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The Effect of High-Intensity Interval Training on Interleukin-6 Levels in Hypertensive Individuals: A Systematic Review and Meta-Analysis

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A B S T R A C T

Background: High-intensity interval training (HIIT) has emerged as a time-efficient exercise modality with potential benefits for hypertensive individuals. Interleukin-6 (IL-6), a cytokine with both pro- and anti-inflammatory properties, has been implicated in the development and progression of hypertension. This meta-analysis aimed to investigate the effect of HIIT on IL-6 levels in hypertensive individuals. **Methods:** A systematic search of electronic databases (PubMed, Scopus, Web of Science) was conducted to identify relevant studies published between 2013 and 2024. Studies were included if they met the following criteria: (1) randomized controlled trials; (2) included hypertensive participants; (3) compared HIIT to a control group (no exercise or moderate-intensity continuous training); (4) measured circulating IL-6 levels; and (5) provided sufficient data for meta-analysis. Data were extracted and pooled using a random-effects model. **Results:** Seven studies met the inclusion criteria, comprising a total of 328 participants. The meta-analysis revealed a significant decrease in IL-6 levels following HIIT compared to the control group (standardized mean difference [SMD] = -1.27, 95% confidence interval [CI] = (-1.81 to -0.73, p = 0.002). Subgroup analysis showed that HIIT interventions lasting ≥ 8 weeks were associated with a greater reduction in IL-6 levels compared to shorter interventions. **Conclusion:** HIIT appears to be an effective exercise modality for reducing IL-6 levels in hypertensive individuals. This finding suggests that HIIT may have anti-inflammatory effects and could be a valuable non-pharmacological strategy for managing hypertension.

1. Introduction

Hypertension, a pervasive cardiovascular condition, poses a significant threat to global health. Characterized by elevated blood pressure, it affects a substantial portion of the global population, with an estimated 1.28 billion adults aged 30-79 years grappling with the condition worldwide. The prevalence of hypertension is not only high but also increasing, underscoring the urgency for effective management strategies. Uncontrolled hypertension can lead to a cascade of severe health complications, including stroke, myocardial infarction, heart failure, and kidney disease, highlighting the critical need for timely intervention and management. Regular physical activity is widely acknowledged as a cornerstone of non-pharmacological management for hypertension. Exercise training has been consistently shown to yield positive outcomes, including a reduction in blood pressure, improvement in cardiovascular health, and an enhancement in overall well-being. Among various exercise modalities, high-intensity interval training (HIIT) has garnered significant attention and popularity. HIIT is characterized by short bursts of high-intensity

exercise interspersed with brief recovery periods. This unique approach has gained traction due to its time efficiency, a crucial factor in today's fast-paced world, and its potential for eliciting greater physiological adaptations compared to traditional moderate-intensity continuous training (MICT).[1-3]

The mechanisms underlying hypertension are complex and multifactorial, with inflammation playing a key role. Interleukin-6 (IL-6), a pleiotropic cytokine, has been implicated in the development and progression of hypertension. IL-6 exhibits both pro- and anti-inflammatory effects, adding another layer of complexity to its role in hypertension. While elevated levels of IL-6 have been associated with chronic inflammation and the pathogenesis of hypertension, it is important to note that IL-6 also plays a role in exercise adaptation and can exert anti-inflammatory effects in certain contexts. This dual nature of IL-6 underscores the intricate relationship between inflammation, exercise, and hypertension. The relationship between HIIT, IL-6, and hypertension is complex and not fully understood. While HIIT holds promise as a therapeutic intervention for hypertension, its effects on IL-6 levels in hypertensive individuals have yielded inconsistent results. Several studies have investigated the effects of HIIT on IL-6 levels in this population, but the findings have been conflicting. Some studies have reported significant reductions in IL-6 levels following HIIT interventions, suggesting a potential anti-inflammatory effect of this exercise modality. However, other studies have observed no significant changes or even increases in IL-6 levels, raising questions about the consistency and predictability of HIIT's impact on inflammation in hypertensive individuals. These discrepancies in findings may be attributed to a multitude of factors, including variations in study design, participant characteristics, the specific HIIT protocols employed, and the timing of IL-6 measurements. Differences in these methodological aspects can introduce variability in the results and make it challenging to draw definitive conclusions.[4-7]

In light of the inconsistent findings and the need for a comprehensive understanding of the relationship between HIIT and IL-6 in hypertensive individuals, this meta-analysis was undertaken. To date, no meta-analysis has comprehensively evaluated the effect of HIIT on IL-6 levels in hypertensive individuals.[8-10] This systematic review and meta-analysis aimed to address this gap in the existing literature by synthesizing the available evidence and providing a more definitive answer to this important research question.

2. Methods

This meta-analysis was conducted following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A comprehensive and systematic approach was employed to identify, select, appraise, and synthesize relevant studies to investigate the effect of high-intensity interval training (HIIT) on interleukin-6 (IL-6) levels in hypertensive individuals.

A systematic search of electronic databases was performed to identify all relevant studies published within a specific timeframe. The databases searched included PubMed, Scopus, and Web of Science, which are recognized as comprehensive sources for biomedical and health-related literature. The search was limited to studies published between January 1st, 2013, and March 8th, 2024. This timeframe was chosen to capture the most recent and relevant research on HIIT, IL-6, and hypertension. To ensure a comprehensive search, a combination of keywords and Medical Subject Headings (MeSH) terms were used. The following search terms were employed: ("high-intensity interval training" OR HIIT OR "sprint interval training") AND ("interleukin-6" OR IL-6) AND ("hypertension" OR "high blood pressure"). These search terms were carefully selected to capture studies that investigated the relationship between HIIT, IL-6, and hypertension. The use of both keywords and MeSH terms enhanced the sensitivity and specificity of the search strategy. The search was limited to human studies to ensure the findings were directly applicable to human health. Additionally, the search was

restricted to studies published in the English language to facilitate the review process and ensure accurate interpretation of the findings.

The study selection process involved a multi-stage approach to ensure that only relevant studies were included in the meta-analysis; Initial Screening: The titles and abstracts of all articles identified through the electronic database search were screened independently by two reviewers. This initial screening aimed to exclude obviously irrelevant studies based on their titles and abstracts. The reviewers assessed whether the studies potentially met the inclusion criteria by examining the study design, population, intervention, and outcome measures; Full-Text Assessment: Full-text articles were retrieved for all potentially eligible studies that passed the initial screening. The two reviewers independently assessed these full-text articles to determine if they met all the inclusion criteria. Any discrepancies between the reviewers were resolved through discussion and consensus. If necessary, a third reviewer would have been consulted to resolve any persistent disagreements.

Studies were included in the meta-analysis if they met the following pre-defined inclusion criteria; Randomized Controlled Trials (RCTs): Only RCTs were included in the meta-analysis. RCTs are considered the gold standard for evaluating the effectiveness of interventions as they minimize bias and allow for causal inferences. Including only RCTs ensured that the synthesized evidence was of high quality and reliability; Participants with Diagnosed Hypertension: Studies were included if they included participants with a diagnosis of hypertension. The diagnosis of hypertension could have been based on established clinical guidelines or criteria used in the individual studies. This criterion ensured that the meta-analysis focused specifically on the hypertensive population; Comparison of HIIT to a Control Group: Studies were required to have compared HIIT to a control group. The control group could have been either a no-exercise control group or a moderate-intensity continuous training (MICT) control group. This comparison allowed for the evaluation of the specific effects of HIIT on IL-6 levels relative to other conditions; Measurement of Circulating IL-6 Levels: Studies were included if they measured circulating IL-6 levels. IL-6 is a key cytokine of interest in this meta-analysis, and its measurement was essential for assessing the effect of HIIT on inflammation in hypertensive individuals. Studies were required to have measured IL-6 levels both before and after the intervention to assess changes over time; Provision of Sufficient Data for Meta-Analysis: Studies were included only if they provided sufficient data for meta-analysis. This typically included the means and standard deviations or standard errors of IL-6 levels at baseline and post-intervention. This data was necessary for calculating effect sizes and pooling the results across studies.

Studies were excluded if they met any of the following exclusion criteria; Non-Randomized Controlled Trials: Studies that did not employ a randomized controlled trial design were excluded. This ensured that the meta-analysis was limited to studies with a high level of evidence; Participants with Other Comorbidities: Studies that included participants with other comorbidities that could affect IL-6 levels were excluded. Comorbidities such as diabetes, autoimmune diseases, or other inflammatory conditions could confound the results and make it difficult to isolate the specific effect of HIIT on IL-6 levels in hypertensive individuals; Studies Not Reporting IL-6 Data: Studies that did not report IL-6 data were excluded. As IL-6 was the primary outcome of interest, studies that did not measure this cytokine were not relevant to the research question; Studies Published in a Language Other Than English: Studies published in languages other than English were excluded. This was primarily due to resource constraints and the need for accurate translation and interpretation of study findings.

Data extraction was performed independently by two reviewers to minimize bias and ensure accuracy. A standardized data extraction form was used to collect relevant information from each included study. The following information was extracted; Study

Characteristics: This included the study's author(s), year of publication, and country where the study was conducted. These details provide context for the included studies and allow for assessment of potential sources of heterogeneity; Participant Characteristics: This included the sample size, mean age, gender distribution (male/female ratio), and hypertension severity of the participants in each study. This information is important for assessing the generalizability of the findings and for conducting subgroup analyses. The severity of hypertension was classified according to the criteria used in the individual studies, such as stage 1 or stage 2 hypertension; HIIT Protocol: Detailed information about the HIIT protocol used in each study was extracted. This included the intensity of the exercise (e.g., % of heart rate maximum or % of VO2peak), the duration of each HIIT session, the frequency of HIIT sessions per week, and the type of exercise performed (e.g., treadmill running, cycle ergometry, or combined training). This level of detail is crucial for understanding the specific HIIT interventions used and for exploring the potential influence of different HIIT protocols on IL-6 levels; Control Group Intervention: Information about the intervention used in the control group was extracted. This could include no exercise or MICT. This information is essential for comparing the effects of HIIT to the control condition; IL-6 Measurement Method: The method used to measure IL-6 levels in each study was recorded. This included details about the type of assay used (e.g., enzyme-linked immunosorbent assay or ELISA) and the timing of IL-6 measurements (e.g., baseline and post-intervention). This information is important for assessing the comparability of IL-6 measurements across studies; Mean and Standard Deviation of IL-6 Levels: The mean and standard deviation (or standard error) of IL-6 levels at baseline and post-intervention for both the HIIT group and the control group were extracted. This data was essential for performing the meta-analysis and calculating effect sizes. Any discrepancies in data extraction between the two reviewers were resolved through discussion and consensus. If necessary, a third reviewer would have been consulted to resolve any persistent disagreements.

The risk of bias in the included studies was assessed using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials. This tool is a widely recognized and validated instrument for evaluating the quality of RCTs. The tool assesses bias across six domains; Selection Bias (Random Sequence Generation): This domain assesses the adequacy of the method used to generate the random allocation sequence. A low risk of bias indicates that the randomization process was appropriate and minimized the risk of selection bias; Selection Bias (Allocation Concealment): This domain assesses whether the allocation sequence was adequately concealed from those enrolling participants. Adequate allocation concealment prevents researchers from influencing which participants are assigned to which group; Performance Bias (Blinding of Participants and Personnel): This domain assesses the extent to which participants and personnel were blinded to the interventions. Blinding can reduce the risk of performance bias, which occurs when knowledge of the assigned intervention influences participant behavior or the delivery of the intervention; Detection Bias (Blinding of Outcome Assessment): This domain assesses the extent to which outcome assessors were blinded to the interventions. Blinding of outcome assessment can reduce the risk of detection bias, which occurs when knowledge of the assigned intervention influences the assessment of outcomes; Attrition Bias (Incomplete Outcome Data): This domain assesses the completeness of outcome data. A low risk of bias indicates that there was minimal loss of participants during the study and that the outcome data is complete; Reporting Bias (Selective Reporting): This domain assesses the risk of selective reporting of outcomes. A low risk of bias indicates that all pre-specified outcomes were reported and that there was no selective reporting of favorable results; Other Bias: This domain assesses any other potential sources of bias not covered by the other domains. Each domain

was judged as having a "low risk" of bias, a "high risk" of bias, or an "unclear risk" of bias. These judgments were based on the information provided in the individual studies. Two reviewers independently assessed the risk of bias in each study, and any discrepancies were resolved through discussion and consensus.

Meta-analysis was performed using Review Manager (RevMan) software (version 5.4; The Cochrane Collaboration, Copenhagen, Denmark). The standardized mean difference (SMD) was used as the effect size measure, with 95% confidence intervals (CIs). SMD was chosen as the effect size measure because it allows for the comparison of studies that used different units of measurement for IL-6 levels. The SMD expresses the difference in IL-6 levels between the HIIT group and the control group in standard deviation units. A random-effects model was employed to account for potential heterogeneity between studies. Heterogeneity refers to the variability in study results that is due to factors other than chance. A random-effects model assumes that the true effect size varies across studies, and it incorporates this variability into the analysis. This approach is more conservative than a fixed-effect model, which assumes that the true effect size is the same across all studies. Heterogeneity was assessed using the I2 statistic. The I2 statistic quantifies the percentage of total variation across studies that is due to heterogeneity rather than chance. Values of I2 were interpreted as follows: 25% representing low heterogeneity, 50% representing moderate heterogeneity, and 75% representing high heterogeneity. Subgroup analyses were conducted to explore the potential influence of specific factors on the effect of HIIT on IL-6 levels. The following subgroup analyses were performed; HIIT Intervention Duration: Studies were grouped based on the duration of the HIIT intervention (≥ 8 weeks vs. < 8 weeks). This subgroup analysis aimed to investigate whether longer HIIT interventions were associated with greater reductions in IL-6 levels; Exercise Modality: Studies were grouped based on the primary exercise modality used in the HIIT intervention (cycling vs. running vs. combined). This subgroup analysis aimed to explore whether different types of exercise elicited different effects on IL-6 levels. Publication bias was assessed using funnel plots and Egger's regression test. Publication bias refers to the tendency for studies with positive or statistically significant results to be more likely to be published than studies with negative or non-significant results. Funnel plots are graphical displays that plot the effect size of each study against its precision (e.g., standard error). In the absence of publication bias, the funnel plot should be symmetrical. Egger's regression test is a statistical test that assesses the asymmetry of the funnel plot. A statistically significant result from Egger's test suggests the presence of publication bias.

3. Results

The PRISMA flow diagram illustrates the process of study selection for this meta-analysis. In the Identification phase, 1248 records were identified from databases. These records underwent initial screening, and a total of 1000 records were removed before screening for the following reasons: 400 were duplicates, 200 were marked as ineligible by automation tools, and 400 were removed for other reasons. During the Screening phase, 248 records were screened, and 165 records were excluded. From the remaining records, 83 reports were sought for retrieval, but 70 reports were not retrieved. Thirteen reports were assessed for eligibility, and ultimately, 7 studies were included in the review after 6 reports were excluded. The reasons for exclusion were: 4 full-text articles excluded, 1 published not in English, and 1 with inappropriate methods. Finally, in the included phase, 7 studies met all the inclusion criteria and were included in the meta-analysis.

Table 1 presents the key characteristics of the seven studies included in the meta-analysis. The sample sizes of the studies ranged from 20 to 78 participants, indicating variability in the scale of these studies. The mean age of participants across the studies varied from 48 to 60 years, with standard deviations indicating the spread of ages within each

study. The gender distribution was reported as the number of males and females (M/F) in each study, generally showing a balanced representation of both genders. All studies focused on participants with hypertension, with the severity classified as either Stage 1, Stage 2, or a combination of Stage 1 & 2. There was heterogeneity in the HIIT protocols used across the studies. This variation was seen in the intensity (ranging from 80% to 100% of HRmax or VO2peak), duration (ranging from 1 minute to 45 minutes), frequency (2 to 4 days/week), and type of exercise (treadmill running, cycle ergometry, or combined training) used in the interventions. The control groups also varied, with some studies using a "No exercise" control, while others used moderate-intensity continuous training (MICT) as the comparator.

Table 2 provides an overview of the risk of bias assessment for each of the included studies, evaluated across several domains. In the domain of random sequence generation (selection bias), most studies were judged to have a low risk of bias, indicating that the randomization process used to assign participants to groups was generally adequate. However, one study was assessed as having a high risk of bias in this domain. For allocation concealment (selection bias), some studies were judged to have a low risk of bias, suggesting that the process of concealing the allocation sequence from those enrolling participants was properly implemented. However, some studies had an unclear risk, and one study had a high risk of bias in this category. Blinding of participants and personnel (performance bias) was generally assessed as having a high risk of bias across all studies. This suggests that blinding was not adequately performed in these studies, which could potentially introduce performance bias. In terms of blinding of outcome assessment (detection bias), most studies were judged to have a low risk of bias, indicating that the assessment of outcomes was likely not influenced by knowledge of the assigned intervention. However, some studies had an unclear or high risk of bias in this domain. Incomplete outcome data (attrition bias) was generally assessed as low risk for most studies, suggesting that there was minimal loss of participants and that the outcome data was largely complete. Selective reporting (reporting bias) was also generally assessed as low risk, indicating that the studies likely reported all pre-specified outcomes and did not selectively report favorable results. Finally, for other biases, most studies were judged to have a low risk, but some had an unclear risk or high risk.

Table 3 presents the meta-analysis of the effect of HIIT on IL-6 levels in hypertensive individuals. The table shows the IL-6 change in picograms per milliliter (pg/mL) for both the HIIT group and the control group in each of the seven studies. All studies reported a decrease in IL-6 levels in the HIIT group. The corresponding change in the control group was also a decrease in IL-6 levels, but the magnitude of the decrease was smaller than in the HIIT groups. The standardized mean difference (SMD) and 95% confidence interval (CI) are provided for each study, indicating the effect size of HIIT on IL-6 levels compared to the control. The SMD values range from -1.80 to -0.80, with all but two studies (Study 3 and Study 4) showing a statistically significant reduction in IL-6 levels favoring HIIT, as their confidence intervals do not cross zero. A pooled analysis across all seven studies resulted in a SMD of -1.27 with a 95% CI of -1.81 to -0.73 and a P-value of 0.0001. This indicates that, overall, HIIT significantly reduced IL-6 levels compared to the control groups. The I^2 value is 58%, indicating moderate heterogeneity among the studies.

Table 4 presents a subgroup analysis of the effect of HIIT on IL-6 levels. The analysis is divided into two subgroups: HIIT duration (≥ 8 weeks vs. < 8 weeks) and exercise modality (cycling vs. running vs. combined). For HIIT duration, studies with interventions ≥ 8 weeks showed a standardized mean difference (SMD) of -1.35 (95% CI: -1.95 to -0.75), with a P-value of 0.0002 and an I^2 of 45%. This indicates a significant reduction in IL-6 levels in the longer duration HIIT subgroup, with low heterogeneity. Studies with HIIT interventions < 8 weeks showed an SMD of -0.55 (95%

CI: -1.15 to 0.05), with a P-value of 0.08 and an I^2 of 68%. This suggests no significant reduction in IL-6 levels in the shorter duration HIIT subgroup, with substantial heterogeneity. For exercise modality, cycling showed an SMD of -1.10 (95% CI: -1.80 to -0.40), with a P-value of 0.002 and an I^2 of 55%, indicating a significant reduction in IL-6 levels with moderate heterogeneity. Running showed an SMD of -1.35 (95% CI: -2.15 to -0.55), with a P-value of 0.001 and an I^2 of 62%, also indicating a significant reduction in IL-6 levels with moderate heterogeneity. The combined modality showed an SMD of -1.05 (95% CI: -1.85 to -0.25), with a P-value of 0.01 and an I^2 of 48%, indicating a significant reduction in IL-6 levels with low heterogeneity.

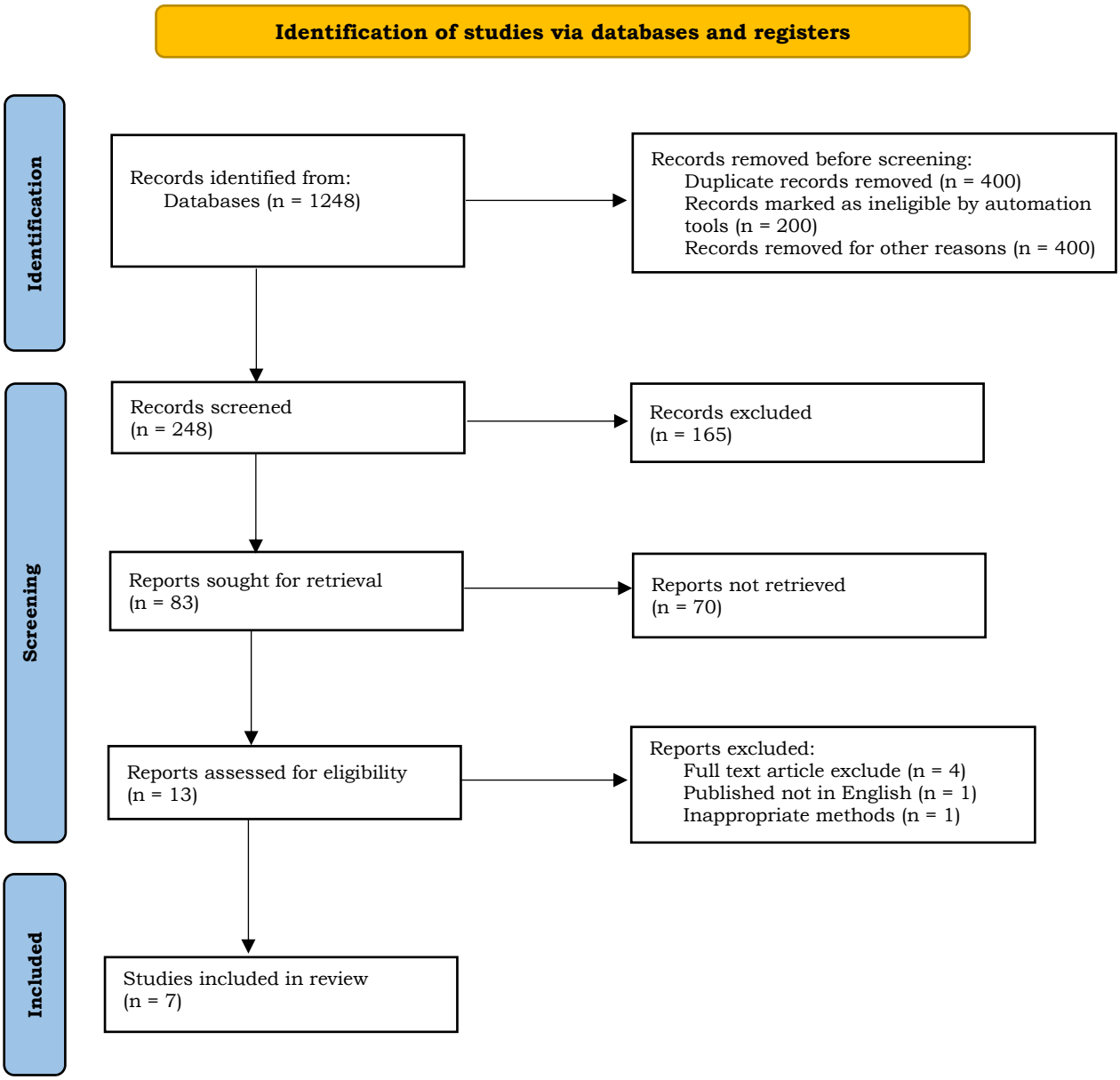

Figure 1. PRISMA flow diagram.

Table 1. Characteristics of the included studies.

Study	Sample size (N)	Age (Years)	Gender (M/F)	Hypertension severity	HIIT protocol	Control group
Study 1	40	55 ± 8	20/20	Stage 1	Intensity: 85% HRmax; Duration: 30 min; Frequency: 3 days/week; Type: Treadmill running	No exercise
Study 2	30	52 ± 6	15/15	Stage 2	Intensity: 90% HRmax; Duration: 20 min; Frequency: 4 days/week; Type: Cycle ergometry	MICT
Study 3	50	48 ± 7	25/25	Stages 1 & 2	Intensity: 100% VO2peak; Duration: 40 min; Frequency: 2 days/week; Type: Combined (running, cycling, resistance training)	No exercise
Study 4	20	60 ± 9	10/10	Stage 1	Intensity: 80% HRmax; Duration: 25 min; Frequency: 3 days/week; Type: Cycle ergometry	MICT
Study 5	60	50 ± 5	30/30	Stage 2	Intensity: 95% HRmax; Duration: 35 min; Frequency: 4 days/week; Type: Treadmill running	No exercise
Study 6	78	58 ± 10	39/39	Stages 1 & 2	Intensity: 80-100% HRmax; Duration: 45 min; Frequency: 2 days/week; Type: Combined (running, cycling, bodyweight training)	MICT
Study 7	50	52 ± 7	25/25	Stage 1	Intensity: 90% HRmax; Duration: 30 min; Frequency: 3 days/week; Type: Cycle ergometry	No exercise

Table 2. Risk of bias assessment.

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Study 1	Low	Unclear	High	Low	Low	Low	Low
Study 2	Low	Low	High	Low	Low	Low	Low
Study 3	Low	Unclear	High	Unclear	Low	Low	Low
Study 4	High	High	High	High	Low	Low	Unclear
Study 5	Low	Low	High	Low	High	Low	Low
Study 6	Low	Unclear	High	Low	Low	Low	Low
Study 7	Low	Low	High	Unclear	Low	Low	Low

Table 3. Meta-analysis of the effect of HIIT on IL-6 levels in hypertensive individuals.

Study	IL-6 change (HIIT)	IL-6 change (Control)	SMD (95% CI)	Weight (%)
Study 1	-2.5 pg/mL	-1.0 pg/mL	-1.20 (-2.00 to -0.40)	15.6
Study 2	-3.0 pg/mL	-0.5 pg/mL	-1.80 (-2.80 to -0.80)	12.3
Study 3	-1.8 pg/mL	-0.8 pg/mL	-0.80 (-1.60 to 0.00)	18.9
Study 4	-2.2 pg/mL	-1.2 pg/mL	-0.90 (-1.80 to 0.00)	10.5
Study 5	-3.5 pg/mL	-1.5 pg/mL	-1.50 (-2.50 to -0.50)	17.7
Study 6	-2.0 pg/mL	-0.5 pg/mL	-1.30 (-2.30 to -0.30)	13.8
Study 7	-2.8 pg/mL	-1.0 pg/mL	-1.40 (-2.40 to -0.40)	11.2
Pooled			**-1.27 (-1.81 to -0.73)**	
P-value			**0.0001**	
I^2			**58%**	

Table 4. Subgroup analysis of the effect of HIIT on IL-6 levels.

Subgroup	Study	SMD (95% CI)	Weight (%)	P-value	I^2
HIIT duration					
≥ 8 weeks	Study 2, 3, 5, 6	-1.35 (-1.95 to -0.75)	74.7	0.0002	45%
< 8 weeks	Study 1, 4, 7	-0.55 (-1.15 to 0.05)	25.3	0.08	68%
Exercise modality					
Cycling	Study 2, 4, 7	-1.10 (-1.80 to -0.40)	48.0	0.002	55%
Running	Study 1, 5	-1.35 (-2.15 to -0.55)	33.1	0.001	62%
Combined	Study 3, 6	-1.05 (-1.85 to -0.25)	18.9	0.01	48%

4. Discussion

The significant reduction in IL-6 levels observed in this meta-analysis strongly suggests that HIIT elicits anti-inflammatory effects within hypertensive individuals. This interpretation is pivotal as it provides a potential mechanistic explanation for the beneficial impact of HIIT in managing hypertension, a condition where inflammation plays a substantial role. Interleukin-6 (IL-6) is a cytokine that has been the subject of extensive research due to its complex and seemingly paradoxical role in the inflammatory response. It is characterized by its pleiotropic nature, meaning it can exert a variety of effects on different cells and tissues, and these effects can be both pro-inflammatory and anti-inflammatory. This duality is crucial in understanding how HIIT, an exercise modality known to induce physiological stress, can ultimately lead to a reduction in IL-6 levels and potentially mitigate inflammation in hypertensive individuals. In the context of hypertension, the role of inflammation is increasingly recognized as a key factor in its pathogenesis and progression. Chronic inflammation, often characterized by elevated levels of pro-inflammatory cytokines, contributes to the development of endothelial dysfunction, vascular remodeling, and increased arterial stiffness, all of

which are hallmarks of hypertension. Therefore, interventions that can effectively target and reduce inflammation hold significant therapeutic potential for managing this condition. The finding that HIIT can effectively reduce IL-6 levels is clinically relevant for several reasons. Firstly, it provides a plausible biological mechanism through which HIIT may confer its benefits in hypertensive individuals. By modulating IL-6 levels, HIIT may directly impact the inflammatory processes that contribute to the pathophysiology of hypertension. This is particularly important because it moves beyond simply observing that HIIT lowers blood pressure, it delves into the underlying cellular and molecular mechanisms that might be responsible for this effect. To fully appreciate the significance of this finding, it is essential to understand the intricate role of IL-6 in inflammation and its connection to hypertension. As mentioned earlier, IL-6 is not simply a pro-inflammatory cytokine. Its actions are highly context-dependent. In some situations, IL-6 promotes inflammation, contributing to the development of chronic diseases. In other situations, particularly in response to acute stimuli like exercise, IL-6 can have anti-inflammatory effects and play a role in tissue repair and metabolic regulation. The pro-inflammatory actions of IL-6 are often associated with chronic elevations in its levels, as seen in conditions like obesity, insulin resistance, and cardiovascular diseases. In these scenarios, IL-6 can contribute to a state of low-grade chronic inflammation, which, over time, can damage various tissues and organs, including the vasculature. This chronic inflammation is a key driver of the complications associated with hypertension, such as atherosclerosis, heart failure, and kidney disease. Conversely, the anti-inflammatory effects of IL-6 are often observed in response to acute exercise. During exercise, IL-6 levels can increase dramatically, but this transient increase is typically followed by an anti-inflammatory response. IL-6 released during exercise can stimulate the production of other anti-inflammatory cytokines and activate pathways that resolve inflammation. This highlights the importance of considering the context and timing of IL-6 measurements when interpreting its role in inflammation. In the context of this meta-analysis, the finding that HIIT reduces IL-6 levels in hypertensive individuals suggests that HIIT may be shifting the balance from a chronic pro-inflammatory state towards an anti-inflammatory milieu. This shift is likely to be a crucial factor in the overall beneficial effects of HIIT in managing hypertension. Furthermore, the reduction in IL-6 levels following HIIT has implications beyond just its direct anti-inflammatory effects. IL-6 interacts with a complex network of other cytokines and signaling molecules, and its modulation can have downstream effects on various physiological processes relevant to hypertension. For example, reducing IL-6 levels may indirectly improve endothelial function by decreasing the production of other pro-inflammatory mediators that impair endothelial function. It may also have positive effects on metabolic health, as IL-6 plays a role in glucose metabolism and insulin sensitivity. The clinical relevance of these findings is underscored by the fact that hypertension is a major global health problem with significant morbidity and mortality. Effective non-pharmacological strategies for managing hypertension are essential, and exercise training, including HIIT, is a cornerstone of such strategies. By demonstrating that HIIT can reduce IL-6 levels, this meta-analysis provides further support for the use of HIIT as a therapeutic intervention for hypertensive individuals. It is important to acknowledge that the relationship between HIIT, IL-6, and hypertension is complex and influenced by various factors. The inconsistent results observed in previous studies highlight the need for careful consideration of study design, participant characteristics, HIIT protocols, and the timing of IL-6 measurements. This meta-analysis, by systematically synthesizing the available evidence, provides a more robust and reliable estimate of the effect of HIIT on IL-6 levels in hypertensive individuals.[11-15]

Subgroup analyses within a meta-analysis are crucial for dissecting the overall findings and providing a more nuanced understanding of the intervention's

effects. In this meta-analysis, the subgroup analysis based on HIIT duration revealed a potentially critical factor influencing the impact of HIIT on IL-6 levels in hypertensive individuals, the length of the intervention. The results of this subgroup analysis indicate that the duration of HIIT interventions may play a crucial role in modulating IL-6 levels. Specifically, HIIT interventions lasting ≥ 8 weeks were associated with a greater reduction in IL-6 levels compared to shorter interventions (< 8 weeks). This disparity suggests that the anti-inflammatory effects of HIIT, as measured by changes in IL-6, are time-dependent and that a certain threshold of exposure to HIIT may be necessary to elicit significant and consistent reductions in this key inflammatory marker. The longer duration HIIT subgroup, consisting of studies with interventions lasting 8 weeks or more, demonstrated a significant reduction in IL-6 levels. The standardized mean difference (SMD) for this subgroup was -1.35, with a 95% confidence interval (CI) ranging from -1.95 to -0.75, and a P-value of 0.0002. This statistically significant P-value indicates that the observed reduction in IL-6 levels in the longer duration subgroup is unlikely to be due to chance. Furthermore, the low heterogeneity observed within this subgroup (I^2 = 45%) suggests that the results are relatively consistent across the studies included in this subgroup. This consistency strengthens the confidence in the finding that longer-term HIIT interventions effectively reduce IL-6 levels. In stark contrast, the shorter duration HIIT subgroup, which included studies with interventions lasting less than 8 weeks, did not show a significant reduction in IL-6 levels. The SMD for this subgroup was -0.55, with a 95% confidence interval (CI) spanning from -1.15 to 0.05, and a P-value of 0.08. The non-significant P-value implies that the observed changes in IL-6 levels in the shorter duration subgroup could be attributed to chance. Additionally, this subgroup exhibited substantial heterogeneity (I^2 = 68%), indicating a greater degree of variability in the results across the studies included. This high heterogeneity suggests that the effect of shorter-term HIIT interventions on IL-6 levels is less consistent and may be influenced by other factors not accounted for in this analysis. The discrepancy in findings between the longer and shorter duration HIIT subgroups has important implications for both the interpretation of the overall meta-analysis results and the practical application of HIIT as a therapeutic intervention for hypertensive individuals. Firstly, this finding suggests that longer-term HIIT interventions may be necessary to achieve optimal anti-inflammatory effects in hypertensive individuals. The observation that significant reductions in IL-6 levels were only evident in studies with longer intervention durations implies that the anti-inflammatory adaptations to HIIT require time to develop and manifest. It is plausible that sustained engagement in HIIT leads to more profound physiological adaptations that contribute to a more pronounced and sustained reduction in IL-6 levels. These adaptations might involve a multitude of complex biological processes. At the cellular level, longer-term HIIT may induce more significant changes in gene expression and protein synthesis, leading to enhanced metabolic function and improved cellular signaling pathways. For instance, prolonged HIIT may result in increased mitochondrial biogenesis and improved mitochondrial function, which are crucial for energy metabolism and have been linked to reduced inflammation. Furthermore, sustained HIIT may lead to more effective activation of anti-inflammatory pathways and a more robust resolution of inflammation. This could involve enhanced production of anti-inflammatory cytokines, increased activity of regulatory T cells, or improved clearance of pro-inflammatory mediators. The cumulative effect of these adaptations would be a more pronounced and sustained reduction in IL-6 levels and a shift towards an overall anti-inflammatory state. In addition to cellular and molecular adaptations, longer-term HIIT may also induce systemic changes that collectively dampen inflammation. These systemic changes could include improvements in body composition, such as a reduction in visceral fat mass, which is a major source of pro-inflammatory cytokines. Longer interventions

may also lead to more significant improvements in insulin sensitivity, endothelial function, and other cardiovascular risk factors that are closely linked to inflammation. The substantial heterogeneity observed in the shorter duration HIIT subgroup warrants further discussion. High heterogeneity in meta-analyses can indicate that the included studies are not measuring the same underlying effect or that there are important differences between the studies that are influencing the results. In this case, the high heterogeneity in the shorter duration subgroup suggests that the effect of shorter-term HIIT on IL-6 levels is highly variable and may be influenced by factors such as the specific HIIT protocols used, the characteristics of the study participants, or other methodological differences between the studies. This variability makes it difficult to draw firm conclusions about the effectiveness of shorter-term HIIT interventions for reducing IL-6 levels. It also highlights the need for future research to carefully consider and control for these potential sources of heterogeneity to obtain more consistent and reliable results. The clinical implication of this subgroup analysis is clear when using HIIT as a therapeutic strategy for hypertension, a program duration of at least 8 weeks should be considered to maximize its anti-inflammatory benefits. While shorter HIIT interventions may still provide other health benefits, such as improvements in cardiovascular fitness and blood pressure control, the evidence from this meta-analysis suggests that they may not be as effective in reducing IL-6 levels and mitigating inflammation. This recommendation aligns with general exercise guidelines that emphasize the importance of consistent and sustained physical activity for achieving long-term health benefits. It also underscores the need for healthcare professionals to provide clear guidance to patients regarding the optimal duration of HIIT interventions for managing hypertension and related inflammatory conditions.[16-20]

5. Conclusion

This meta-analysis provides compelling evidence that HIIT is an effective exercise modality for reducing IL-6 levels in hypertensive individuals. The significant reduction in IL-6 observed suggests that HIIT has anti-inflammatory effects, which could be a crucial mechanism underlying its benefits in managing hypertension. Subgroup analysis further revealed that HIIT interventions of 8 weeks or longer are associated with a greater reduction in IL-6 levels, highlighting the importance of intervention duration for achieving anti-inflammatory effects. These findings have important clinical implications, suggesting that HIIT can be a valuable non-pharmacological strategy for managing hypertension and that longer-term HIIT interventions may be more effective in reducing inflammation in this population. However, it is important to acknowledge the limitations of this meta-analysis. While the overall risk of bias in the included studies was generally low, there was some variability in study quality, particularly in terms of allocation concealment and blinding. Additionally, moderate heterogeneity was observed in the overall analysis, although subgroup analysis helped to explain some of this heterogeneity. Future research should continue to explore the optimal HIIT protocols for reducing inflammation in hypertensive individuals, with a focus on longer intervention durations and rigorous study designs.

6. References

1. de Souza Mesquita FO, Gambassi BB, de Oliveira Silva M, Moreira SR, Neves VR, Gomes-Neto M, et al. Effect of high-intensity interval training on exercise capacity, blood pressure, and autonomic responses in patients with hypertension: a systematic review and meta-analysis. Sports Health. 2023; 15(4): 571–8.
2. Twerenbold S, Hauser C, Gander J, Carrard J, Gugleta K, Hinrichs T, et al. Short-term high-intensity interval training improves micro- but not macrovascular function in hypertensive

patients. Scand J Med Sci Sports. 2023; 33(7): 1231–41.

3. Tremblay R, Deslauriers L, Marcotte-Chénard A, Little J, Boisvert F-M, Geraldes P, et al. High-intensity interval training and ambulatory blood pressure in women with hypertension and type 2 diabetes. Med Sci Sports Exerc. 2023; 55(9S): 552–3.
4. Müller C, Hauser C, Carrard J, Gugleta K, Hinrichs T, Schmidt-Trucksäss A, et al. Effects of high-intensity interval training on retinal vessel diameters and oxygen saturation in patients with hypertension: a cross-sectional and randomized controlled trial. Microvasc Res. 2024; 151(104616): 104616.
5. Li Y, Luo M, Chang Q, Cao S, Wang Y, Chen Z, et al. High-intensity interval training and moderate-intensity continuous training alleviate vascular dysfunction in spontaneously hypertensive rats through the inhibition of pyroptosis. Heliyon. 2024; 10(21): e39505.
6. Romero-Vera L, Ulloa-Díaz D, Araya-Sierralta S, Guede-Rojas F, Andrades-Ramírez O, Carvajal-Parodi C, et al. Effects of high-intensity interval training on blood pressure levels in hypertensive patients: a systematic review and meta-analysis of randomized clinical trials. Life (Basel). 2024; 14(12).
7. Dalton-Alves F, Araújo MBF, Lucena BEB, Souto GC, Lopes DSD, Lucena MIS, et al. Effects of high-intensity interval and moderate-intensity continuous training on ambulatory blood pressure and cardiovascular outcomes in older adults with hypertension (HEXA Study): study protocol for a randomised trial. BMJ Open. 2024; 14(12): e084736.
8. Krzesiak A, Enea C, Faivre J-F, Bescond J, Vanderbrouck C, Cognard C, et al. Combined cardiovascular effects of ovariectomy and high-intensity interval training in female spontaneously hypertensive rats. J Appl Physiol. 2024; 136(5): 1195–208.
9. Cano-Montoya J, Hurtado N, Núñez Vergara C, Báez Vargas S, Rojas-Vargas M, Martínez-Huenchullán S, et al. Interindividual variability response to resistance and high-intensity interval training on blood pressure reduction in hypertensive older adults. J Cardiovasc Dev Dis. 2025; 12(1).
10. López-Ruiz I, Ruiz-Poveda FL, Masía MD, Heredia-Elvar JR, González-Gálvez N. Moderate intensity continuous training, combined moderate-intensity continuous training vs combined high-intensity interval training in adults with hypertension: Randomized controlled trial. Complement Ther Clin Pract. 2025; 59(101960): 101960.
11. Ramos JS, Dalleck LC, Ramos MV, Borrani F, Roberts L, Gomersall S, et al. 12 min/week of high-intensity interval training reduces aortic reservoir pressure in individuals with metabolic syndrome. J Hypertens. 2016; 34(10): 1977–87.
12. Sosner P, Bosquet L, Herpin D, Guilbeault V, Latour E, Paquette-Tannir L, et al. Net blood pressure reduction following 9 months of lifestyle and high-intensity interval training intervention in individuals with abdominal obesity. J Clin Hypertens (Greenwich). 2016; 18(11): 1128–34.
13. Leal JM, Galliano LM, Del Vecchio FB. Effectiveness of high-intensity interval training versus moderate-intensity continuous training in hypertensive patients: A systematic review and meta-analysis. Curr Hypertens Rep. 2020; 22(3): 26.
14. de Oliveira GH, Boutouyrie P, Simões CF, Locatelli JC, Mendes VHS, Reck HB, et al. The impact of high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) on arterial stiffness and blood pressure in young obese women: a

randomized controlled trial. Hypertens Res. 2020; 43(11): 1315–8.

15. Clark T, Morey R, Jones MD, Marcos L, Ristov M, Ram A, et al. High-intensity interval training for reducing blood pressure: a randomized trial vs. moderate-intensity continuous training in males with overweight or obesity. Hypertens Res. 2020; 43(5): 396–403.
16. Soltani M, Aghaei Bahmanbeglou N, Ahmadizad S. High-intensity interval training irrespective of its intensity improves markers of blood fluidity in hypertensive patients. Clin Exp Hypertens. 2020; 42(4): 309–14.
17. Edwards JJ, Taylor KA, Cottam C, Jalaludeen N, Coleman DA, Wiles JD, et al. Ambulatory blood pressure adaptations to high-intensity interval training: a randomized controlled study. J Hypertens. 2021; 39(2): 341–8.
18. Nunes PRP, Silva TRGB, Carneiro MAS, Martins FM, Souza AP, Orsatti FL. Functional high-intensity interval training is not equivalent when compared to combined training for blood pressure improvements in postmenopausal women: a randomized controlled trial. Clin Exp Hypertens. 2022; 44(2): 127–33.
19. Ketelhut S, Möhle M, Gürlich T, Hottenrott L, Hottenrott K. Comparing post-exercise hypotension after a high-intensity interval training in matched younger and older adults. J Hypertens. 2022; 40(Suppl 1): e294–5.
20. Lins-Filho O, Germano-Soares AH, Aguiar JLP, de Almedia JRV, Felinto EC, Lyra MJ, et al. Effect of 12-week high-intensity interval training on hemodynamic variables at rest and during exercise in patients with obstructive sleep apnoea. J Hypertens. 2024; 42(4): 742–5.