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SKELETAL MUSCLE TRANSCRIPTIONAL AND REGULATORY SIGNALING ADAPTATIONS TO HIGH-INTENSITY INTERVAL TRAINING VERSUS MODERATE-INTENSITY CONTINUOUS TRAINING: A SYSTEMATIC REVIEW

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ABSTRACT

The p53 (tumor protein 53), mitochondrial transcription factor A (TFAM) and peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) are an integrated network of transcriptional regulators of mitochondrial biogenesis in skeletal muscle. The question of whether high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) produce similar activation of these upstream regulatory pathways in humans is not well understood. A recent meta-regression has synthesized training impacts on mitochondrial content markers but has not considered regulatory signaling particularly. Our search was a systematic review of randomized and quasi-randomized comparative trials on healthy adults to examine the effects of HIIT compared with MICT on transcriptional and regulatory comparative signatures of mitochondrial biogenesis on human skeletal muscle. A structured search strategy in PubMed/MEDLINE, Cochrane CENTRAL, and Embase up to April 2026 was used, including interval training, skeletal muscle, and regulatory signaling outcomes. Two reviewers individually screened 298 deduplicated records, evaluated full texts, and elicited data. Cochrane RoB 2 was used as the instrument to evaluate the risk of bias. There were 4 trials (n=81 good individuals) that passed all the eligibility criteria. PGC-1α was measured in 5 HIIT-versus-comparator comparisons, p53 and TFAM were each measured in 2 comparisons in a single 3-arm trial. HIIT and MICT enhanced the expression of PGC-1α in three of four trials, in which training duration was at least six weeks, and there was no clear difference in effectiveness of either modality. Only the all-out sprint interval training arm activated p53 signaling and PGC-1α, in contrast to work-matched HIIT and continuous training, in a four-week intervention. There was no change of TFAM with any modality. The evidence base is small and does not permit quantitative pooling and additional direct head-to-head comparisons have to be conducted.

KEYWORDS: High-intensity interval training; Sprint interval training; Mitochondrial biogenesis; PGC-1α; Skeletal muscle; Systematic review

INTRODUCTION

Endurance exercise results in an amazing plasticity of skeletal muscle, and the increase in mitochondrial content and oxidative capacity is one of the distinctive adaptations (Lundby and Jacobs, 2016). The peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) -transcriptional coactivator which coordinates the synchronized expression of nuclear and mitochondrial genes encoding electron transport chain components, the tricarboxylic acid cycle, and mitochondrial DNA replication and transcription machinery (Sturm, 2024). These components form a convergence point of the signaling cascade that drives mitochondrial biogenesis (PGC-1α is upstream activated by 5-AMP-activated protein kinase (AMPK), p38 mitogen-activated protein kinase, calcium/calmodulin-dependent protein kinase II (CaMKII) and the tumor suppressor protein 53 (p53), which respond to different aspects of contractile activity including energy stress, calcium flux and oxidative load (Bartlett et al., 2012). Below PGC-1α, mitochondrial transcription factor A (TFAM) and nuclear respiratory factors NRF1 and NRF2 mediate the extension of the mitochondrial proteome and mitochondrial genome replication (Gureev et al., 2019).

Mitochondrial content and aerobic capacity of the human skeletal muscle increase both with moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT). HIIT, alternating intense exercise with periods of rest has gained significant attention since it has the ability to induce similar mitochondrial changes as longer continuous exercise with a much smaller overall exercise volume and time investment (Burgomaster et al., 2008;

Gibala et al., 2009). The most extreme form of this principle is called sprint interval training (SIT), where intervals are conducted at supramaximal or all-out levels (Kavaliauskas, 2022). Whether or not HIIT, SIT, and MICT use the same underlying regulatory machinery is a question of some mechanistic and practical interest, since the same content endpoints in mitochondria may be achievable via a variety of signaling pathways which differ in their longevity or in their cross-bridging with other physiological needs.

Recently, a meta-regression by Mølmen and colleagues synthesized the effects of endurance training, HIIT, and SIT on mitochondrial content and capillarization of skeletal muscle of humans, based on over 350 trials (Mølmen et al., 2025). Their results were based on the indices of mitochondrial content e.g., citrate synthase activity and protein content of cytochrome c oxidase and ratios of capillary to fiber (Mølmen et al., 2025). They reported that SIT elicits especially fast initial improvements in mitochondrial content whereas sustained and high-intensity training persists in inducing content changes in a more gradual but steady manner across longer time courses. Their work, though, did not integrate the upstream transcriptional and regulatory signaling responses that cause such content changes (Mølmen et al., 2025). This difference is mechanistically significant: the mitochondrial content is the cumulative outcome of the biogenesis, whereas regulatory signals like PGC-1α, TFAM, p53 are the signaling stimulus per se. The same two interventions that result in the same content adaptations can act on these regulators in different ways and a synthesis based on signaling can help to explain whether HIIT and MICT activate biogenesis by similar or different molecular mechanisms.

As such, the current systematic review seeks to answer the following question: in healthy adults, how high-intensity interval training versus moderate-intensity continuous training alters transcriptional and regulatory signaling markers of mitochondrial biogenesis in skeletal muscle? Primary outcomes were pre-specified as PGC-1α (mRNA, total protein, nuclear protein or phosphorylation status) and TFAM, and nuclear respiratory factors NRF1 and NRF2. Upstream regulatory kinases and co-regulators, such as AMPK and phospho-AMPK (Thr172), p38 MAPK, p53, CaMKII, sirtuin 1 (SIRT1) and the peroxisome proliferator-activated receptors PPARδ or PPARγ, were used as secondary outcomes. The primary outcome set did not include mitochondrial content markers (citrate synthase, cytochrome c oxidase), or metabolic adaptation markers (glucose transporter type 4, hexokinase II) to keep its scope independent of the current meta-regression.

MATERIAL AND METHODS

Protocol and reporting

The review was done and reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021). The screening was arranged internally before actual screening. Full-text screening completion revealed a recently published meta-regression of similar scope (Mølmen et al., 2025); at that, the outcome measure of the current review was reduced before data extraction to include transcriptional and regulatory signaling markers of mitochondrial biogenesis only and eliminated mitochondrial content and metabolic adaptation markers as a criterion of inclusion. This modification to the protocol was put on paper before data were extracted. The internal protocol can be requested of the respective author.

Eligibility criteria

Population

The studies had to have healthy adult humans who were 18 years and above to qualify. The participants were both trained and untrained; nevertheless, the studies were not of clinical populations such as type 2 diabetes mellitus, cardiovascular disease, chronic obstructive lung disease, chronic kidney disease, cancer, neurological disease, and obesity with metabolic syndrome.

Intervention and comparator

HIIT or SIT at least two weeks in duration was the intervention of interest, which was described as a training regimen of repeated high-intensity bouts, which were at 80% of maximal aerobic power output (Wmax), 80% of maximal oxygen uptake (VO_2max), 85% of maximal heart rate (HRmax), or all-out supramaximal effort, interspersed with active/passive recovery (Westmacott et al., 2022). The comparator was MICT, tradition continuous endurance training, aerobic training or any continuous moderate-intensity exercise at either 55-75 percent of VO_2max or in 60-80 percent of HRmax (Pernick, 2017). The two-arm trials were to be done in the same study in order to be able to compare within the trial.

Outcomes

The main outcomes were transcriptional regulators of mitochondrial biogenesis in skeletal muscle: PGC-1α (mRNA, total protein, nuclear protein, or the state of phosphorylation), TFAM (mRNA or protein), NRF1 and NRF2 (mRNA or protein). Upstream regulatory kinases and co-regulators in skeletal muscle (total and phosphorylated AMPK (Thr172), p38 MAPK, p53, CaMKII, SIRT1, and PPARδ or PPARγ) were the secondary outcomes. Papers which described markers of mitochondrial content only or metabolic enzyme activities only, without an in-scope regulatory or signaling marker, were eliminated.

Study design and other criteria

The designs were limited to eligible designs that were original primary research, parallel HIIT and MICT arms, either randomized controlled trials or non-randomized comparative trials with matched-pair allocation. Excluded were single-arm trials, crossover trials in the absence of parallel comparator arm, secondary bioinformatics analysis, conference abstracts, theses, protocols, narrative review, systematic review, meta-analyses, and editorials, and case reports. Co-intervention studies that confounded the effect of HIIT or MICT such as supplementation, concurrent resistance training or diets were excluded. Only publications in English were eligible.

Information sources and search strategy

Three electronic databases were searched: PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) through Cochrane Library, and Embase through Elsevier. Access to Web of Science, Scopus and SPORTDiscus was limited and thus not searched. The last search was done in April 2026 with no date limit. The search strategy included three concept blocks: high-intensity interval training, skeletal muscle, and transcriptional and regulatory signaling outcomes. MICT comparator block was not included as a search limit since it was identified in pilot searching in order to rule out a large number of eligible trials in which the comparator arm was characterized with legacy terms like endurance training, aerobic training, or the mere control. Status of comparator was determined at title-and-abstract screening. Boolean operators were used in combination with field tags, controlled vocabulary terms (PubMed Medical Subject Headings and Cochrane; Embase Emtree), and free-text searching. Database interface filters used were English language, human studies and adult age. The entire database-specific search queries can be found in Supplementary Table S1.

Study selection and screening

Each database was viewed and the records stored in RIS format were imported into Zotero (Corporation for Digital Scholarship) to manage the records. Internal duplicates were first done within-database, and then cross-database deduplication. The deduplicated record set was uploaded to Rayyan where it was screened (Ouzzani et al., 2016). Titles and abstracts were independently screened by two reviewers using a blind mode to hide the decisions of each reviewer to the other. Before the full round of screening, a calibration round was performed on the first 30 records, during which both reviewers had a perfect agreement (Cohen κ is 1.0) (Sun, 2011). Records that progressed to the full-text screening were accessed via institutional access and direct contact with the person at hand where necessary. Both the reviewers evaluated full texts on their own and compared them with the eligibility criteria. Conflict at the two screening levels was solved through dialogue between the two reviewers without the involvement of a third arbitrator.

Data extraction

Two reviewers independently extracted the data into a structured spreadsheet template, and reconciled by discussion. Fields were extracted (study names, trial design, sample size and sample characteristics per arm, status of training, baseline VO_2max, intensity prescription and protocols per arm), baseline VO_2max and training status, intensive training, baseline VO_2max- normalization, pre and post intervention mean and variance estimates per arm with sample size, between group statistical comparisons and the positions in the source article where each data point was found. In the case of those studies where the pre- and post-intervention values were only reported as graphs and not in tables or the text, the means were estimated by visual inspection of the figures by both reviewers and rounded to one decimal value. Figure-derived estimates are noted with negative numbers as not numerically reported where the type of variance (standard deviation or standard error of the mean) is stated by the authors. The statistical significance and direction of change are reported after the initial analyses.

Risk of bias assessment

The Cochrane risk of bias 2 (RoB 2) tool was used to determine the risk of bias of each included trial that involved randomized and matched-pair randomized trials (Sterne et al., 2019). Five areas were assessed: bias created by randomization procedure, bias created by non-adherence to planned interventions, bias created by absence of outcome data, bias created by measuring the outcome and bias created by choice of the reported outcome. A rating of low risk, some concerns or high risk was assigned to each domain and an overall decision was made on each trial. Both reviewers independently carried out RoB assessment and judgment was reached by discussion (Sterne et al., 2019). Evaluation based on the signaling outcomes on regulation within the context of this review.

Synthesis

Quantitative meta-analysis was not conducted due to the small number of eligible trials and the heterogeneity of regulatory markers, methods of measurement, time of biopsy and training durations across studies. Results are summarized in a narrative way, firstly according to molecular outcome (PGC-1α, p53, TFAM) and secondly by intra-trial between-arm comparison. Direction of change and reported statistical significance are condensed in a tabular form of outcomes. The association between training properties (intervention length, intensity prescriptions, work to comparator) with regulatory marker responses is discussed qualitatively in the Discussion.

RESULTS

Study selection

A total of 449 records were obtained through database searches (145 PubMed/MEDLINE, 136 Cochrane CENTRAL Trials, and 168 Embase). Deduplication in-database detected six in-house duplicates (two in Cochrane CENTRAL and four in Embase), and the number of records was narrowed to 443. Deduplication of cross databases eliminated 144 duplicates. Another cross-database duplicate was found in initial screening and this resulted in a final deduplicated pool of 298 records to undergo title and abstract screening. Among them, 285 records were removed at title and abstract due to the violation of one or more eligibility criteria. The 13 records that were retained were further screened to full-text, of which 9 were excluded based on lack of intervention intensity (n = 2), single-arm design (n = 1), lack of continuous comparator co-intervention by resistance training (n = 1), publication type (secondary bioinformatics analysis, n = 1), and results that were not in the regulatory signaling domain of the review (n = 4). The qualitative synthesis included four trials, which met all eligibility criteria (Burgomaster et al., 2008; Granata et al., 2016; Gunnarsson et al., 2019; Li et al., 2025). Figure 1 shows the PRISMA flow diagram.

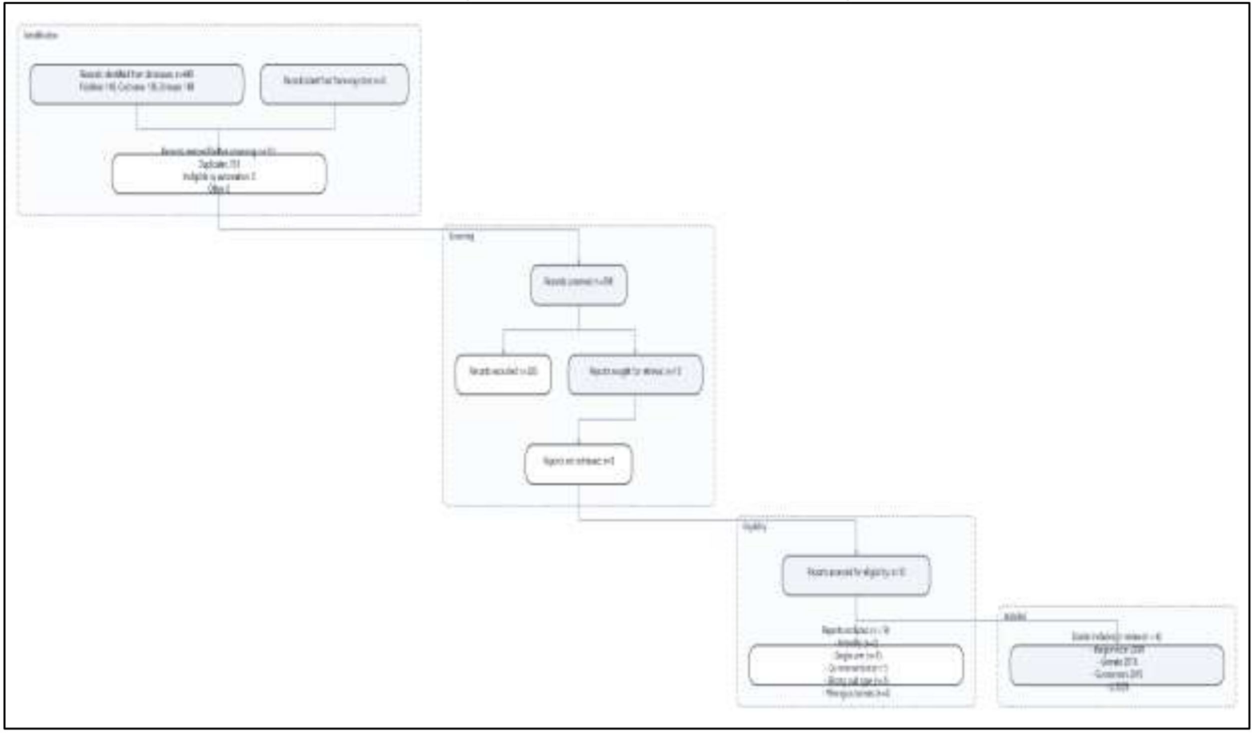

Figure 1. PRISMA 2020 flow diagram for the systematic review of HIIT versus MICT effects on skeletal muscle transcriptional and regulatory signaling markers of mitochondrial biogenesis.

Study characteristics

Table 1 summarizes characteristics of the four included trials. The study involved 81 subjects in the trials of HIIT, SIT, and the continuous comparator. Three of the trials did not include any women (Granata et al., 2016; Gunnarsson et al., 2019; Li et al., 2025), whereas only one trial had both men and women in equal numbers (Burgomaster et al., 2008). Mean ages were an approximation of between 21-26 in arms. The status of training was active (untrained) (Burgomaster et al., 2008), moderately trained (Granata et al., 2016; Li et al., 2025), and physically active and well-trained (Gunnarsson et al., 2019), with a range of baseline VO2peak of about 41 to 54 mL/kg/min. Intervention durations were 4 weeks (Granata et al., 2016), 6 weeks (Burgomaster et al., 2008; Li et al., 2025), and 8 weeks (Gunnarsson et al., 2019). Cycle ergometry was used as an exercise modality in all four trials. All studies yielded vastus lateralis biopsies, and the time of post-intervention biopsy was varying among the four studies; about 2 hours following the last session (Gunnarsson et al., 2019), up to 24, 72 and 96 hours following the last session in the other studies respectively. Two studies reported complete work-matching in the intervention arms (Granata et al., 2016) when comparing HIIT to continuous training; Gunnarsson et al., 2019 and the other two studies did not match work across arms.

Table 1. Characteristics of included studies.

Study	Country	Sex; n (HIIT/MICT)	Training status	HIIT/SIT protocol	Continuous comparator	Wks
Burgomaster et al., 2008	Canada/Australia	M+F; 10/10	Active untrained	SIT: 4–6 × 30 s all-out Wingate; 4.5 min recovery; 3×/wk	ET: 40–60 min at ~65% VO_2peak; 5×/wk	6
Granata et al., 2016	Australia	M; 10–11/10	Moderately trained	SIT: 4–10 × 30 s all-out (4 min recovery); HIIT: 4–7 × 4 min at 90% Wpeak (2 min recovery); 3×/wk	STCT: 20–36 min at 90–97.5% W at lactate threshold; 3×/wk	4
Gunnarsson et al., 2019	Denmark	M; 7/7	Physically active	C+S: 6 × 30 s sprints at near-max W within continuous session; 3×/wk	C: 60 min continuous at ~60% VO_2max; 3×/wk	8
Li et al., 2025	China	M; 10/10	Moderately trained	HIIT: 4 × 4 min at 90% Wmax (3 min active recovery); 4×/wk	MICT: 40 min at 60% Wmax; 4×/wk	6

ET = endurance training; HIIT = high-intensity interval training; M = male; F = female; MICT = moderate-intensity continuous training; SIT = sprint interval training; STCT = sub-threshold continuous training; VO_2peak = peak oxygen uptake; Wmax = maximal aerobic power; Wpeak = peak power; Wks = weeks.

Risk of bias

RoB 2 was used to judge three of the four trials based on low overall risk of bias (Burgomaster et al., 2008; Granata et al., 2016; Li et al., 2025). A single trial was considered to be of low overall risk but with certain issues related to the missing outcome data area (Gunnarsson et al., 2019), which occurred because of the loss of biopsy material in one participant and a post-test missed in another. In the case of Li et al. (2025), the measurement bias of the outcome field was categorized as some concerns; the qPCR results were coded by labeling the samples, but the results with regard to technical replicates and operator Blinding of the in-scope PGC-1α mRNA assay were not reported to the full extent. Table 2 shows domain-level judgments.

Table 2. Risk of bias judgments per RoB 2 domain.

Study	D1 Random.	D2 Deviations	D3 Missing data	D4 Outcome meas.	D5 Reporting	Overall
Burgomaster et al., 2008	Low	Low	Low	Low	Low	Low
Granata et al., 2016	Low	Low	Low	Low	Low	Low
Gunnarsson et al., 2019	Low	Low	Some concerns	Low	Low	Low
Li et al., 2025	Low	Low	Low	Some concerns	Low	Low (some concerns)

D1 = randomization process; D2 = deviations from intended interventions; D3 = missing outcome data; D4 = measurement of the outcome; D5 = selection of the reported result.

Effects on PGC-1α

The total number of included trials that measured PGC-1α was four, providing a total of five comparisons of HIIT-versus-comparator. Two trials were based on the measurement of PGC-1α as messenger RNA (Gunnarsson et al., 2019; Li et al., 2025), and two on its total protein content (Burgomaster et al., 2008; Granata et al., 2016). Table 3 summarizes direction of change and significance of each comparison.

Table 3. PGC-1α responses to HIIT/SIT versus continuous training.

Study	Wks	Marker	HIIT arm	Comparator	HIIT change	Comparator change	Between-arm
Burgomaster 2008	6	Total protein	SIT	ET	↑ ($P < 0.05$)	↑ ($P < 0.05$)	ns
Granata 2016 (a)	4	Total protein	SIT	STCT	↑ ($P = 0.011$)	→ (ns)	$P < 0.05$
Granata 2016 (b)	4	Total protein	HIIT	STCT	→ (ns)	→ (ns)	ns
Gunnarsson 2019	8	mRNA	C+S (sprints)	C	↑ ($P < 0.01$)	↑ ($P < 0.01$)	ns
Li 2025	6	mRNA	HIIT	MICT	↑ ($P = 0.005$)	↑ ($P = 0.033$)	Sig. (HIIT > MICT)

↑ = significant increase; → = no significant change; C = continuous training; C+S = continuous training plus sprints; ET = endurance training; HIIT = high-intensity interval training; MICT = moderate-intensity continuous training; ns = not significant; SIT = sprint interval training; STCT = sub-threshold continuous training; Wks = weeks.

Three studies reported large effects of PGC-1α in the three instances when using HIIT/SIT as well as the continuous comparator, with no statistically significant difference observed between arms. Burgomaster et al. (2008) found that 6 weeks of SIT (4-6 all-out 30-s Wingate sprints per session done three times a week) led to an increased PGC-1α total protein content that was comparable to that of 6 weeks of endurance training (about 65% VO_2peak) done 5 times a week (40-60 minutes a session). The authors emphasized that this resemblance was achieved even in the case when the SIT arm was doing around 90 percent of a lesser training volume in a week than the ET arm (Burgomaster et al., 2008). Gunnarsson et al. (2019) compared 8 weeks of continuous training (60 min at approximately 60% VO_2max) with the same continuous training with 60 seconds sprints per session. The whole-muscle PGC-1α mRNA in both arms was significantly increased at 2 hours following the last session and there was no difference between arms. The authors however observed that downstream mitochondrial protein adaptations (citrate synthase, cytochrome c oxidase) were only observed in the sprint-augmented arm and that similar mRNA responses did not always map onto similar protein-level adaptations (Gunnarsson et al., 2019). Li et al. (2025) compared 6 weeks of HIIT (4 x 4min Wmax 90) and 6 weeks of MICT (40 min Wmax 60) which were carried out four times a week. The increase of PGC-1α mRNA was significant in both arms; however, the HIIT arm increased above the MICT arm at the 6-week time period (Li et al., 2025).

The four-week trial by Granata et al. (2016) is the most informative direct comparison between the intensity forms, due to the fact that three parallel arms were used (SIT, HIIT, and continuous training at close-to-lactate-threshold intensity), with the HIIT and continuous arms matched in terms of total work. The all-out SIT arm was the only one which significantly increased total protein content of PGC-1α ($P = 0.011$); both work-matched HIIT arm at 90% of Wpeak and sub-threshold continuous arm had no significant change (Granata et al., 2016). Between-arm comparison showed that SIT was superior compared to continuous arm ($P < 0.05$), but not between HIIT and continuous comparator. This trend suggests that supramaximal sprint intensity, despite a relatively brief intervention period, caused the PGC-1α activation that could not be replicated by the submaximal high-intensity interventions with equal total work.

Effects on p53

p53 was also only evaluated by Granata et al. (2016), and was also reported as total protein content. Similar to PGC-1α, the SIT arm showed a significant change in protein p53 (approximately 1.9-fold; $p = 0.004$) but neither did the work-matched HIIT arm (approximately 1.5-fold; not significant) nor the sub-threshold continuous arm (approximately 1.1-fold; not significant). The between arm comparison was in favor of SIT as compared to continuous arm; there was no statistically significant HIIT-versus-continuous. The p53 response thereby matched the PGC-1α response during the same trial where only the supramaximal sprint stimulus elicited the activation of both regulators after four weeks (Granata et al., 2016).

Effects on TFAM

Total protein content was only observed in Granata et al. (2016), where TFAM was assessed. None of the three training arms resulted in statistically significant TFAM protein change (SIT about 1.1-fold; HIIT about 1.2-fold; continuous arm about 1.2-fold; all $P > 0.05$). No differences between arms were observed. The lack of TFAM response in the same trial which showed significant PGC-1α and p53 activation in the SIT arm argues that the upstream transcriptional regulators could be activated prior to the identification of a change in TFAM protein content change within a four-week intervention (Granata et al., 2016).

Other regulatory markers

All the four of them do not specify NRF1, NRF2, AMPK or phospho-AMPK (Thr172), p38 MAPK, CaMKII, SIRT1, PPARδ or PPARγ in their eligibility criteria leaving both HIIT and continuous comparator arm pre- and post-intervention values inaccessible. As a result, these markers cannot be synthesized, and this is an evidence gap that the current review presents.

DISCUSSION

The systematic review was an integration of four randomized controlled trials on transcriptional and regulatory signaling adoptions to HIIT and MICT in skeletal muscle of humans. The available evidence brings out two key observations. First, both HIIT and continuous moderate-intensity training enhance mRNA or protein expression of PGC-1α in response to a minimum duration of training (at least six weeks), and the degree of this stimulation is overall similar across the two modes despite the HIIT arm potentially being based on a fraction of the total weekly volume of training the continuous arm. Second, sprint interval training involves PGC-1α and p53 signaling during shorter interventions and at the supramaximal end of the intensity spectrum that work-matched submaximal high-intensity intervals and submaximal continuous training do not. Both of these observations are consistent with each other and indicate that both the period and magnitude of the training stimulus jointly relate to which parts of the regulatory network are recruited and within what time interval.

PGC-1α as a shared endpoint of HIIT and MICT

PGC-1α is generally considered to be the master controller of mitochondrial biogenesis that combines numerous upstream signals that react to the contractile activity (Lin et al., 2005). High or moderate intensity acute exercise has been known to increase PGC-1α to mRNA in human vastus lateralis hours post-exercise indicating a transient transcriptional activation and not a durable protein-level remodeling (Pilegaard et al., 2003). The results that are synthesized here fit that image on the chronic adaptation level: at the same level of six weeks of training (or longer), persistent exposure to HIIT or MICT increases the steady-state level of PGC-1α in a similar manner (Crea, 2024). The trial conducted by Burgomaster et al. (2008) is especially instructive in this regard, as it showed that the PGC-1α protein acquisition was the same, even though the cumulative amount of training per week was significantly lower in the SIT arm as compared to the ET arm. The given volume-independence is mechanistically explainable in case the regulating threshold of the PGC-1α activation is achieved within a high-intensity bouts and is not further increased by further submaximal work below this threshold (Tanaka et al., 2017).

The fact that Gunnarsson et al. (2019) find no differences between whole-muscle PGC-1α mRNA responses between continuous and sprint-augmented training, and find that downstream mitochondrial content adaptations favored the sprint-augmented arm, creates a significant caveat. Single timepoint mRNA levels capture a fleeting transcriptional response as opposed to the accumulated response of the signaling stimulus throughout training (Granata et al., 2016; Tanaka et al., 2017). Variations in the area-under-the-curve of PGC-1α activation across numerous sessions might not be evident in an individual post-training biopsy and still be able to mediate divergent protein-level changes (Pruthi, 2026). This argument states that care should be used when making inferences of training-induced regulatory equivalence using single-timepoint comparisons of mRNA.

Distinct signaling signature of supramaximal sprint training

The only study that compared three intensity levels (all-out SIT, work-matched submaximal HIIT, and sub-threshold continuous training) in the same four-week intervention was the Granata et al. (2016) trial. This increase in PGC-1α and p53 protein content during SIT arm as opposed to neither the HIIT nor continuous arm cannot be explained by the variation in total work since both HIIT and continuous training were specifically work-matched (Granata et al., 2016; Furrer et al., 2023). This, reduces the cumulative work, and makes the intensity of the individual contractions, instead of the cumulative work, the discriminating stimulus during a short intervention. A number of mechanistic candidates may be promoted. Supramaximal contractions cause intracellular ATP depletion and increased AMP which is not attained by submaximal high-intensity work and increases AMPK activation; AMPK can further phosphorylate PGC-1α and stabilize p53 (Arhen et al., 2023). The supramaximal contractions cause larger transient Ca ions in the muscle, which activates CaMKII, and leads to higher fluxes of reactive oxygen species, which have been associated with p38 MAPK and p53 signaling (Gehlert et al., 2015). The question of whether any of these candidate mechanisms can explain the observed response in the data of Granata has no resolution in this synthesis as none of the trials used in this synthesis reported any measurement of AMPK, CaMKII, or p38 in a form that could be extracted. The mechanistic reason behind the SIT signature is therefore a hypothesis generating question to be dealt with in future research.

TFAM and downstream effectors

Only one trial that measured TFAM found no difference with any training arm; although both SIT and p53 arm M measures showed considerable PGC-1α and p53 activation (Granata et al., 2016). This association aligns with TFAM being basal in the PGC-1α-TFAM biogenic signaling cascade and accumulating over a more protracted time frame than the upstream regulators (Abu Shelbayeh et al., 2023). The cumulative regulatory drive may not be enough to be found in a four-week intervention to bring about a change in TFAM protein content that can be detected (Granata et al., 2016). Whether there is a response of TFAM to longer training programs and whether rates of TFAM accumulation are different between training modalities are not answerable based on the data found here. The lack of measurements of NRF1 and NRF2 in the trials included is an important evidence gap as these factors play a central role in mediating PGC-1α -induced nuclear respiratory gene expression.

Relationship to existing synthesis

Recent meta-regression studies like that by Mølmen et al. (2025) integrated more than 350 trials of training effects on the mitochondrial contents and capillarization of human skeletal muscle to report that SIT results in more rapid early effects than content adaptation with prolonged training courses, with continuous endurance and high-intensity training. By considering transcriptional and regulatory signaling but not mitochondrial content, the current review, in addition to the synthesis of content, provides mechanistic support of the upstream stimulus that induces the changes in content. The trend in this case, where rapid SIT-specific activation of PGC-1α and p53 are observed in brief interventions, and the effect of both HIIT and MICT on PGC-1α expression are convergent in longer interventions, is mechanistically consistent with the Mølmen content results. The combination of the two syntheses supports an interpretation where sprint-type stimuli invigorate the regulatory cascade steepest during early training, and prolonged submaximal training induces gradual but continued recruitment of the identical cascade. This interpretation will need longer experiments with serial measurement of regulatory markers in addition to content endpoints to be directly mechanistically confirmed.

Strengths and limitations

This review has a number of strengths. The eligibility criteria were closely established to narrow down to a mechanistic question that is different to the current syntheses. Two independent reviewers, who used structured tools to conduct screening, produced a high inter-rater agreement (Chaturvedi and Shweta, 2015). The in-scope outcomes were consistently assessed using a modern tool to determine the risk of bias. The protocol amendment to reduce the outcomes to regulatory signaling that was done before data were extracted in reaction to the recognition of a recent overlapping meta-regression is recorded publicly.

The synthesis is limited in a number of ways. The access limits were assessed as PubMed/MEDLINE, Cochrane CENTRAL, Embase and therefore instead of four to five sources that were sometimes suggested to be used in a biomedical systematic review, three databases were searched, potentially lowering the sensitivity of the search, but hand-searching of reference lists of included trials and the Mølmen et al. (2025) review did not yield any more eligible trials. Second, the restrictive outcome scope resulted in 4 eligible trials, which did not permit any quantitative pooling and implied that various pre-specified secondary outcomes (NRF1, NRF2, AMPK, p38 MAPK, CaMKII, SIRT1) were not reported in any of the included trials. Third, a number of pre-intervention values needed to be estimated based on graphical data instead of being obtained by reading numerical data in a text or table; these estimates were rounded to a single decimal point and were only used to summarize the direction of change and not to make any quantitative argument. Fourth, the timing of the biopsy was highly inconsistent across the included trials (between about two hours and 96 hours following the last session), indicating the heterogeneity of the experimental priorities (acute response versus stable adaptation) and making comparison of trials across which the biopsy was performed more difficult; again this is a characteristic of the underlying literature rather than of the synthesis itself, but dilutes the strength of any inference about chronic adaptation Fifth, the three out of four trials used only men, and it is only possible to generalize the findings to women. Lastly, the majority of the participants were young adults; the regulatory responses of older adults that are depicted in this context are still unknown.

Implications and future directions

The synthesized findings have some practical and research implications. When training is prolonged, both HIIT and MICT can be anticipated to induce PGC-1α-mediated mitochondrial biogenesis, and the modality selection can be informed by factors other than regulatory equivalence (time efficiency, perceived exertion, adherence, joint loading) (Granata et al., 2016; Vabishchevich et al., 2026). Sprint interval training can provide a highly beneficial early signal to activate the PGC-1α/p53 axis in untrained or moderately trained athletes, but the ergonomic and tolerability limits of all-out cycling are after all (Granata et al., 2016; Taylor et al., 2016). In the case of mechanistic research, lack of trials reporting entire upstream signaling cascade (AMPK phosphorylation, p38 MAPK, CaMKII, p53, SIRT1) and PGC-1α in the same biopsy material under work-matched comparison conditions comparing HIIT, SIT and MIC is the main evidence gap. These experiments, preferably with enough time to measure acute and stable adaptation timepoints, with both sexes and a variety of training conditions, would clarify the issue on whether HIIT and SIT differ on the molecular pathways of reaching the same or different mitochondrial content endpoints.

CONCLUSION

Four randomized comparative trials of 81 healthy adults showed that with at least six weeks of sustained training, HIIT and MICT induced skeletal muscle PGC-1α expression that was otherwise widely comparable. During a shorter intervention duration, supramaximal sprint interval training was able to elicit PGC-1α and p53 signaling in a way that was not mirrored by work-matched submaximal high-intensity interval training or by continuous moderate-intensity training. The only trial that measured TFAM did not differ between modalities. The existing body of evidence concurs with the idea that the regulatory cascade of mitochondrial biogenesis is recruited intensity-dependently over time but due to the limited number of evidence pieces, the lack of age and sex distribution, and the lack of upstream signaling kinases being reported, several pieces of the mechanism remain unclear. To describe the molecular signature of the difference between sprint, high-intensity, and continuous training adaptations, trials that report the entire upstream signaling cascade of PGC-1α in the presence of work conditions matched to those of the study are required.

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SUPPLEMENTARY MATERIAL

Table S1. Database-specific search strategies for PubMed/MEDLINE, Cochrane CENTRAL, and Embase, including controlled-vocabulary terms and field tags.

Table S2. Study-level extracted data including population, intervention protocol, biopsy details, and outcome values for the four included trials.