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Review article

The Effects of Combined Exercise with Citrulline Supplementation on Body Composition and Lower Limb Function of Overweight Older Adults: A Systematic Review and Meta-Analysis

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Abstract
The combined exercise with citrulline (CIT) supplementation is a potential adjuvant treatment approach to address the declining body composition and lower limb function of overweight older adults. However, research on this approach is limited. Thus, this study performed a meta-analysis review to explore the effects of combined exercise with CIT supplementation on body composition and lower limb function among overweight older adults. The search strategy and manuscript development of this study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Eligible studies were first searched through four databases (Web of Science, Scopus, PubMed, and EBSCO) from January 2003 until April 2023, followed by screening. The main inclusion criteria for the article selection are as follows: 1) Randomized Controlled Trial studies; 2) Participants aged over 55; 3) Studies involved exercise with CIT supplementation for the experimental group and exercise with Placebo (PLA) supplementation for the control group; 4) Body composition and lower limb function were measured at pre- and post-intervention. Subsequently, the Cochrane risk of bias assessment tool was utilized to evaluate the selected studies' quality. The Standardized Mean Difference (SMD) was chosen as the suitable effect scale index, and the mean differences of the data from the selected articles were analyzed using Revman 5.4 software with a 95% Confidence Interval (CI). A total of seven studies fulfilled the inclusion criteria and were selected for the meta-analysis. The included studies involved 105 males and 198 females, where 157 belonged to the PLA group and 146 from the CIT group. Significant improvements were observed among overweight older adults with CIT supplementation in 6-Minute Walking Test (6MWT) ($P = 0.04$, $I^2 = 4\%$), SMD (95% CI) = -0.28 (-0.54, -0.01), and Lower Limb Strength (LLS) ($P < 0.01$, $I^2 = 30\%$), SMD (95% CI) = -0.38 (-0.65, -0.12) compared to those with PLA supplementation. Combined exercise with CIT supplementation could be an effective non-pharmaceutical intervention to improve the physical function of overweight older adults by increasing their muscle strength.

Key words: Aging, frailty, human health, physical function, strength.

Introduction

The aging process promotes body fat storage and physical deterioration due to the progressive loss of muscle strength (Bouchard et al., 2009). The loss of muscle function accompanying aging was strongly associated with mobility and autonomy impairment, falls, and mortality in severe cases (Bouchard and Janssen, 2010). As the global aging population increases, the research community seeks effective interventions to address these concerning health issues. Concurrently, older adults are more likely to become overweight due to a slower metabolic rate (Al-Nimr, 2019). Overweight was a significant factor that triggers various metabolic diseases, such as hypertension and diabetes (Marques et al., 2018).

One of the most outstanding strategies to conserve muscle mass and strength among overweight older adults is to practice regular physical exercise (Saint-Maurice et al., 2019). For instance, resistance and aerobic training have been shown to enhance endurance, muscle strength (Li et al., 2021a), functional ability (Li et al., 2021b), as well as reduce obesity among older adults (Barbat-Artigas et al., 2014). Therefore, exercise is a promising non-pharmacological means of boosting physical fitness among overweight older adults.

Meanwhile, the citrulline (CIT) amino acid has been used to alleviate physical performance in older adults. Oral CIT supplementation has also been proven to boost skeletal muscle mass and muscle protein synthesis, fiber size, and strength (Osowska et al., 2006; Faure et al., 2012, 2013), besides reducing adipose tissue, as observed in old malnourished rats (Faure et al., 2013). In fact, a systematic review described that CIT supplementation could benefit the older adults with various comorbidities, such as malnourished, hypertensive, obese, and dynapenic-obese (Aubertin-Leheudre and Buckinx, 2020). Moreover, CIT supplementation promotes lean muscle formation (Bouillanne et al., 2019) and aerobic capacity (Ashley et al., 2018) and reduces fat mass (Figueroa et al., 2015) compared to placebo (PLA).

CIT is found abundantly in fruits, such as watermelon, and is synthesized from arginine and ornithine, with plasma glutamine and arginine as the main precursors (Marini, 2012). It contributes to arginine bioavailability and the subsequent nitric oxide (NO) synthesis due to the role of CIT as a precursor to arginine (Viribay et al., 2022). Nevertheless, CIT differs from arginine as it is directly transported to the kidneys without arginase enzyme catabolism (Breuillard et al., 2015). Additionally, CIT could limit arginase action and arginine to ornithine catabolism (Figueroa et al., 2017). Thus, dietary CIT is potentially superior to arginine supplementation in boosting arginine bioavailability and NO synthesis (Marini, 2012; Figueroa et al., 2017). CIT may be able to improve peripheral vascular relaxation/perfusion and subsequent muscle O_2 utilization

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by increasing the bioavailability of NO in active skeletal muscles, thereby enhancing exercise performance (Wang et al., 2001; Smith et al., 2002).

Interestingly, past literature has reported that combined exercise training and CIT supplementation may be beneficial for improving body composition and function. One study by Buckinx et al. (2020) compared the effect of intervention among overweight older adults. The intervention protocol was performed thrice weekly for 12 weeks. The experimental group was subjected to 85% maximum heart rate (HR_{max}) of High-intensity Interval Training (HIIT) with CIT supplementation (10 g/day tablets), while the control group underwent HIIT combined with PLA supplementation with the same dose as CIT supplementation. The results showed that those who exercised and consumed CIT in the experimental group exhibited improved fat and lean mass compared to those in the control group. However, Marcangeli et al. (2022) applied the same intervention plan and reported a contradicting finding. The study found that the fat and lean mass between the two groups were insignificantly different.

Despite the potential benefits of CIT supplementation and exercise on overweight older adults, no meta-analysis has been performed to examine this intriguing correlation. Therefore, this meta-analysis was conducted to explore the effects of combined exercise with CIT supplementation on body composition and lower limb function in older overweight adults.

Methods

Study selection and data collection

The review protocol was then registered at PROSPERO international prospective register of systematic reviews (CRD42023416669). The search strategy and manuscript development were designed by 2 researchers, as detailed in Appendix A and the results section was prepared based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The article search was performed from February 2023 to April 2023 in Web of Science, Scopus, PubMed, and EBSCO databases. The list of keywords used included "Citrulline," "Training," and "Exercise." The screening process (title and abstract) was conducted by two independent investigators. Subsequently, the selected full articles were screened again according to the inclusion and exclusion criteria. Finally, the two independent investigators performed a quality assessment and data extraction process for the full articles. All data were obtained from published literature. Any discrepancies were resolved by inviting another independent investigator to weigh in on the decision until a consensus was achieved. The respective reference was acquired manually once a study inclusion was confirmed. Figure 1 summarizes the article selection process.

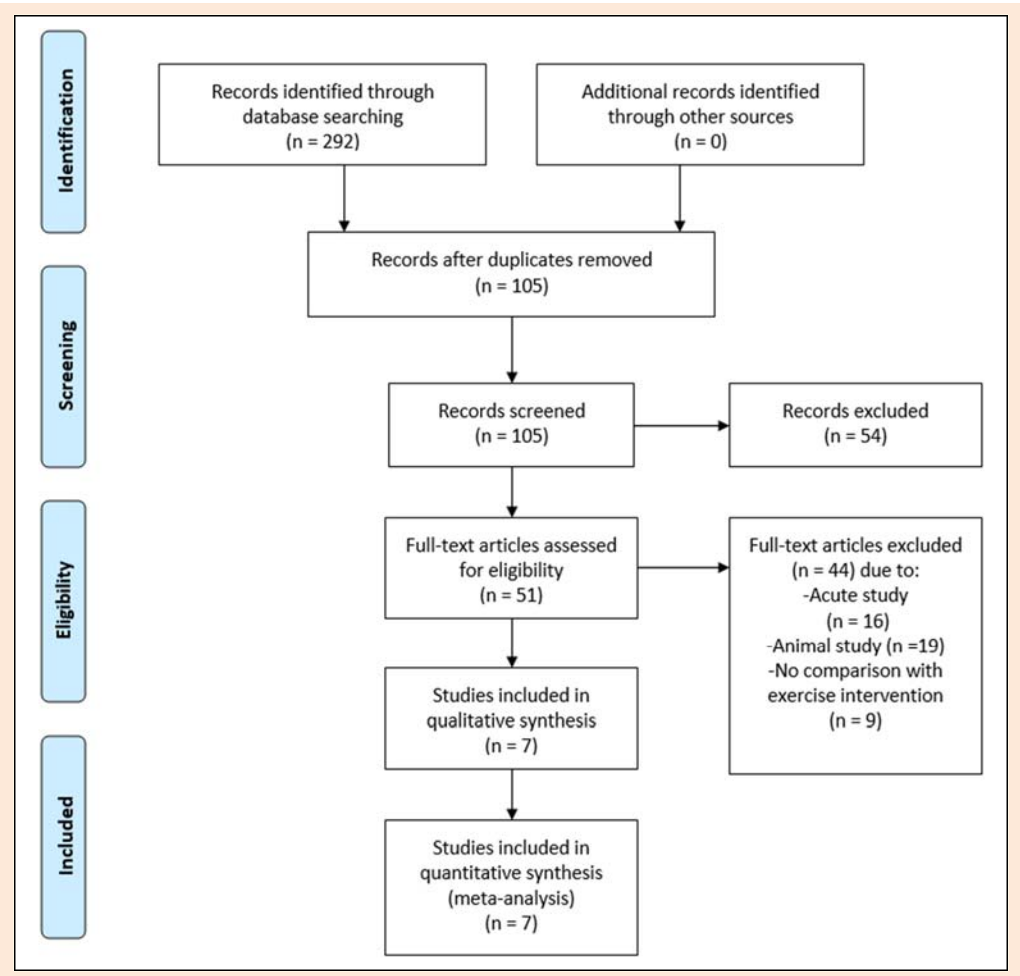

Figure 1. The flow diagram of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) employed in this study.

Inclusion and exclusion criteria

The inclusion criteria for the article selection are as follows: 1) Randomized Controlled Trial (RCT) studies; 2) Participants aged over 55; 3) Studies involved exercise with CIT supplementation for the experimental group and exercise with PLA supplementation for the control group; 4) Body composition and lower limb function were measured at pre- and post-intervention; 5) Study results were recorded in the form of mean ± standard deviation or median (interquartile range); 6) Published between January 2003 and April 2023 and 7) Full article must be available in English. Meanwhile, the exclusion criteria for this study are abstracts, conference proceedings, and posters.

Quality assessment

The Cochrane risk of bias assessment tool was utilized to evaluate the selected studies' quality (Higgins et al., 2019). The assessed quality included allocation concealment, blinding of outcome assessment, incomplete outcome data, participants and personnel blinding, random sequence generation, and selective reporting (Li et al., 2023). Each article was given a score of either "yes," "no," or "unclear." Two independent investigators evaluated each study, and if there were any disputes, another investigator facilitated consensus.

Sensitivity Analysis

Sensitivity analysis was performed if more than five studies included the same indicator. Specifically, the sensitivity analysis was conducted by excluding each study sequentially to determine the stability of the meta-analysis results.

Data extraction

The data retrieved from the selected studies were tabulated as follows: age, gender, Body Mass Index (BMI), duration, exercise program, CIT dose, and measured outcomes, as shown in Table 1.

Data analysis

Review Manager (Version 5.4.1, Copenhagen: The Nordic Cochrane Center, The Cochrane Collaboration, 2020) was employed in this study for the meta-analysis. The Standardized Mean Difference (SMD) was chosen as the suitable effect scale index, given that the study's output contains continuous variables with different test methods. Study findings expressed as median (range) were then converted to mean ± standard deviation (Hozo et al., 2005).

Furthermore, the I^2 statistics were utilized to determine the study heterogeneity. Briefly, a small I^2 suggests a low heterogeneity between the studies, while an $I^2 < 50\%$ indicates homogeneous studies. In this case, the fixed effect model was applied to analyze the data. On the contrary, an $I^2 \geq 50\%$ implies heterogeneous studies. Thus, the random effect model was applied for analysis (Li, Y. et al., 2021). The funnel plot was also used to assess the publication bias, while the SMD was evaluated using the Forest plot. Finally, uncertainty was measured at a 95% confidence interval (95% CI).

Table 1. Characteristics of the included studies.

Study	Age(y)	Participants	Disease	BMI	Duration	Exercise program	Dosage of citrulline	Measured outcomes
Buckinx (2018)	66.9 ± 4.2	28M, 28F	-	30.5 ± 4.5	12 weeks; 3x/week	HIIT; 30s 85%HRmax: 90s 65%HRmax; 10sets	10g/day	↑LLS ↔BMI; WC; FM; 6MWT; TUG
Buckinx (2020)	67.8 ± 4.2	21M, 23F	-	26.1 ± 2.55	12 weeks; 3x/week	HIIT; 30s 85%HRmax: 90s 65%HRmax; 10sets	10g/day	↓FM ↑TUG ↔BMI; WC; 6MWT; LLS
Caballero (2021)	65.1 ± 4.0	18M, 26F	Sarcopenia	25.8 ± 2.6	6 weeks	AT; RPE14; 10min. RT; RPE16; 20min	3g/day	↑6MWT ↔TUG
Figueroa (2015)	58.0 ± 1.0	27F	-	34.4 ± 1.0	8 weeks; 3x/week	WBVT; 25-40Hz; OA= 1-2 mm; Semi-squats, wide-stance semi-squats, calf raises and squats; 60s; 5sets; Side-alternating vibrations.	6g/day	↔LM; FM; LLS
Kang (2023)	62.5 ± 1.5	24F	Hypertension	29.4 ± 1.4	4 weeks; 3x/week	RT; Leg press, leg extension, leg curl, and calf raise; 50%1RM; 25min	10g/day	↑LM; LLS ↔BMI; WC; FM;
Marcangeli (2022)	67.7 ± 4.5	38M, 43F	-	29.2 ± 4.7	12 weeks; 3x/week	HIIT; 30s 85%HRmax: 90s 65%HRmax; 10sets	10g/day	↑LLS ↔WC; LM; FM; 6MWT; TUG;
Wong (2015)	58.0 ± 3.5	27F	-	34.4 ± 3.7	8 weeks; 3x/week	WBVT; 25-40Hz; OA= 1-2 mm; Semi-squats, wide-stance semi-squats, calf raises and squats; 60s; 5sets; Side-alternating vibrations.	6g/day	↔BMI

M=Male; F=Female; BMI= Body mass index; HIIT= High intensity interval training; AT= Aerobic training; RT= Resistance training; WBVT= Whole body vibration training; WC= Waist circumference; FM= Fat mass; 6MWT= 6-minute walking test; TUG= Timed Up and Go; LLS= Lower limb strength; LM= Lean mass; OA= Oscillation amplitude.

Results

Eligibility of studies

This study included seven RCT articles that met the inclusion criteria (Figueroa et al., 2015; Wong et al., 2016; Buckinx et al., 2018, 2020; A. Caballero-García et al., 2021; Kang et al., 2022; Marcangeli et al., 2022). All experimental protocols were approved by the respective institutions. The consistency level between the two independent investigators during screening was high, with a Cohen kappa coefficient of 0.92. Out of 303 participants in the included articles, 105 were males and 198 were females, with 157 belonging to the PLA group and 146 to the CIT group. Both groups performed the same exercise protocol with a study duration of six to 12 weeks. The CIT dose was 10 g/day in four studies (Buckinx et al., 2018, 2020; Kang et al., 2022; Marcangeli et al., 2022), 6 g/day in two studies (Figueroa et al., 2015; Wong et al., 2016), and 3 g/day in one study (Caballero-García et al., 2021).

Quality assessment

Figure 2 presents the potential risk of bias and methodological quality of the seven selected studies. Most studies recorded a low risk of bias (69.4%), while the remaining exhibited a high (10.2%) and unclear (20.4%) bias. Regardless, the overall quality of the seven selected studies was relatively high.

Sensitivity analysis

Overall, the analysis type was modified, the impact size was changed, and after individual studies were excluded, the meta-analysis did not show any significant changes in each group, indicating the reliability of the research results.

Quantitative synthesis

Four studies evaluated the effects of exercise with CIT or PLA on the BMI, Waist Circumference (WC), Lean Mass (LM), 6-Minute Walking Test (6MWT), and Time Up and Go (TUG) test among older overweight adults. Meanwhile, five studies compared the impacts of exercise with CIT or PLA on the fat mass (FM) and Lower Limb Strength (LLS). Accordingly, significant improvements were observed with CIT supplementation with 6MWT (P = 0.04, z = 2.05), SMD (95% CI) = -0.28 (-0.54, -0.01) (Figure 3a), and LLS (P < 0.01, z = 2.85), SMD (95% CI) = -0.38 (-0.65, -0.12) (Figure 3c) among overweight older adults compared to the PLA supplementation. In addition, no significant heterogeneity was detected between each study (Heterogeneity test of 6MWT: P = 0.37, I^2 = 4%; Heterogeneity test of LLS: P = 0.22, I^2 = 30%) (Figure 3a and Figure 3c).

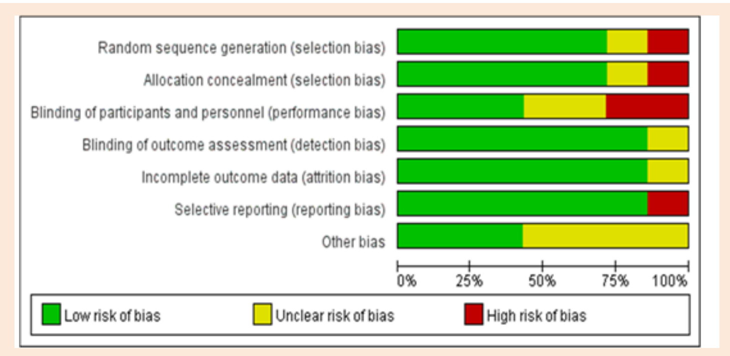

Figure 2. Analysis of the risk of bias according to Cochrane Collaboration guideline.

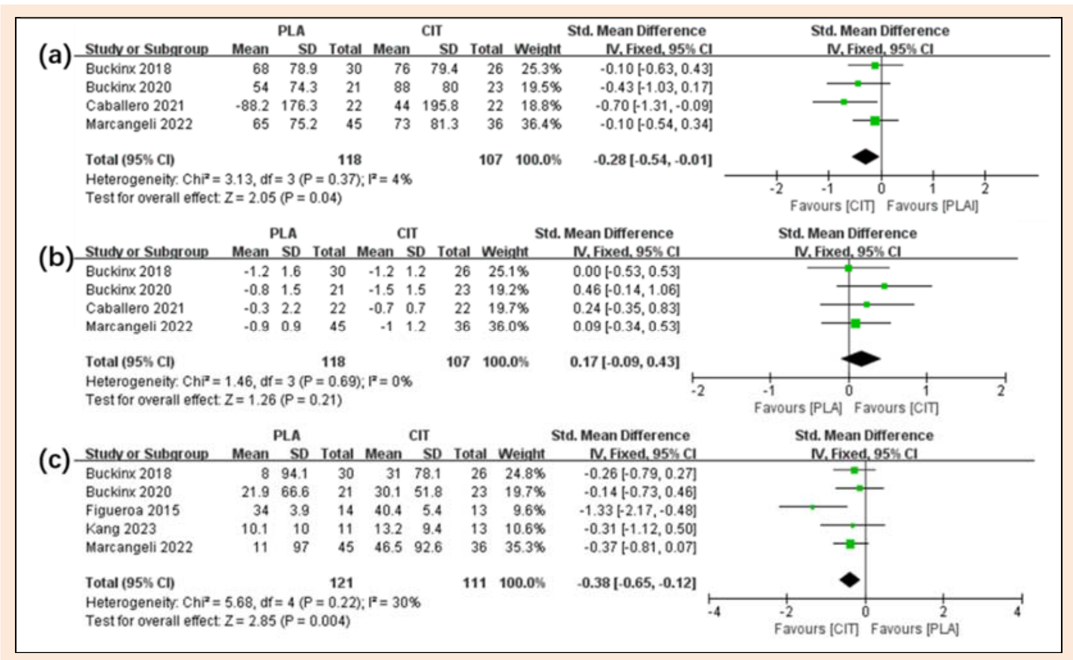

Figure 3. Forest plot depicting the effects of CIT vs. PLA supplementation on 6-minute walking test (a), time up and go test (b), and lower limb strength (c). CIT citrulline group; PLA placebo group.

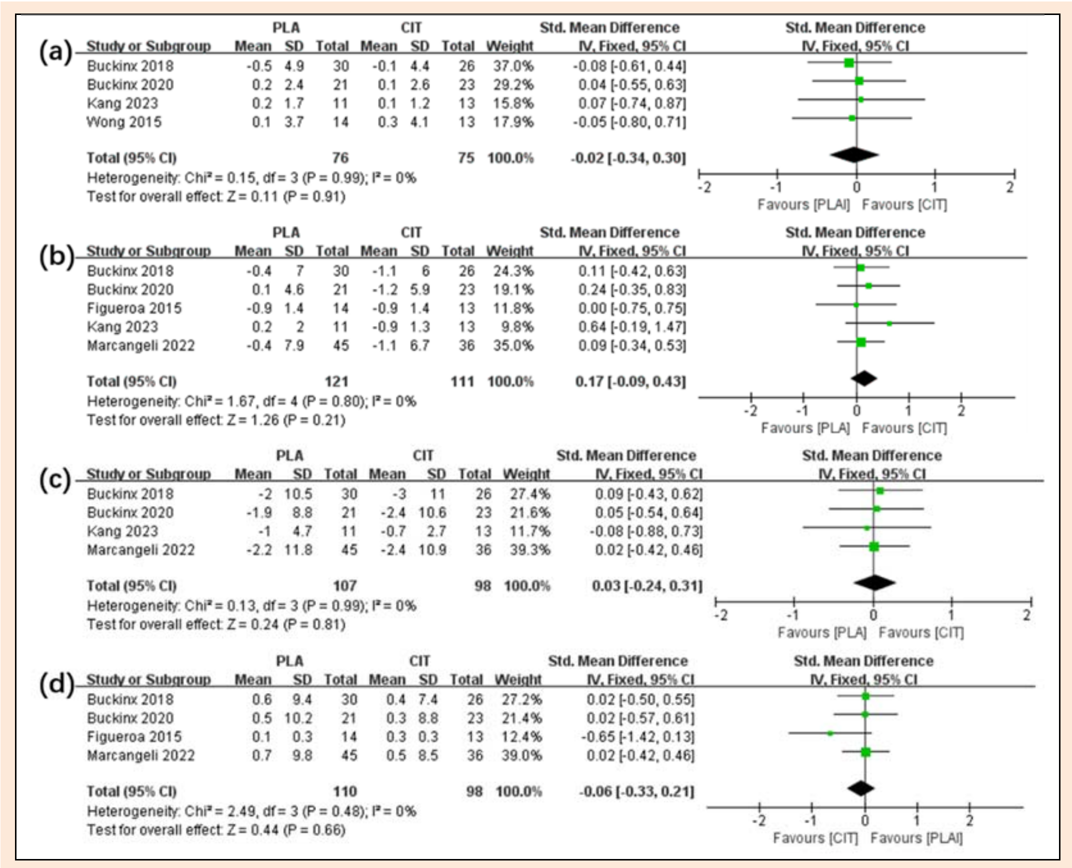

Figure 4. Forest plot illustrating the effects of CIT vs. PLA supplementation on body mass index (a), body fat (b), waist circumference (c), and lean mass (d). CIT citrulline group; PLA placebo group.

Apart from that, the BMI (P = 0.91, z = 0.11), SMD (95% CI) = -0.02 (-0.34, 0.30) (Figure 4a), FM (P = 0.21, z = 1.26), SMD (95% CI) = 0.17 (-0.09, 0.43) (Figure 4b), WC (P = 0.81, z = 0.24), SMD (95% CI) = 0.03 (-0.24, 0.31) (Figure 4c), LM (P = 0.66, z = 0.44), SMD (95% CI) = -0.06 (-0.33, 0.21) (Figure 4d) and TUG (P = 0.21, z = 1.26), SMD (95% CI) = 0.17 (-0.09, 0.43) (Figure 4b) between the CIT and PLA groups were insignificantly different. Likewise, heterogeneity was not detected across the studies (BMI: P = 0.99, I^2 = 0%; FM: P = 0.80, I^2 = 0%; WC: P = 0.99, I^2 = 0%; LM: P = 0.48, I^2 = 0%; TUG: P = 0.69, I^2 = 0%).

Publication bias analysis

The seven selected studies fulfilled the minimum requirement of using the funnel plot for the publication bias analysis. As such, the analysis generated a left-right symmetrical distribution, suggesting a low chance of publication bias (Figure 5 and Figure 6).

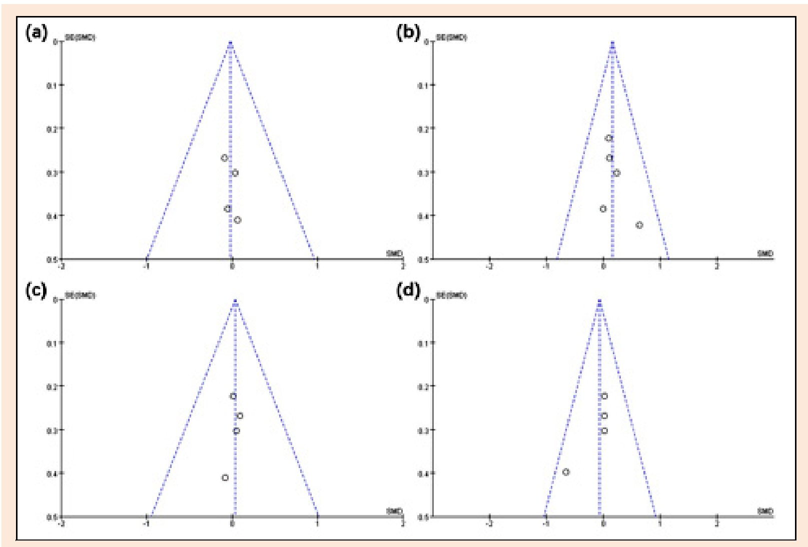

Figure 5. Funnel plot of publication bias for body mass index (a), body fat (b), waist circumference (c), and lean mass (d) in the CIT vs. PLA.

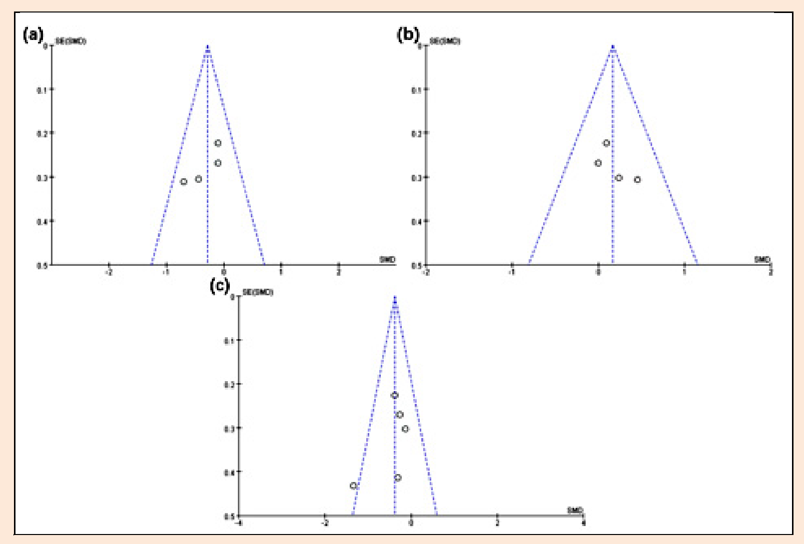

Figure 6. Funnel plot of publication bias for 6-minute walking test (a), time up and go test (b), and lower limb strength (c) in the CIT vs. PLA.

Discussion

The current study explored the impact of combined exercise with CIT supplementation on the body composition and lower limb function of overweight older adults. Based on the developed search strategy, seven studies with participants' BMI greater than 25 kg/m^2 were selected for the meta-analysis. The findings showed that the combined exercise with CIT supplementation enhanced 6MWT and LLS among overweight older adults more than with PLA supplementation. However, body composition was unaffected by the intervention protocol.

The study findings also suggested that the CIT supplementation effectively improved the physical function of overweight older adults, consistent with earlier reports. For instance, a six-week exercise program with CIT supplementation (3g/day) (Caballero-García et al., 2021) (N = 44) reported significant improvements in the walking speed of older adults in the CIT group compared to those in the PLA group. The results may be attributed to the enhanced muscle strength post-intervention. Therefore, CIT supplementation was considered a viable alternative rehabilitation plan for overweight older adults to improve their physical function.

Muscle strength is an indicator of daily physical function among older adults. Reduced physical activity results in weakened lower limbs and causes anabolic resistance, which is critical for regaining muscle mass (Breen et al., 2013; Devries et al., 2015). Muscle strength also declines with age, particularly in the legs, impairing physical performance and increasing the mortality risk (Manini and Clark, 2012). Therefore, overweight older adults should maintain their leg muscle mass and strength (Janssen et al., 2000). This review noted a more significant improvement in muscle strength in the CIT group than in the PLA group, which agrees with previous reports (Buckinx et al., 2020; Kang et al., 2022).

Although the mechanism of increased muscle mass is currently unclear, the increase in exercise performance may be related to changes in oxygen (O_2) transport and more regular utilization of skeletal muscles. Another study reported the impact of one week oral CIT supplementation (6 g/day) on muscle O_2 delivery and utilization in healthy young adults to increase muscle oxygenation index and lower the pattern of muscle deoxyhemoglobin during high-intensity cycling (Bailey et al., 2015). It was postulated that improving O_2 availability and distribution within the muscle microvasculature enhanced their performance during exercise.

Besides, the effect of CIT supplementation (2.4 g/day) for a week on healthy trained men was previously assessed (Suzuki et al., 2016). Following the CIT supplementation, they were able to complete 4 km of cycling for a much shorter time with increased power output, although no significant difference in O_2 consumption between the PLA and CIT groups was detected. Likewise, male athletes supplemented with CIT (3 g/day) for a week recorded an improved pedaling speed and average power output (Terasawa and Nakada, 2019).

The recent study also revealed that CIT supplementation resulted in exercise performance and anti-fatigue during high-intensity exercise (Terasawa and Nakada, 2019). This improvement could be attributed to enhanced peripheral vasodilation and perfusion. The benefits of CIT on exercise performance may be attributed to improving peripheral vascular relaxation/perfusion and subsequent muscle O_2 utilization by increasing the bioavailability of NO in active skeletal muscles, as studies have shown that CIT may be an important source of NO and may affect muscle function (Wang et al., 2001; Smith et al., 2002). CIT supplementation could also prevent the elevation of exercise-induced blood ammonia in mice, resulting in prolonged exhaustion (Takeda et al., 2011).

Intense exercise and fatigue lead to ammonia accumulation in the muscle, which is associated with various functional and metabolic neurological disturbances. Furthermore, ammonia accumulation was reported to inhibit mitochondrial oxidation of pyruvate to acetyl-CoA and reduced ATP output via the Krebs cycle, leading to muscle fatigue (Mutch and Banister, 1983; Takeda et al., 2011). Since CIT is a component of the urea cycle, CIT supplementation may promote ammonia elimination via the urea cycle, but the mechanism has yet to be elucidated. Hence, an in-depth mechanism of ammonia elimination through CIT supplementation should be examined.

It is worth highlighting several limitations in this review study. First, the sample size only encompassed seven studies, which was considered fairly small. In addition, the review solely considered the combined effects of exercise with CIT supplementation. Thus, the impact of CIT supplementation alone on the measured outcomes was unknown. Therefore, the intervention results were interpreted exclusively based on the influence of exercise. It is recommended that future research should include more high-quality RCT studies with varying populations to improve the accuracy and impact of the study outcome.

Conclusion

The meta-analysis in this study demonstrated that combined exercise with CIT supplementation could be an effective non-pharmaceutical intervention to improve the physical function of overweight older adults by increasing their muscle strength.

Acknowledgements

The authors report there are no competing interests to declare. The present study complies with the current laws of the country in which it was performed. The datasets analysed in this research are available from the corresponding author upon reasonable request.

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Key points

- Exercise or CIT supplementation may improve the physical function and body composition of older adults.
- Exercise with CIT supplementation showed greater improvement in the lower limb function and strength of overweight older adults than without CIT.
- Exercise with CIT supplementation may not improve body fat percentage and muscle mass of older adults.

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