Caffeine intake and its influences on heart rate variability recovery in healthy active adults after exercise: a systematic review and meta-analysis

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HIGHLIGHTS

- This is the first systematic review with meta-analysis that investigated CAF influences on HRV
- RMSSD and HF indexes not demonstrated slower recovery after exercise
- Caffeine did not affect HRV recovery following exercise

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ABSTRACT

Aims: Results regarding the effects of caffeine (CAF) intake on the autonomic control of heart rate recovery exercise remain inconclusive. Thus far, no study has used effect measures to pool the results of different experiments. We aim to assess the acute effect of CAF intake before exercise on the recovery of heart rate variability (HRV) after exercise through a systematic review and meta-analysis. **Data synthesis**: Randomized controlled clinical trials were included; sample composed of physically active or trained adults; CAF should be offered/ingested before exercise, with dosage between 100-400 mg or between 2-6 mg/kg and administration/ingestion route analogous in the protocols; studies required to present results of HRV indices before and after exercise. Bias risk analysis and meta-analysis were performed. Twelve studies were included in the qualitative synthesis and five studies were encompassed in the quantitative synthesis (meta-analysis). For the Root-mean-square standard deviation (RMSSD) index we revealed p=0.67, Total 95% confidence interval (95% CI) ranged from -0.45 to 0.29, and 66.7% for heterogeneity between groups were reported. Concerning the High Frequency (HF) index, we observed p=0.22, Total 95% CI that ranged from -0.34 to 0.30, and 44% for heterogeneity between groups. **Conclusions**: CAF intake did not affect heart rate variability recovery after exercise.

Keywords: caffeine; exercise; autonomic nervous system; heart rate variability; post-exercise; systematic review.

Introduction

Caffeine (CAF) is a methylxanthine alkaloid capable of causing obstruction of adenosine receptors (A1, A2A and A2B) and thus raise the activity of the central nervous system (Barcelos et al. 2020) [1]. For these motives, CAF is a substance vastly consumed for different reasons globally, including improvement of sports performances, cognitive or thermogenic purposes [2-5]. The U.S. Food and Drug Administration (FDA) and the European Food Safety Authority expect that the daily consumption of equal to 400mg of CAF is not associated with adverse cardiovascular effects or bodily toxicity [6].

The increased release of catecholamines in the bloodstream promoted by CAF intake results in adjustments to the cardiac autonomic modulation that induce consequent tachycardias [7]; which directed quite a few studies to explore the safety of CAF use before the practice of physical exertions. Koenig *et al.* [8] in their systematic review about caffeine and heart rate variability (HRV) revealed an increase in vagal flow via frequency domain indexes, but that result does not allow for exercise interventions.

The recovery of HRV after exercise is considered one of the most reliable methods to measure and predict adverse cardiovascular events and subsequent mortality [9], and CAF may disturb this response [6]. Through the consecutive heartbeat intervals (RR-intervals) it is likely to indirectly investigate the behavior of the autonomic nervous system (parasympathetic and sympathetic) on the heart [10,11]. Accordingly, delayed vagal (parasympathetic) reactivation after exercise might be considered an undesirable cardiac outcome [9,12].

Others studies have assessed the influence of CAF on HRV recovery after exercise and its effects remain inconclusive. While CAF has been recognized in a similar population (e.g., physically active and/or trained athletes) the significances of these studies remain contradictory. For this reason, a recent systematic review was unable to refute or support the safety of CAF evaluated through HRV recovery [13]. Furthermore, this study had methodological limitations (e.g., years of included studies, absence of quantitative analysis and inclusion of studies with the use of substances mixed with CAF) that may have led to erroneous results [13]. Up till now, no study has enforced effect measures to pool the outcomes of different studies and provide a global estimate of the influences of CAF on HRV recovery.

With the objective of clarifying the previously mentioned queries, our study intended to execute a systematic review and meta-analysis of randomized and controlled clinical trials to evaluate the effects of CAF intake on HRV recovery after exercise.

Material and methods

Registration

The review was pronounced according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes [14] and is registered in the PROSPERO database (CRD42021273706).

Search strategy and study selection

The searches were accomplished using five databases (EMBASE, Cochrane Library, MEDLINE (via PubMed), Web of Science, and SCOPUS) and the application of the keywords "Autonomic Nervous System" OR "Heart Rate Variability" AND "Caffeine" AND "Exercise".

After distinguishing the appropriate studies, the articles were exported to the Rayyan QCRI program (Qatar Computing Research Institute, Qatar) to reject the duplicates revealed in the search. Then, the studies were screened in the Rayyan program by adding the filter: "study in humans" and, then, the studies were later screened by reading the title and abstract. The eligibility stage was the final selection phase for inclusion of articles, and was performed by two independent reviewers (AAP and CJRB) fully reading the articles. If at this stage there was a dispute about a study, an additional reviewer was invited to give a verdict (VEV).

The studies needed to be sourced from peer-reviewed journals, published from the beginning of the database until March 2021. For inclusion, the articles needed to attain all the criteria described below: randomized clinical trial (RCT) design; participants greater than 18 years old, healthy, physically active, and trained. CAF needed to be consumed before exercise, in any format (e.g., capsules, pills, drink, gum, coffee, glue or spray) and its dosage needed to vary between 100-400 mg or between 2-6 mg/kg, in conformity with the limits established by the FDA. For the placebo protocol, the studies necessitated offering an intervention physically and visually comparable to the CAF format (e.g., dextrose capsule, opaque gelatin, starch, maltodextrin or cellulose, CAF-free coffee, bottled mineral water with artificial refreshment) and with an identical taste. These studies all necessitated reporting the linear values (time or frequency domain), geometric values and/or non-linear HRV indices logged before and after exercise.

Data Extraction

Information about the author, study design, features of the study participants, intervention and the results of the respective studies were stated. After resolving the identified inconsistencies via a discussion, missing data were requested by contacting the corresponding study authors. When the authors' correspondent did

not reply, the Web Plot Digitizer® was enforced to extract data presented in charts. This stage was finalized by two reviewers (CJRB and LAG) from the research group self-reliantly.

Assessment of the risk of bias

The risk of bias analysis was initiated via the Cochrane organization guidelines [15], using the Review Manager program (RevMan 5.4.1). The authorization for calculating the risks of bias in randomized clinical trials is an instrument based on the domain assessment, specifically, a critical assessment achieved distinctly to different aspects of the risk of bias [16]. The assessment was split into seven cohorts: "Random sequence generation", "Allocation concealment", “Blinding of participants and personnel", “Blinding of outcome assessment", "Incomplete outcome data", "Selective reporting" and "Other Bias". The classification was split into three responses, "Low risk" for low risk of bias, "Unclear risk" for questions not explained by the author of the original article and "High risk" for high risk of bias. Our decisions were based on the “Reviewer's judgment and criteria for judgment” table [16]. The risk of bias analysis was completed by two independent authors (AAP and LAG), and another (VEV) was consulted if there were any disagreements in their choices.

GRADE analysis

The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group [17] was followed so as to analyze the certainty of evidence, including study design, broadly categorized as observational studies (low evidence) and randomized trials (high evidence). Study quality (detailed study methods and execution) and significant limitations secondarily were measured using strength of evidence analysis [18]. Summary of Findings was formed using GRADEpro GDT® version 4 (McMaster University, ON, Canada)

Data Analysis: Systematic Review

A descriptive synthesis was implemented to describe detailed data about how each study was conducted. The key details for each study were described in texts and tables. The outcome of the individual qualitative analysis for each study was achieved by studying HRV indices at rest versus the recovery values after exercise with and without CAF.

For the HRV indices estimations, all indices measured were specified by the studies: RMSSD = square root of the mean of the square of the differences between adjacent normal RR intervals; SDNN =

standard deviation of all normal RR intervals recorded in a time interval, expressed in ms. HF = high frequency component of power spectral analysis, which ranged from 0.15 Hz to 0.44 Hz in absolute units (ms^2) and normalized units (n.u.) (vagal component); LF = low frequency component, which ranged between 0.04 and 0.15 Hz in absolute units (ms^2) and normalized units (n.u.) (sympathetic and parasympathetic influence); LF/HF = low and high frequency ratio; SD1 (pointcare plot) = standard deviation of the instantaneous variability of the beat-to-beat heart rate; SD2 ((pointcare plot) = standard deviation of long-term continuous RR interval variability; and, ApEn = Approximate Entropy.

Data Analysis: Meta-analysis

The insertion of the HRV values in the meta-analysis was the performance of the RMSSD and HF indices. The effects of the CAF interventions on each index were measured using the mean and standard deviation (MSD). MSD were assessed as the difference between the intervention and control groups before (baseline) and after exercise. The data required to construct the meta-analysis was the first period recorded following the exercise. The datasets were arranged in Microsoft Excel, and then prepared in the Review Manager Program (RevMan 5.4.1) to perform the meta-analysis.

Heterogeneity was assessed using the I^2 statistic, wherein a number greater than 50% was recognized as indicating substantial heterogeneity between the tests [19].

For the values of "CI" and "Test for size of the general effect", values of $p < 0.05$ (or, <5%) were considered significant. Similarly, we enforced a random effects model, in preference to a fixed effect model, because this was a more conventional technique that allows that the heterogeneity of the study may deviate beyond chance, offering extra generalizable results [20]. As a result of the low number of articles, no meta-regression was undertaken. All data was generated by the Review Manager Program (RevMan 5.4.1)

For HRV analysis; linear methods were computed in the time (RMSSD - square root of the square mean of the differences between adjacent normal RR-interval in a time interval, expressed in ms) and frequency domains (HF – high frequency, 0.15 to 0.4 Hz) [10].

Results

A total of 1026 studies were recognized by searches in the five databases. After removal of duplicates (*n*=454), 586 publications were screened for inclusion. Amongst them, 475 records were dismissed after reviewing the title and/or abstract. The remaining 111 papers were selected for full text reading and 99 were excluded. Finally, 12 studies were included in the qualitative synthesis (systematic review) and 5 studies were used for the quantitative synthesis (meta-analysis). The search process and selection stage

details are illustrated in the Flow Diagram of the PRISMA protocol (Figure 1).

[Figure 1 near here]

Analysis of the risk of bias

[Figure 2 near here]

All studies presented the "High Risk" or "Unclear Risk" bias consistent with the authors' judgment (Figure 2). The majority of the problems arose from the area "Blinding of outcome assessment" (12 out of 13 studies) or "Random sequence Generation", wherein most authors were unclear about the procedure adopted for this field. The "Other Bias" domain asked questions regarding: populations with different body mass indexes (BMI) [21,22] underestimation of VO2 values because of the lack of verbal encouragement from the researcher throughout the test [23], controlled breathing during the recovery period, inducing an unnatural recovery [25], lack of information about the menstrual period for the female subjects [25,26] and heterogeneous groups [25]. In the article by Lopes-Silva *et al.* [27], it was necessary to study the effects of CAF in a fight situation, but, since the apparatus for HRV evaluation was located on the athletes' torso, the fight protocol was adapted, greatly restricting the athletes' movements during the fight simulation. This made the findings in a real competitive situation ambiguous [27].

CAF and its impact on HRV recovery parameters

The studies included in our systematic review were published between 2002 and 2021. The total sample size is 232 participants (Table S1). The studies evaluated HRV via linear (time and frequency domain), geometric and non-linear indices (Table S2). Benjamim *et al.* [22] stated that CAF delayed the recovery of the HRV parameters after exercise in healthy males. Bunsawat *et al.* [28] detected a delay in post-exercise vagal reactivation, Gonzaga *et al.* [30] explained that CAF delayed parasympathetic recovery in physiologically healthy subjects and subjects with Vo2peak<42.46 mL/kg/min [31]. Nishijima *et al.* [24] established a significant increase in the LF and Total power indices in the post-exercise period, and Yeragami *et al.* [25] explained the increase in the LF index in the group that consumed CAF in the same period. Thomas *et al*. [26] detected that CAF intake induced a decrease in cardiac vagal control linked to the placebo group via the ApEn index. Nevertheless, Rolim *et al.* [31] stated that CAF accelerated parasympathetic reactivation after submaximal exercise in physically active males. Blake *et al.* [21], Karayigit *et al.* [32], Lopes-Silva *et al.* [27], and Sarshin *et al.* [33] revealed no outcome of CAF on HRV indices after exercise.

Five studies encountered the inclusion criteria for our meta-analysis [22,26,29,30,32]. Gonzaga *et al.* [31] and Karayigit *et al.* [32] inspected two experimental groups: the first study with different peak VO2 values and the second with changed CAF doses, and a control group for the two protocols, all groups were included. During the creation of the meta-analysis graph, the groups were divided into subgroups to verify whether the type of exercise could influence HRV recovery. The first group “CAF in resistance exercise” represents studies whose protocol included resistance exercises. The second group “CAF in aerobic exercise” denoted studies whose protocol included aerobic exercises. The remaining deviations and 95% confidence intervals (CI) constant with the HRV indices for each assay are illustrated in Figures 3A and 3B.

[Figures 3 (A and B) near here]

Figure 3A shows the forest plot graphs to compare the time domain index (RMSSD) between individuals who consumed CAF and individuals that consumed placebo. We enforced random effects model and standard mean difference to measure the effect size (black diamonds); the proportion of the center of the diamonds represents the 95% CI. A negative effect specifies impact on the group that ingested CAF related to controls. No significant change was noticed for the RMSSD, for “Test for overall effect” as we revealed p=0.19 and a heterogeneity of 63%. In the subgroup “CAF in resistance exercise” the subtotal (CI) was -0.39 (95% CI: -0.98, 0.20)”. The subgroup "CAF in aerobic exercise" offered for "Test for overall effect", as p=0.22 and a heterogeneity of 58%. The subtotal (CI) was 0.20 (95% CI: -0.12 to 0.51) for this subgroup. The total outcome of the meta-analysis for this index revealed p=0.67, a “Total (CI)” was -0.08 (95% CI: 0.45 to 0.29), and 66.7% for heterogeneity between groups.

Figure 3B shows the forest plot graphs to link the frequency domain (HF) index between individuals who ingested CAF and individuals that consumed placebo. We imposed a random effects and standard mean difference model (Std. Mean Difference) to quantify the effect size (black diamonds); the quantity for the center of the diamonds represents the 95% CI. A negative effect designates impact on the group that consumed CAF compared to controls. No significant change was documented for HF, for “Test for overall effect”, we discovered p=0.36 and a heterogeneity of 45%. The subtotal (CI) was -0.22 (95% CI: -0.70 to 0.26) for the “CAF in resistance exercise” subgroup. The subgroup "CAF in aerobic exercise" offered for "Test for overall effect", as p=0.40 and a heterogeneity of 20%. The subtotal (CI) was 0.15 (95%

CI: -0.20 to 0.51) for this subgroup. The total outcome of the meta-analysis for this index revealed p=0.22, "Total (CI)" was 0.02 (95% CI: -0.34 to 0.30), and 44% for heterogeneity between groups.

Discussion

Our study was commenced to evaluate the acute effects of pre-exercise CAF intake on post-exercise HRV recovery through a systematic review and meta-analysis. The present meta-analysis delivers evidence that CAF intake did not significantly influence HRV post-exercise recovery compared to the placebo based on the time (RMSSD) and frequency domain (HF) indices. The "total (CI)" values were close to zero, assumed to be the line of nullity of the statistic.

CAF is often ingested in sports for improvement in cognitive performance [34], its effects are mostly related to the adenosine receptors blockade and increased central nervous system activity. This core mechanism justifies that CAF be considered as an ergogenic resource as it can enhance physical performance. CAF effectiveness in enhancing the athletes' performance in diverse sports training profiles (e.g., endurance, strength) has made it the most prescribed substance in sports [3,4]. CAF use can be prescribed in low (<3mg/kg), moderate (≥3mg/kg up to 6mg/kg) and high (9mg/kg) doses [4]. Its use is recommended by the International Society for Sports Nutrition (ISSN) [2] and the International Olympic Committee (IOC), and permitted by World Anti-Doping Agency (WADA) [3]. Moreover, the safety of CAF estimated though cardiac autonomic control remains uncertain and presents controversial data, as it might be influenced by many variables such as the dose consumed and the body's' physiological sensitivities [35,36].

Consistent with the FDA, consumption of up to 400 mg of CAF per day (≈6 mg of CAF per kilogram of body weight) is not related to the adverse effects of CAF e.g., anxiety, headaches, nausea and restlessness in healthy adults [37]. CAF dosage in the chosen studies in this meta-analysis imposed doses ranging from 3.0 to 6.0 mg/kg, values considered harmless consistent with the FDA [6]. Yet, there is an extensive range with regards the degree of sensitivity to the CAF effects, as chronic CAF consumption in regular consumers can generate tolerance [35].

In non-habitual consumers, one of the key effects of CAF are the HR increase and peaks in systolic blood pressure. All the same, these effects have a tendency to be gradually reduced with continued CAF intake [38]. In regular coffee drinkers, CAF ingested at concentrations of 100 mg and 200 mg had no significant effects on HRV [39] in healthy young persons. Yet, when evaluated at the same concentrations

in young healthy non-habitual drinkers, CAF promoted a reduction in the parasympathetic indices related to modulation of the heart (RMSSD, HF, SDNN, pNN50) [40].

The different behavior of CAF responses to intake about its typical consumption may be connected to an adjustment of the adenosine receptors [40]. In 1979, Fredholm [42] revealed an increase in the number of adenosine binding sites in the cerebral cortex of rats treated for two weeks with 10 mg/kg/day of CAF. This response supports the theory that chronic CAF ingestion might result in newly created adenosine receptors, partly reducing the blocking action of CAF and thus lessening its stimulant effects [42].

Thus, the studies in this meta-analysis offered heterogeneous criteria and assessments of habitual CAF consumption, which is an imperative variable that needs to be controlled, as it impacts the size of the effects of CAF on the autonomic nervous system as reported above. In the study by Bunsawat *et al.* [28] they considered as an exclusion factor consumption of beverages with CAF greater than the equivalent of three cups of coffee per day (>285 mg/day). Nevertheless, in the study by Thomas *et al.* [26] all participants consumed low to moderate in CAF intake (≤300 mg/day).

Some studies measured higher values for the usual consumption of CAF; Nishitjima *et al*. [24] studied regular CAF users (≤500 mg per day). Whereas, in the study directed by Blake *et al.* [21] participants were included who consumed CAF between ≥100 mg and ≤500 mg per day.

In research by Rolim *et al.* [31] and Sarshin *et al.* [33], they involved subjects who did not routinely consume CAF (<120 mg/day; <3 times/week). Lopes-Silva *et al.* [27] studied the level of habitual consumption of the subjects (n=10) and they revealed that two subjects were considered to have a high level of CAF consumption (greater than six cups of coffee each day), while others reported a low-level consumption (less than two cups of coffee each day).

Members in the study completed by Yearagani *et al.* [25] have a low level of habitual CAF intake specified as 62 ± 14mg per day. Further research did not provide the required information for their subjects [22,29,30].

Also, the modification in CAF metabolism can be influenced by gender as a result of hormonal differences, for instance in females during the menstrual cycle. In the study led by Skinner *et al.* [43], no alteration was documented in the extent of the ergogenic effect in males and females, after consuming 3 mg/kg of CAF 90 minutes before an exercise assessment. Still, higher post-exercise CAF concentrations were noted in females, suggesting a greater physiological CAF durability .

It is notable that the majority of studies involving CAF supplementation are conducted in males. One of the reasons is the sampling complexity caused by the menstrual cycle and the use of contraceptives that adjust CAF metabolism [44].

This scenario was noticed in our review, where the majority of the nominated articles were conducted solely in males [21,22,24,27,29-31,33]. In the study by Bunsawat *et al.* [28], experiments were completed in the first seven days of the female subjects' menstrual cycle to balance the effects of sexual hormones on HRV. Still, the studies by Thomas *et al.* [26] and Yeragani *et al.* [25] did not present evidence about the menstrual period of their subjects. Karayigit *et al.* [32] completed a single study that started its tests entirely in females.

Considering that CAF has its peak concentration between 30-60 minutes after ingestion [45], the study of Nishijima et al. [24] brings important pharmacokinetics aspects, namely the time of CAF supply. CAF was offered 120 minutes before exercise; despite this, HRV was slowly recovered in the group that ingested the caffeine in this study. Smith et al. [46] ensure that the half-life of caffeine in healthy individuals occurs between 2 h to 8.5 h after ingestion. This fact may be enough to interfere with recovery from HRV after exercise.

While the CAF stimulant effect has been recognized, there are still many practical aspects similar to the influence of CAF on post-exercise autonomic recovery, as some of the nuances about its use remains unstandardized. We anticipate that the features identified in this meta-analysis will offer some guidelines for further studies, to improve comprehension of the effects of CAF on the autonomic nervous system. The results conclude that CAF is a benign supplement for the cardiovascular system and can be used in competitive sports to enhance performance

The result limitations are that the studies included in this review investigated the effects of CAF in a physically active and apparently healthy young population and, so, these results cannot be extrapolated to other populations. Adolescent athletes can be routinely approached with nutritional strategies to use CAF as ergogenic support; but we do not have evidence to guarantee its safety by assessing HRV after exercise. We cannot neglect CAF is one of the fat burners most used in clinical practice so as to help with weight loss in combination with physical exercise [47]. Consequently, we highlight those studies evaluating the effects of caffeine on cardiac recovery in overweight and obese individuals are still required to clarify the impacts of CAF on the cardiovascular health of this population.

In conclusion, the current meta-analysis provides statistical consequences that CAF intake did not significantly affect HRV post-exercise recovery compared to placebo in healthy or physically active individuals based on HRV indices that reflect the parasympathetic cardiac regulation.

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Table caption list

Table 1. Description of the characteristics of the study population of articles by author and year, sample, age (years), weight (kg), height (cm), BMI (kg/m²) (mean ± SD), exercise, average peak oxygen (ml/kg/min), exercise intensity.

Author/ years	Study Design	Sample	Age (years)	Weight (kg)	Height (cm)	BMI (kg/m²)	Exercise	Average Peak Oxygen (ml/kg/min)	Exercise Intensity
Benjamim et al. (2021)	RCT	30 healthy men	23.33 ± 3.15	71.14 ± 12.31	163 ± 4.51	23.00 ± 2.75	Resistance (Leg press, squat, abductor and extensor chair)	Not reported	75% 1RM
Blake et al. (2020)	RCT	12 resistance-trained men	22.75 ± 4.51	91.05 ± 17.77	183.4 ± 7.3	Not calculated	Resistance (Elbow flexion and extension)	Not reported	Maximal peak isometric force at 0º degrees and 60º for both peak elbow flexion and extension
Bunsawat et al. (2015)	RCT	18 healthy individuals	26 ± 1.0	Not reported	Not reported	23.9 ± 0,8	Treadmill	Not reported	Maximum oxygen consumption (VO2max), followed by 2 minutes active recovery at a speed of

									3.5kmh and grade of 0%.
Gonzaga et al. (2017)	RCT	32 healthy and physically active men	23,59 ± 3, 45	78.87 ± 12.1 4	179 ± 7.14	24.40 ± 2. 82	Treadmill	44.00 ± 12.25	60% on VO2max during 30minutes
Gonzaga et al. (2019)	RCT	32 healthy physically active men	23.69 ± 3.75	78.38 ± 6.92	180 ± 4.0	24.33 ± 2.04	Treadmill	Group: High VO_2: 53.32 ± 8.79 Low VO_2: 34.69 ± 6.92	60% on VO2max during 30minutes
Karayigit et al. (2021)	RCT	17 resistance-trained female	23.0 ± 2.0	64.0 ± 4.0	168.0 ± 3.0	Not calculated	Resistance (Squat and Bench press)	Not reported	Squat and bench press repetitions to failure at 40% 1RM
Lopes-Silva et al. (2016)	RCT	10 men athletes (experienced in taekwondo)	21 ± 4,0	71.0 ± 12.9	180 ± 8,0	Not calculated	Fight	Not reported	Each combat consisted of Three 2-min rounds with 1-min intervals

Nishijima et al. (2002)	RCT	8 healthy men	25.5 ± 0.8	68.3 ± 1.7	172.2 ± 4.3	Not calculated	Cycle ergometer	Not reported	Between 40-50% ventilatory thresholds
Rolim et al. (2018)	RCT	21 young physically active men	22.3 ± 2.9	Not reported	Not reported	25.2 ± 2.7mg/kg²	Treadmill	Not reported	3 minutes of warm-up at 3km/h and 2.5% of slope. In sequence, increments 1km/h each minute until reach 85% of Maximal HR, test was interrupted.
Sarshin et al. (2020)	RCT	20 recreationally active males	24.0±2.0	74.70 ± 7.07	178.8 ±4.6	Not calculated	Cycle ergometer	Not reported	4-min standardized warm-up against a fixed load of 1 kilopond and three separate 2s sprints were performed against a load of 0.075 kp·kg− 1 of body mass were interspersed with 45-s of active recovery.
Thomas et al. (2017)	RCT	21 (13 males) healthy subjects	25.5 ± 3.5	Not reported	Not reported	26.2 ± 4.6	Cycle ergometer	32.2 ± 6.4	Cycled workload at 75% VO2max during 15 minutes.
Yeragani et al. (2005)	RCT	11 (6 males)	M: 29.0 ± 7.0	Not reported	Not reported	Not calculated	Cycle ergometer	Not reported	Exercise began with pedaling intensity initiated at 25 W, and

	heathy subjects	F: 23.05 ± 7.0	increased by 25 W increments at every 3 min stage.

HR= heart rate; RCT= randomized controlled trial; RM= repetition maximum; W= watts VO2= oxygen volume consumed during exercise; VO2Max= maximum oxygen volume consumed during effort test.

Table 2. Description of the selected articles by author and year, time ingestion CAF, CAF dose, placebo, analysis time, HRV index and main conclusions.

Author/years	Ingestion CAF (before exercise)	CAF dose	Placebo	Analysis Time	HRV Index	Main conclusions
Benjamim et al. (2021)	45 minutes	(~4.21mg/kg) 300mg	Capsule (starch)	0-5, 5-10, 10-15, 15-20, 25-25 and 25-30 minutes post-exercise	SDNN, RMSSD, RRTri, TINN, SD1, SD2, LF and HF(ms2)	CAF protocol delayed HRV recovery after strength exercise.
Blake et al. (2020)	30 minutes	(~3.84mg/kg) 350mg	Capsule (starch)	Immediately (<1 minute) and 60 minutes post-exercise	RMSSD	CAF protocol did not affect HRV recovery after exercise.
Bunsawat et al. (2015)	45 minutes	(~5.06mg/kg) 400mg	Pills	5, 15 and 30 minutes post-exercise	LF/HF	CAF protocol delayed vagal reactivation after exercise.
Gonzaga et al. (2017)	45 minutes	(~3.80mg/kg) 300mg	Capsule (starch)	0-5, 5-10, 10-15, 25-30, 35-40, 45-50 and 55-60 minutes post-exercise	RMSSD, SD1, SDNN, HF, LF and LF/HF	Intake CAF before exercise delayed the parasympathetic recovery following moderate aerobic exercise.

Gonzaga et al. (2019)	45 minutes	(~3.80mg/kg) 300mg	Capsule (starch)	0-5, 5-10, 10-15, 25-30, 35-40, 45-50, 55-60 minutes post-exercise	SDNN, RMSSD, SD1, SD2, LF(n.u.), HF(n.u.) and LF/HF	CAF slows parasympathetic recovery from exercise in individuals with lower cardiorespiratory capacity (VO2peak<42.46 mL/kg/min).
Karayigit et al. (2021)	60 minutes	(3mg/kg) 192 ± 12mg and (6mg/kg) 384 ± 24mg	Decaffeinated coffee	Immediately post-latest exercise (<1 minute)	SDNN, RMSSD, TP, HF (ms2) LF (ms2), LF/HF, HF(n.u.) and LF(n.u.)	CAF protocols did not demonstrate changes in HRV recovery between interventions.
Lopes-Silva et al. (2016)	60 minutes	(5mg/kg) 355± 64,5mg	Capsule (Cellulose)	180, 360 seconds post-exercise	RMSSD	CAF did not delay vagal reactivation between 180 and 360 seconds following exercise.
Nishijima et al. (2002)	120 minutes	(~4.39mg/kg) 300mg	Capsule	5-10, 15-20 and 25-30 minutes post-exercise	TP, HF and LF	CAF protocol demonstrated significant changes in HRV indexes (LF and power total) at 30 minutes after exercise when compared to placebo.
Rolim et al. (2018)	60 minutes	3mg/kg	Capsule	60 to 300 seconds post-exercise, with the treadmill velocity reduced to 2.4km/h.	SD1 and SD2	CAF accelerated parasympathetic reactivation in the submaximal exercise test in the first three minutes.
Sarshin et al. (2020)	45 minutes	(3mg/kg) 224.1 ± 21.2 and (6mg/kg) 448.2± 42.4	Capsule (dextrose)	0-5 and 30-35 minutes post-exercise	SDNN and RMSSD	CAF improved HRV recovery post-exercise.

Thomas et al. (2017)	10 minutes	300mg	Gum	0-5minutes and 5-10 minutes after exercise	SDNN, RMSSD, LF(nu), HF (nu), LF/HF, SD2 (ms), ApEn	CAF did not impaired HRV indexes recovery after exercise.
Yeragani et al. (2005)	60 minutes	5mg/kg	Cola drink	0-5minutes after exercise	LF (ms2), HF (ms2), LF/HF, ApEn	CAF delayed HRV recovery after exercise.

Figure caption list

Figure 1. Flowchart Prisma.

Figure 2. Bias risk analysis judgment by study and bias domains.

Figure 3A. Effects of CAF intake before exercise on HF indices recovery following effort.

Figure 3B. Effects of CAF intake before exercise on RMSSD indices recovery following effort.

Figure 1

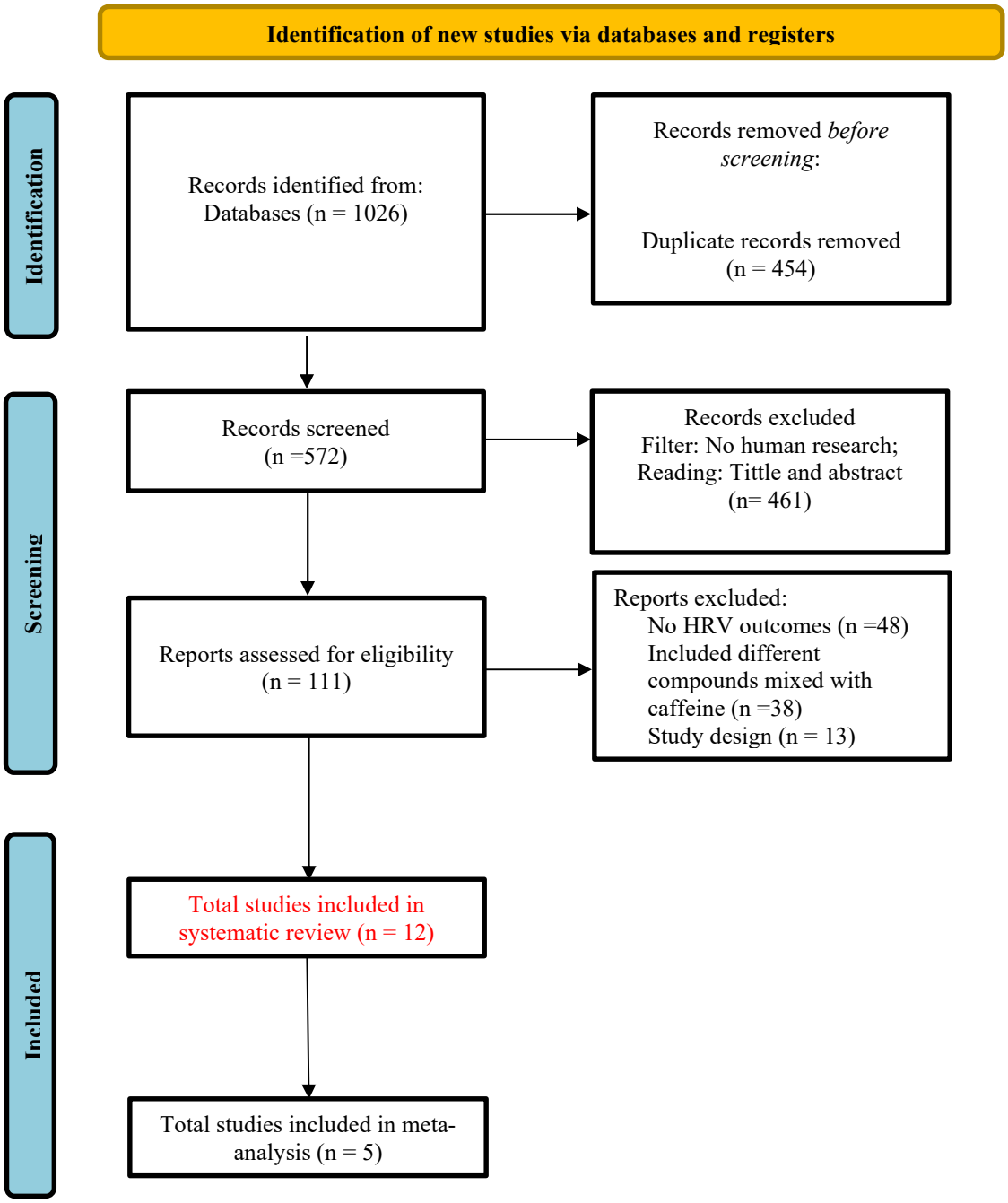

Identification of new studies via databases and registers
Identification
Records identified from:
Databases (n = 1026)
Records removed *before screening*:
Duplicate records removed
(n = 454)
Screening
Records screened
(n =572)
Records excluded
Filter: No human research;
Reading: Tittle and abstract
(n= 461)
Reports assessed for eligibility
(n = 111)
Reports excluded:
No HRV outcomes (n =48)
Included different compounds mixed with caffeine (n =38)
Study design (n = 13)
Included
Total studies included in systematic review (n = 12)
Total studies included in meta-analysis (n = 5)

Figure 2

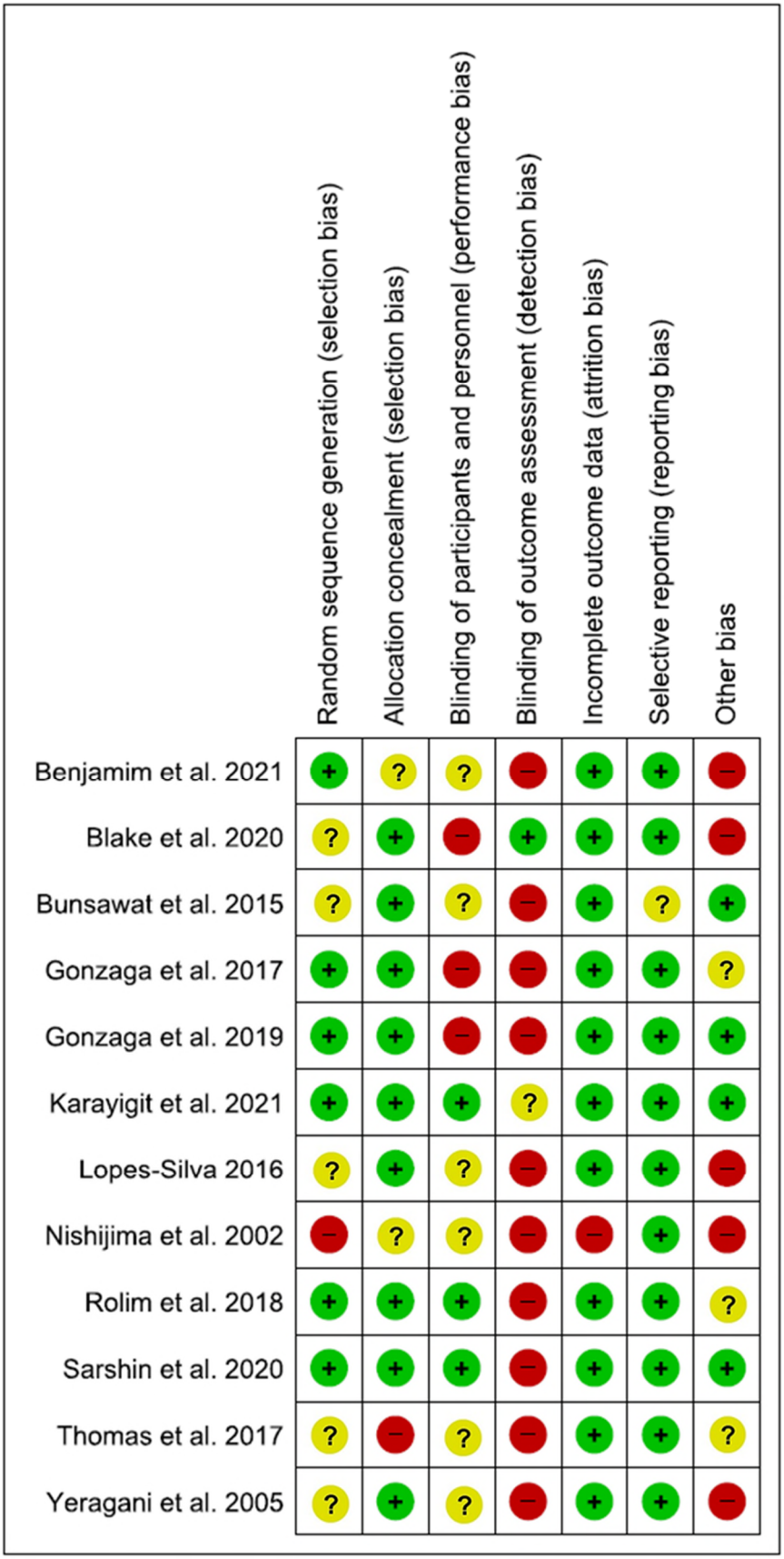

Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Benjamim et al. 2021
Blake et al. 2020
Bunsawat et al. 2015
Gonzaga et al. 2017
Gonzaga et al. 2019
Karayigit et al. 2021
Lopes-Silva 2016
Nishijima et al. 2002
Rolim et al. 2018
Sarshin et al. 2020
Thomas et al. 2017
Yeragani et al. 2005

Figure 3A

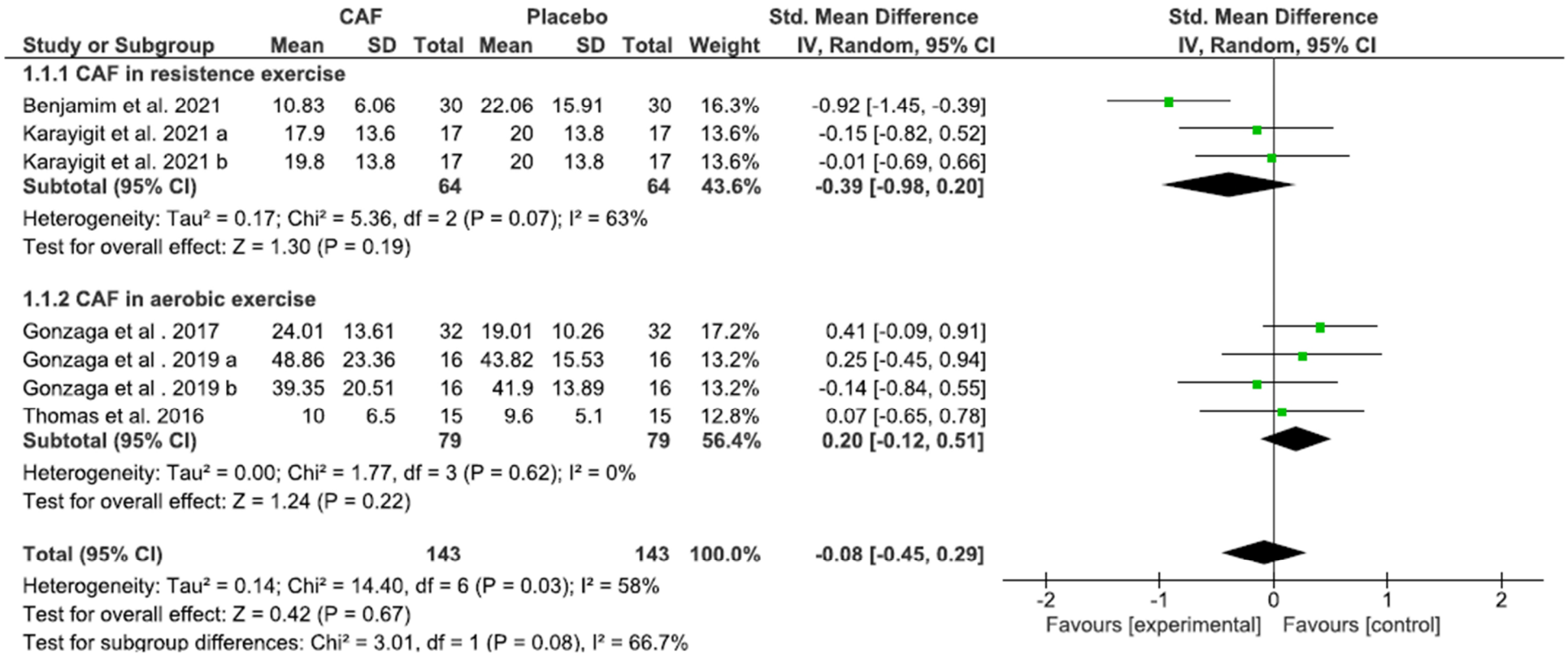
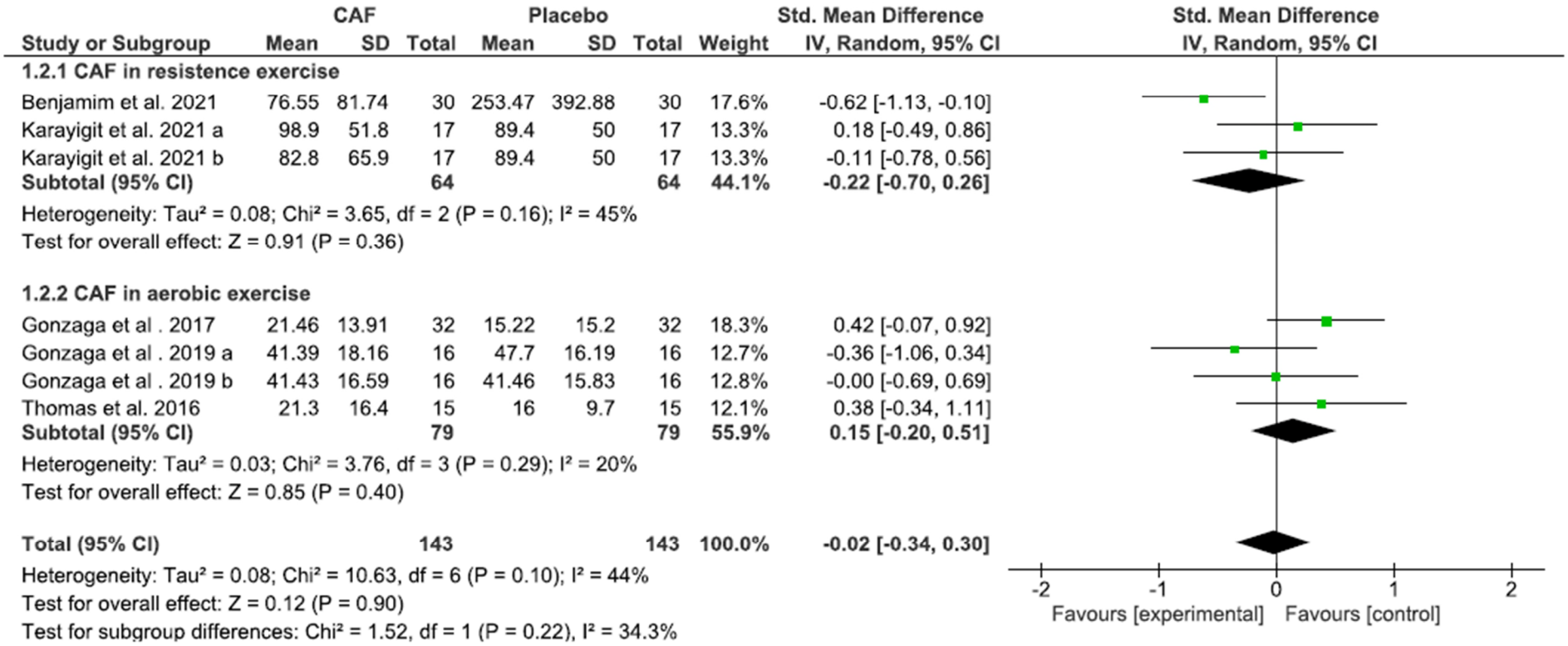

CAF
Placebo
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.1.1 CAF in resistence exercise
Benjamim et al. 2021 10.83 6.06 30 22.06 15.91 30 16.3% -0.92 [-1.45, -0.39]
Karayigit et al. 2021 a 17.9 13.6 17 20 13.8 17 13.6% -0.15 [-0.82, 0.52]
Karayigit et al. 2021 b 19.8 13.8 17 20 13.8 17 13.6% -0.01 [-0.69, 0.66]
Subtotal (95% CI) 64 64 43.6% -0.39 [-0.98, 0.20]
Heterogeneity: Tau² = 0.17; Chi² = 5.36, df = 2 (P = 0.07); I² = 63%
Test for overall effect: Z = 1.30 (P = 0.19)
1.1.2 CAF in aerobic exercise
Gonzaga et al . 2017 24.01 13.61 32 19.01 10.26 32 17.2% 0.41 [-0.09, 0.91]
Gonzaga et al . 2019 a 48.86 23.36 16 43.82 15.53 16 13.2% 0.25 [-0.45, 0.94]
Gonzaga et al . 2019 b 39.35 20.51 16 41.9 13.89 16 13.2% -0.14 [-0.84, 0.55]
Thomas et al. 2016 10 6.5 15 9.6 5.1 15 12.8% 0.07 [-0.65, 0.78]
Subtotal (95% CI) 79 79 56.4% 0.20 [-0.12, 0.51]
Heterogeneity: Tau² = 0.00; Chi² = 1.77, df = 3 (P = 0.62); I² = 0%
Test for overall effect: Z = 1.24 (P = 0.22)
Total (95% CI) 143 143 100.0% -0.08 [-0.45, 0.29]
Heterogeneity: Tau² = 0.14; Chi² = 14.40, df = 6 (P = 0.03); I² = 58%
Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Chi² = 3.01, df = 1 (P = 0.08), I² = 66.7%
-2
-1
0
1
2
Favours [experimental]
Favours [control]

Figure 3B


CAF
Placebo
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
1.2.1 CAF in resistence exercise
Benjamim et al. 2021 76.55 81.74 30 253.47 392.88 30 17.6% -0.62 [-1.13, -0.10]
Karayigit et al. 2021 a 98.9 51.8 17 89.4 50 17 13.3% 0.18 [-0.49, 0.86]
Karayigit et al. 2021 b 82.8 65.9 17 89.4 50 17 13.3% -0.11 [-0.78, 0.56]
Subtotal (95% CI) 64 64 44.1% -0.22 [-0.70, 0.26]
Heterogeneity: Tau² = 0.08; Chi² = 3.65, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 0.91 (P = 0.36)
1.2.2 CAF in aerobic exercise
Gonzaga et al . 2017 21.46 13.91 32 15.22 15.2 32 18.3% 0.42 [-0.07, 0.92]
Gonzaga et al . 2019 a 41.39 18.16 16 47.7 16.19 16 12.7% -0.36 [-1.06, 0.34]
Gonzaga et al . 2019 b 41.43 16.59 16 41.46 15.83 16 12.8% -0.00 [-0.69, 0.69]
Thomas et al. 2016 21.3 16.4 15 16 9.7 15 12.1% 0.38 [-0.34, 1.11]
Subtotal (95% CI) 79 79 55.9% 0.15 [-0.20, 0.51]
Heterogeneity: Tau² = 0.03; Chi² = 3.76, df = 3 (P = 0.29); I² = 20%
Test for overall effect: Z = 0.85 (P = 0.40)
Total (95% CI) 143 143 100.0% -0.02 [-0.34, 0.30]
Heterogeneity: Tau² = 0.08; Chi² = 10.63, df = 6 (P = 0.10); I² = 44%
Test for overall effect: Z = 0.12 (P = 0.90)
Test for subgroup differences: Chi² = 1.52, df = 1 (P = 0.22), I² = 34.3%
-2
-1
0
1
2
Favours [experimental]
Favours [control]

Summary of findings:

Caffeine compared to placebo for HRV recovery after exercise

Patient or population: Physically active/healthy subjects.

Intervention: Caffeine

Comparison: Placebo

Outcome № of participants (studies)	Anticipated absolute effects (95% CI) Intervention (Difference)	Certainty	What happens
[RMSSD] № of participants: 286 (5 RCTs)	MD **0.42 ms higher** (0.45 lower to 0.29 higher)	⊕⊕⊕◯ MODERATE Due to serious risk of bias. Due to serious inconsistency. Upgraded because all plausible confounding would reduce demonstrated effect.	CAF results in no difference versus placebo protocol to RMSSD index recovery after exercise.
[HF] № of participants: 286 (5 RCTs)	MD **0.02 ms lower** (0.34 lower to 0.30 higher)	⊕⊕⊕◯ MODERATE Due to serious risk of bias. Due to serious inconsistency. Upgraded because all plausible confounding would reduce demonstrated effect.	CAF results in no difference versus placebo protocol to HF index recovery after exercise.

***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect