MWT: 6 Minute Walk test.

**Table II.** Characteristics of included studies: HIIT and Older Adults with Comorbidities.

Author, year	Population	Intervention	Control or comparison group and exercise intensity	Duration (weeks)	No. Of sessions/ week	Outcomes	Results	Quality index score
Gaitan et al, 2019 [72]	Obese adults with prediabetes (N=22) IG; (n=11) male/female: 2/9 Mean (SD) age: 60.1 (2.3) Mean BMI (SD): 32.7 (1.6) CG; (n=11) male/female: 3/8 Mean (SD) age: 65.6 (2.9) Years Mean BMI (SD): 31.8 (1.8)	IG: The exercise consists of alternating intervals of 3 min at 90% HRpeak and 3 min at 50% HRpeak for a total of 60 min on a cycle ergometer Warm-up: NR Cooldown: NR	CG: 70% HRpeak for the entire 60 min	2 weeks supervised session	Total no. of session 12	Body Mass (kg) BMI Waist Circumference (cm) Fat oxidation VO2peak	Body mass reduced and VO2peak increased more in the intervention group compared to the control group. High-intensity INT training enhances fat oxidation during the same relative intensity exercise in people with prediabetes. No Significant change were observed in WC	27
Terada et al, 2013 [73]	Individuals with T2DM (N=15) HIIE; (n=8) male/female: 4/4 Mean (SD) age: 62 (3) Mean BMI (SD): 28.4 (4.1) Mean T2DM duration (SD) Y: 6(4) MICE; (n=7) male/female: 4/3 Mean (SD) age: 63 (5) Years Mean BMI (SD): 33.1(4.5) Mean T2DM duration (SD) Y: 8(4)	HI-IE: Stationary cycling and treadmill walking was performed alternately for exercise variety. HI-IE protocol involved alternating between 1-min intervals at 100% VO2R followed by 3-min recovery intervals at 20% VO2R (average = 40%) except for one day (Wednesday) when they performed MI-CE protocol. Warm-up: NR Cooldown: NR	MI-CE: continue exercise at 40% VO2R	12 weeks supervised session	5session per week	Body composition HbA1c VO2peak Adherence rate	Total body fat percent, Leg fat, and subcutaneous fat width were significantly reduced in both groups. HbA1c did not change from baseline. VO2peak did not change in either group HI-IE training did not negatively impact exercise adherence and retention compared to MI-CE. Therefore, HIIE training can be a feasible intervention in individuals with type 2 diabetes mellitus.	28
Maillard et al, 2016 [74]	Postmenopausal women with T2DM (N=17) (69 ± 1 years; BMI: 31 ± 1 kg.m <sup>-2</sup> ) HIIT; (n=8) Mean BMI (SD): 32.6 (1.7) MICT; (n=9) Mean BMI (SD): 29.7 (1.2)	HIIT: Training dose: [60 × (8 s at 77–85% HRmax, 12 s of active recovery)]	MICT: Training dose: 40 min at 55–60% of their HRR	16 weeks	2 days/ week	Body composition Fat mass	HIIT showed significant loss of total abdominal and visceral FM. HIIT program in postmenopausal women appeared to be more effective for reducing central obesity than MICT	29
Jaureguizar et al 2016 [35]	Patients with ischemic heart disease (Stable New York Heart Association functional class I or II coronary artery disease with angina pectoris or myocardial infarction and no heart failure) N=32 HIIT: Mean (SD) age: 58 (11) Years Mean BMI (SD): 29.6(4.4) MCT: Mean (SD) age: 58 (11) Years Mean BMI (SD): 29.5(4.1)	HIIT: 1 <sup>st</sup> week: 15 repetitions* 2 <sup>nd</sup> week: 20 repetitions* 3 <sup>rd</sup> week: 25 repetitions* 4 <sup>th</sup> week: 30 repetitions* 5 <sup>th</sup> -8 <sup>th</sup> week: 30 repetitions* * 20s repetitions at an intensity corresponding to 50% of the maximum load followed by 40s recovery periods at 10%. Warm-up: 12-5 minute at 25W Cool down: 13-5 minute at 25W Mode of exercise training: cycle ergometer	MCT: 1 <sup>st</sup> week: 15 min at V T 1 2 <sup>nd</sup> week: 20 min at V T 1 3 <sup>rd</sup> week: 25 min at V T 1 4 <sup>th</sup> week: 30 min at V T 1 5 <sup>th</sup> -8 <sup>th</sup> week: 30 min at (V T 1 + 10%)	8 weeks	40 minutes per sessions, 3 days per week (total of 24 sessions over 2 months).	VO2peak VT 6MWT HRQOL: SF-36	High-intensity interval training resulted in a significantly greater increase in VO2 compared with MCT. VT 1 increased by 21% in HIIT and 14% in MCT Significant increases in the 6-minute walk distance in HIIT group compared with MCT group. Both training protocols improved the quality of life. HIIT reported a greater increase in functional capacity compared with MCT without any increase in cardiovascular risk. No adverse events were reported in either of the groups.	29
Izadi et.al, 2017 [75]	Older treated hypertensive individuals (N=44) Total drop out 7 in each group HIIT; (n=15) male/female: 8/7 Mean (SD) Male age: 60.87 (5.71) Mean (SD) Female age: 64.57 (4.70) Mean Male BMI (SD): 25.23 (0.55) Mean Female BMI (SD): 25.68 (0.72) CG; (n=15) male/female: 9/6 Mean (SD) Male age: 62.44 (5.10) Mean (SD) Female age: 58.33 (7.25) Mean Male BMI (SD): 25.17 (0.84) Mean Female BMI (SD): 25.33 (1.18)	HIIT: 35 min of HIIT cycling, consisting of 10 × 1.5-min intervals at 85–90% of HRR. Each interval was separated by 2 min of the active pause at 50–55% of HRR Warm-up: 3 min of cycling at 40% of HRR. Cool-down: 5 min of cycling at 40% of HRR	CG: The control group subjects were encouraged to maintain their daily activities	6 weeks	3 times/ week Exercise time: (09:00–12:00)	VO2peak BMI	VO2peak increased following the 6-week HIIT. There were no significant changes in body fat percentage, body weight, and body mass index after 6 weeks of HIIT	28

Author, year	Population	Intervention	Control or comparison group and exercise intensity	Duration (weeks)	No. Of sessions/week	Outcomes	Results	Quality index score
Martins et al, 2018 [76]	Older postmenopausal women (N=28) 6 discontinued at follow-up in each group. HIBWT: (n=8) Mean (SD) age: 64.3 (6.7) Mean (SD) postmenopausal time in years: 17.7 (9.5) COMT: (n=8) Mean (SD) age: 65.0 (6.3) Mean (SD) postmenopausal time in years: 19.1 (9.3)	<u>HIBWT:</u> 60 seconds of high-intensity exercise (>85% MHR/Borg scale at 7-8/10) interspersed by a recovery period of 60 seconds of low-intensity exercise (light walk). High-intensity exercise: 30 seconds of stepping up and down on a 16 cm step and 30 seconds of bodyweight squat with 90-degree knee flexion. <u>Progression:</u> Week 1-4: 60 s of high-intensity exercise x recovery period of 4 min of low-intensity exercise (4 sets) Week 4-12: 60 seconds high-intensity exercise x recovery of 60 s of low-intensity exercise (10 sets)	<u>COMT:</u> 30 min walk on the flat floor of moderate-intensity (70% of HRmax/ Borg scale at 5-6/10) on following by 8-12 reps of 5 resistance exercise at 70% 1RM (45-degree half squat, bench press, leg curl, rowing machine and unilateral leg extension). <u>Progression:</u> Week 1: walk at 70% of HRmax or Borg scale at 5-6 (15 mins) and one set of 5 resistance exercises (8-12 repetitions at 70% of 1RM) Week 2: 20 min walk and two sets, with a 1.5 min rest period between sets. Week 3: 25 min walk and two sets. Week 4 to 12: 30 min walk and three sets.	12 weeks	3 days per week (no consecutive days)	Body composition Muscle function (1-RM test) Blood samples 6MWT	HIBWT showed effects similar to COMT. Muscle mass index (MMI) increased in both groups. Muscle strength increased only in the COMT group. 6MWT increased in both groups. Fasting glucose, glycated hemoglobin, Insulin, HOMA-IR were decreased in both groups.	28
Taylor et al 2014 [77]	Participants with T2DM (18 to 69 years) (N=21) HIGH: (n=11) Mean (SD) age: 54.4 (5.6) Mean (SD) Body Mass (kg): 106.7 (15.7) MOD: (n=10) Mean (SD) age: 52.2 (12.6) Mean (SD) Body Mass (kg): 111.7 (23.5)	<u>HIGH:</u> <u>Resistance Training</u> Intensity: 100% of 8-RM Volume: 4 sets of up to 8 repetitions Frequency: 2 days per week Rate of Progression: Resistance increased based on a prescribed percentage of the weekly established 8-RM <u>Aerobic Training:</u> Intensity: 50 – 65% of heart rate reserve Volume: 20 minutes Frequency: 3 days per week Rate of Progression: Treadmill speed or the grade increased as tolerated each training day, based on the prescribed percentage of HRR.	<u>MOD:</u> <u>Resistance Training:</u> Intensity: 75% of 8-RM Volume: 4 sets of up to 8 repetitions Frequency: 2 days per week Rate of Progression: Resistance increased based on a prescribed percentage of the weekly established 8-RM. <u>Aerobic Training:</u> Intensity: 30 – 45% of HRR Frequency: 3 days per week Rate of Progression: Treadmill speed or grade increased as tolerated each training day, based on the prescribed percentage of HRR.	12 weeks	5 days per week	Muscle strength Physical function (Patient-Specific Functional Scale questionnaire) Exercise Capacity	Participants in both the MOD group and HIGH group demonstrated significant and similar gains in muscle strength, exercise capacity, and physical function.	29
Kamilla Munch Winding et al, 2017 [78]	Individuals with type 2 diabetes (N=26) HIIT: (n=13) Mean (SD) age: 54(6) Mean (SD) Time since diagnosis (years): 8(4) END: (n=12) Mean (SD) age: 58(8) Mean (SD) Time since diagnosis (years): 6(4) CG: (n=7) Mean (SD) age: 57(7) Mean (SD) Time since diagnosis (years): 7(5)	<u>HIIT:</u> Warm-Up: 5-minute cycling at 40% of Wpeak 20 min cycling with 1 min at 95% Wpeak and 1 minute of active recovery (20% Wpeak) <u>END:</u> Warm-Up: 5-minute cycling at 40% of Wpeak 40 min cycling at 50% of peak workload <u>CG:</u> No intervention		11 weeks	3 days per week HIIT: 75 min per week END: 135 min per week	Body composition Blood samples (plasma glucose, lipids, HbA1c, C-peptide, and serum insulin) VO2peak	HIIT was proven as a time-efficient treatment for individuals with type 2 diabetes. Whole-body and android fat mass decreased in HIIT compared with CG. Visceral fat mass, HbA1c, fasting glucose, postprandial glucose, glycaemic variability, and HOMA-IR decreased after HIIT. HIIT resulted in better improvements in physical fitness, body composition, and glycaemic control compared to END. VO2peak increased in HIIT compared with END despite lower total energy expenditure and time usage during the training sessions.	29
Da Silva et al, 2019 [36]	Older men and women (N=39)	<u>HIIT:</u> Strength: 2 sets of 8-15 repetitions, with a recovery interval of 1 to 2 minutes (20mins/ session) HIIT: Participants ran for 3 minutes, with the intensity of 80-90% HRmax, 3 times/session and walking for 3 minutes with an intensity of 55-65% HRmax, 2 times/session Flexibility: static stretches (10-15 sec hold, 1-2 reps for large muscle group)	<u>CT:</u> Strength: 2 sets of 8-15 repetitions, with a recovery interval of 1 to 2 minutes (20mins/ session) Aerobic: 25 minutes of walking respecting a moderate to vigorous intensity (60-70% HRmax) Flexibility: static stretches (10-15 sec hold, 1-2 reps for large muscle group)	12 weeks	3 sessions/week	HRQOL	High-intensity interval training improves health-related quality of life in adults and older adults with diagnosed cardiovascular risk.	29

**Abbreviations:** BMI: Body mass index; CG/CON: Control Group; COMT: combined training; CT: concurrent training; END: Endurance Training; HbA1c: glycosylated hemoglobin; HIIT: High-intensity interval training; HIGH: High-intensity training; HI-IE: High-intensity intermittent exercise; HIBWT: High-intensity Bodyweight training; HRmax: Maximum Heart rate; HRpeak: peak heart rate; HRR: Heart Rate Reserve; HRQOL: health-related quality of life; IG: intervention group; MICT: Moderate Intensity continuous training; MI-CE: Moderate-intensity continuous exercise; MOD: Moderate Intensity training; MHR: Maximum Heart rate; NR: Not reported; RM: Repetition maximum; SF-36; short form- 36; T2DM: type 2 diabetes mellitus; VO2peak: peak oxygen consumption; VO2R: VO2 reserve VT1: aerobic threshold; WC: waist circumference; 6MWT: 6 Minute Walk Test.

## Impact of HIIT on cardio-metabolic health markers

### 1. Body composition and aerobic fitness

An individual's body composition is subject to change as one ages, due to a considerable increase in fat mass with a decrease in muscle mass and bone mineral density [80,81]. Despite the discordance in the available literature, HIIT has been shown to efficiently improve body composition within 2 to 18 weeks [29-32,72,74]. An improvement in whole-body fat oxidation with significant reductions in fat mass, and waist and hip circumferences were some of the prominent findings observed. [67,72,74] Furthermore, a single session of HIIT of lower frequency (LfHIIT) has shown a considerable reduction in augmented body fat with an increase in Lean Body Mass (LBM) [67,82]. Additionally, when combined with circuit training (HIICT), there is a reduction in Body Mass Index (BMI) in less than 18 weeks of training [32]. This disparity in responses is explained by the lack of uniformity in training protocols and the unparalleled training volumes and duration [83]. Training protocols varied in intensity and duration, from 25-30-minute exercise sessions above 80% of maximum heart rate ( $HR_{max}$ ) to shorter sessions of around 90% peak heart rate ( $HR_{peak}$ ) [30-32,38]. In addition, some interventions investigated the effects by interspersing mesocycles of concurrent training [32]. Studies ranged from about 2 to 18 weeks with most interventions lasting for about 12 weeks [29-32,72,74]. Furthermore, nutrition has shown to play a key role in any form of alterations in body composition with HIIT [31].

In terms of cardiovascular fitness, aerobic capacity ( $VO_{2max}$ ), conveyed as peak oxygen consumption ( $VO_{2peak}$ ), is a well-established unbiased prognosticator of all-cause mortality and cardiovascular health [66]. As we know, aging results in a drop in maximal aerobic capacity, gradually progressing over the lifespan [15]. HIIT has been shown to serve as a time-efficient and feasible exercise intervention to improve  $VO_{2peak}$  among older adults [34,69,71,72,84,85]. The mechanism, although unclear, hypothesized it to be either due to central [85] or peripheral adaptations [66,86]. Central adaptations have been shown to partly contribute to aerobic capacity through its small improvement in systolic function observed with HIIT [25,87]. Correspondingly, reduced peripheral vascular resistance and improvement in endothelial function were identified to contribute to peripheral adaptations [81]. Moreover, some of the acute physiological responses observed after HIIT was an increase in the concentration of epinephrine, norepinephrine, growth hormone, interleukin 6, free cortisol, adrenocorticotropic hormone (ACTH), Adenosine triphosphate (ATP), phosphocreatine (PCr), and glycogen stores. These hormones play a significant role in lipolysis [23]. In addition, a decrease in the parasympathetic reaction was also observed

which was attributed to increased sympathetic activity and accumulation of metabolites during training. This resulted in an increased fat loss, thus improving aerobic fitness. Another study [88] showed an increase in lactate concentration following 5 weeks of HIIT. Higher lactate concentration was shown yielding higher anaerobic energy, thus leading to better performance [89]. Furthermore, these changes were attributed to an increment in the skeletal muscle oxidative capacity due to an expansion of the mitochondrial processes [70,72].

### 2. Cardiovascular health

Altered lipoprotein levels are significant risk markers for cardiovascular disease and mortality in all age groups [90]. The literature recommends aerobic exercise in older adults to improve lipid parameters due to its feasibility in terms of low cost and to avoid the need for pharmacological intervention [91]. High intensity interval training has shown to escalate muscle oxidative capacity and regulate triglycerides (TG) and low-density lipoproteins (LDL) by improving mitochondrial biogenesis markers and functioning markers in less than 6 sessions among both healthy and ill individuals [69]. In addition, a study among youth observed substantial reductions in total cholesterol (TC), LDL, and TG, within just 12 weeks of training, thus eliciting a prominent improvement in lipid profile [92]. Currently, it is difficult to explain the diverse nature of these findings due to the paucity of quality evidence. There is a lack of standardization of the measurement methods, mixed training protocols, and difference in population parameters like age, gender, etc [69]. Evidence highlights the need for amalgamation of dietary modification to help regulate lipids.

HIIT also showed a marked reduction in blood pressure. This could be because HIIT improves endothelial function through increases in apelin in nitric oxide. These two factors significantly improve vascular function through endothelial vasodilation [23].

### 3. Metabolic health

Older adults are at greater risk of developing insulin resistance in association with a sedentary lifestyle and increased adiposity. The glucose metabolizing capacity of the skeletal muscle decreases, and insulin resistance increases [93]. The underlying mechanism is associated with a sequence of changes occurring in the skeletal muscle with aging [91]. HIIT showed remarkable improvement in whole-body insulin levels [38,68,94] with a 26% decline in insulin resistance in older adults [23,65]. An increase in skeletal muscle adaptation causing fatty acid oxidation and glycolytic enzymes, and muscle glucose uptake after HIIT has shown a significant decrease in insulin resistance and improved insulin sensitivity [23]. Insulin sensitivity is also said to improve as a result of improved body composition [23].

Normal aging also contributes to the global decline

in glucose uptake and metabolism in the human brain, the justifications for which remain poorly understood [95]. These improvements in insulin profile led to a better fasting brain glucose uptake. [38,68,95,96] The caudate nucleus, parietal and temporal lobes were subject to glucose uptake after HIIT [68]. Glucose is the primary source of fuel for the brain. Increased glucose uptake in these areas indicated robust improvement in their respective brain functions, thus reducing the risk for degenerative or cognitive disorders [98]. Though small, gains are vital and thus are consistent with the fact that HIIT has the potential to prevent the development of degenerative brain diseases [68,98]. Another mechanism that could explain this increment is that HIIT also led to a decrease in insulin concentration [38]. Increased insulin concentration above fasting levels is reported to impair brain glucose uptake [38,68]. Thus, in substantiation with the above findings, it can be concluded that HIIT improves brain metabolism and may offer exercise-induced improvement in insulin production or secretion [38].

#### 4. Neuromuscular benefits

HIIT has been shown to positively impact skeletal muscle strength. 12-weeks of low volume HIIT has demonstrated remarkable improvements in upper and lower body strength [30,37,71]. Furthermore, HIIT has also been proven as an effective training modality to increase lower limb muscle strength in sedentary aging men [67]. Though trivial, HIIT when implemented in weight training, has proven to amplify gains over a brief period when applied with lower repetitions and rest time [99].

Good lower limb strength accounts for good postural stability. Aging results in deterioration in postural control due to low bone mineral density, strength, and flexibility, further contributing to the increased risk of falls in the elderly [100]. Postural control in gait is a highly pertinent variable used to assess falls. Thus, the timed up & go test (TUG) was employed by most studies to assess dynamic balance following HIIT. Even the slightest significant improvement noticed in a TUG is of utmost relevance to detect dynamic balance and to prevent falls [101]. Thus, when we assessed the literature for the same, inconsistent findings were observed. HIIT resulted in temporary improvements wherein long-term benefits could not be commented upon. Although temporary, it was reported that HIIT can improve dynamic balance [30,32]. Increase in lower limb strength and nervous system adaptation may contribute to this. The performance of exercise in standing could precisely contribute to the neural adaptations and thus transmit a positive impact onto the dynamic balance, gait, and lower limb strength [32]. However, in terms of static balance, no improvements were observed [67]. These inconsistencies in literature, due to the dearth of quality evidence, currently make it difficult to comment on its practicability.

#### 5. Health-related Quality of Life (HRQOL)

Despite the discrepancies in literature in terms of body composition, lipids, and postural control, HIIT has successfully promoted a positive impact on HRQOL among older adults [32,34-37]. HRQOL is vital for an individual's insight into healthy aging [69]. Despite the ambiguity in mechanism, improvement in HRQOL could be hypothesized as a result of changes in body composition, elevation in mood due to the release of endorphins and monoamines [32].

#### Physiological effects of HIIT on mitochondrial function

A decline in nicotinamide adenine dinucleotide (NAD<sup>+</sup>) among aging skeletal muscle is evident due to an upsurge in its breakdown, suggesting that aging may hinder mitochondrial biogenesis [102]. Consequently, skeletal tissue is extremely prone to age-related alterations in response to day-to-day nutrient consumption, physical inactivity, and hormonal influences [80]. The response of HIIT on metabolism in skeletal muscle increases the oxidative capacity of mitochondria [6]. The experimental work of Karlsson and Saltin has examined the molecular effects of HIIT within the skeletal muscle. They observed that while exercising, oxygen consumption and lactate levels increased significantly, but interestingly lactate values did not increase as the exercise load progressed after the first exercise burst [103]. Production of lactic acid and plasma glucose is usually higher following HIIT compared to MICT [104-106]. The need for oxygen in the tissue temporarily increases during HIIT. The rest period restores the oxygen deficit by the local metabolic capacities like CP, ATP and mitochondrial enzymes so that the accumulation of lactic acid is slower, and the onset of fatigue can be delayed [102]. Also, the energy demand of HIIT can activate AMPK, and activation of AMPK enhances cellular metabolism in skeletal muscle, liver, and adipose tissue. Furthermore, AMPK integrates signaling circuits between peripheral tissues and the hypothalamus to regulate food intake and whole-body energy expenditure [102,106,107].

In addition, Robinson et al. investigated the effect of aging and HIIT on isolated mitochondria (derived from human skeletal muscle biopsy sample) by measuring maximum mitochondrial oxygen consumption rate (using high-resolution respirometry) during both resting and fasting. The study revealed that HIIT significantly increased the maximal absolute mitochondrial respiration in both young and older individuals [47]. Collectively, these data suggest that changing or decreasing the content of mitochondrial proteins directly affects the respiratory capacity of mitochondria with aging and HIIT could contribute significantly to this capacity gain. As per available research, HIIT substantially enhanced

platelet citrate synthase (CS) activities and succinate dehydrogenase (SDH), with elevation in respirations related to Complex I and II [108,109]. Followed by HIIT, the oxygen-consuming rate (OCR) in platelets increased, which implies improvements in mitochondrial capacity and increased ATP production rate [110,111].

### Conclusion

This review offers various perspectives on the effects of HIIT on mitochondrial biogenesis and its impact on cardio-metabolic health outcomes in older adults. This analysis also sparks new concepts, studies, and advancements in this area of study. Therefore, we contribute to the growing body of literature that HIIT is a safe, time-efficient, and feasible exercise strategy for improving cardio-metabolic risk markers among the elderly. Furthermore, it has also shown to effectively prevent or delay the onset of comorbidities, thus efficiently contributing to the reversal of functional decline with aging.

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