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REVIEW ARTICLE

Effects of Cardiac Rehabilitation on Executive Function in Sedentary Older Adults: A Systematic Review

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ABSTRACT

Cardiac rehabilitation(CR) can help improve cognitive function in sedentary older adults. However, there is no systematic review about effects of CR on cognitive function in these older adults. We have performed a systematic review to assess the validity of the current data, including recent randomized controlled trial(RCT) and prospective studies that the effect of CR on cognition in older adults. All studies were searched on the PubMed and Cochrane Library from January 1, 2000 to September 30, 2016. Seven hundred sixty-eight studies were identified using the database as described in the Methods section. After removal of duplicates and determined whether it met inclusion criteria, 68 full-text studies were assessed for eligibility. Sixty-one studies were excluded, leaving 7 studies that were eligible for review. A total of 7 studies were included in the analysis. Only two studies were RCT. The majority (n=5) were categorized as prospective studies. a meta-analysis of two studies demonstrated that improved executive function in sedentary older adults after CR sessions when compared to controls. In conclusion, our meta-analysis showed that CR improved executive function in sedentary older adults.

<Key-words>

cardiac rehabilitation, physical exercise, executive function, cognitive function

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I. Background

Much in the decline can be attributed to effective management of risk factors associated with the disease (Anazodo, Shoemaker, Suskin, et al., 2013). However, cardiovascular disease (CVD) still remains the leading cause of non-communicable disease deaths in 2012 and was responsible for 17.5 million deaths, or 46% of non-communicable disease deaths. Of these deaths, an estimated 7.4 million were due to heart attacks (ischaemic heart disease) and 6.7 million were due to strokes (WHO, 2014).

One growing concern is the potential link between cardiovascular disease risk factors and neurological impairment in older adults (Anazodo, Shoemaker, Suskin, et al., 2013). A number of studies have demonstrated that risk factors for CVD are associated with accelerated brain decay and alterations to the natural age-related decline in cerebrovascular functions (Friedman, Tang, de Haas, et al., 2014; de Toledo Ferraz Alves, Ferreira, & Busatto, 2010).

Interestingly, when older adults with CVD performed aerobic exercise training, typically included in cardiac rehabilitation (CR) program, improved coronary flow, lower the risk of myocardial reinfarction, lower mortality rates, and improve overall cardiac function (Shephard & Balady, 1999). CR can also help improve cognitive function in sedentary older adults. Observational studies have demonstrated that physical activity is associated with a slowing in age-related decline of cognition and reduction in cognitive impairment (Weuve, Kan, Manson, et al., 2004; Abbott, White, Ross, et al., 2004).

However, the effect of exercise on cognitive function remains controversial. One RCT reported that moderate-intensity physical activity program focused on walking strength, flexibility, and balance training compared with a health education program did not result in improvements in global or domain-specific cognitive function (Sink, Espeland, Castro, et al., 2015). Furthermore, according to a recent Cochrane review, revealed that there was no clear evidence of benefit from exercise on cognitive functioning in people with dementia (Forbes, Forbes, Blake, et al., 2015). However, this review included various types of exercise intervention such as walking, catching, throwing, kicking balls, leg weight exercise, parachute reaches, passing a bean bag, playing volleyball, and dance. Higher-intensity aerobic training programmes, supplemented by resistance training, have been recommended and deemed safe for CR patients by many authorities (Price, Gordon, Bird, et al., 2016). Exercise prescription for aerobic and resistance training that is based on evaluation findings, risk stratification, patient and program goals and resources. Aerobic exercise as CR program is consisted of walking, treadmill, cycling, rowing, stair climbing, arm ergometry, and others. On the other hand, resistance exercise as CR program is consisted of elastic bands, cuff/hand weights, dumbbells, free weights, wall pulleys, or weight machines (Balady, Ades, Comoss, et al., 2000).

Although the documentation of neuropsychological changes in patients who are affected by exercise has not been recognized, CR programs combining aerobic and

resistance training together, may be more beneficial for cognitive function than aerobic exercise or resistance training alone (Schopfer & Forman, 2016). However, there is no systematic review about effects of CR on cognitive function in sedentary older adults.

In this study, we have performed a systematic review to assess the validity of the current data, including recent RCT and prospective studies that provide a broad-based view of the effect of CR on cognition in older adults.

II. Methods

1. Data searches and sources

All studies were searched on the PubMed and Cochrane Library from January 1, 2000 to September 20, 2016. We used Medical Subject Headings (MeSH) terms to find studies of CR including: cardiac rehabilitation/aerobic exercise/physical fitness. To reduce our findings to studies that measured cognitive function and CR, we searched using the following MeSH terms: (cognition*, cardiovascular diseases/rehabilitation*) (cognition disorders/rehabilitation*, cardiovascular diseases*), and (cognition/physiology*, cardiovascular diseases*). To further reduce our findings to studies that focused on human subjects, we searched using the MeSH terms: clinical trials*, and humans*.

2. Inclusions criteria

1) Type of studies

We included in our analysis only those studies that met the following criteria: 1) they addressed randomized clinical trials (RCT), case-control surveys or prospective study; 2) the reported data were suitable for analysis; 3) they were published in English.

2) Type of participants

We included only participants met the following criteria: 1) they were 50 years or older; 2) they have attended at least one CR program of walking, treadmill, cycling, rowing, stair climbing, arm ergometry, and others; 3) they diagnosed with New York Heart Association (NYHA) heart failure class II, III, or IV; 4) they had an myocardial infarction (MI), had undergone revascularization (coronary artery bypass grafting [CABG] or percutaneous coronary intervention [PCI]), or had angina pectoris or coronary artery disease [CAD] defined by angiography; 5) they reported 1 or more of the cognitive outcomes: global cognitive function, memory, language, executive function and so on.

3. Exclusions criteria

Studies were excluded if they were: 1) non-intervention studies; 2) review studies; 3) animal studies; 4) abstracts; 5) participants had a history or current diagnosis of a significant neurological disorder (dementia, stroke, or Parkinson's disease), head injury, severe psychiatric disorder, or substance abuse/dependence.

4. Interventions

CR is a comprehensive secondary prevention program that has evolved as a standardized component of the cardiovascular armamentarium (Schopfer & Forman, 2016). In this study, CR program was considered to be any aerobic exercise of any intensity, duration, or frequency that aimed to improve cognitive function.

5. Outcome measures

All selected studies should be assessed cognitive function. There were no limitations to the measurements taken as long as quantitative and objective measures of cognition (e.g., global cognitive function, memory, language, or executive function) were recorded.

6. Risk of bias

Risk of bias of included RCT studies was assessed using the Cochrane Collaboration's core risk of bias items (Higgins & Green, 2011). Studies reporting significant effects of CR programs on cognitive functions are more likely to be published as compared to studies in which no significant results were found. However, it is unlikely that this publication bias would affect our results since we focused on cognitive function as the main outcome of cardiac rehabilitation.

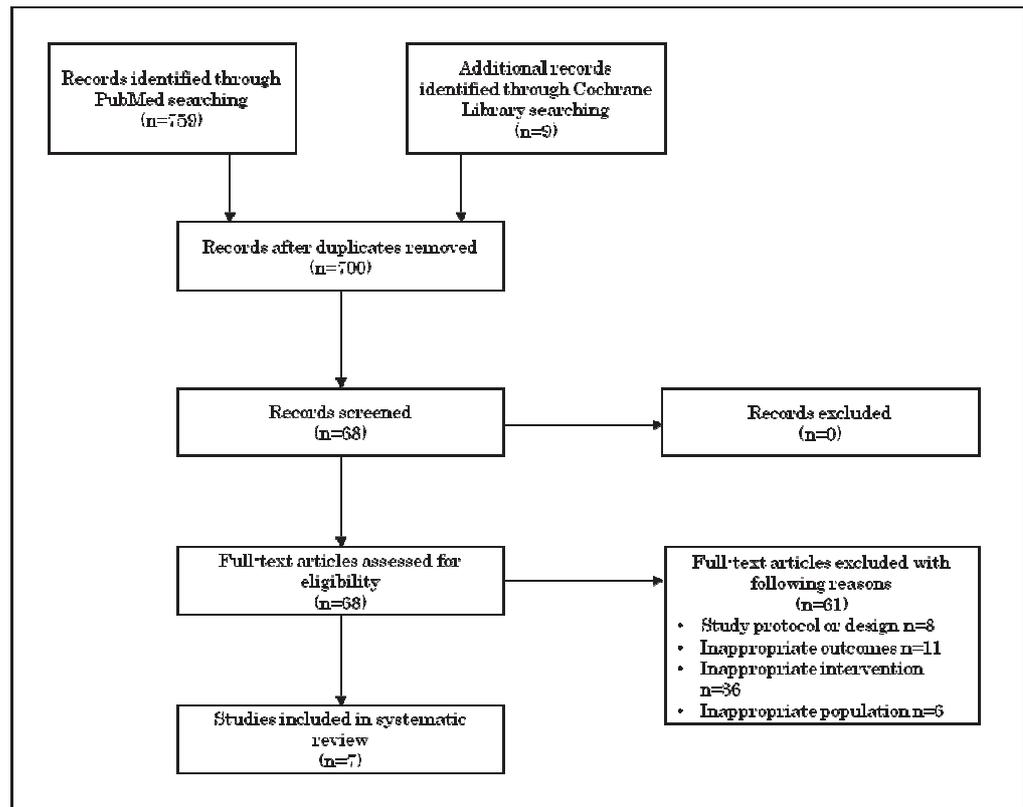
7. Data analysis

Mean scores and standardized deviations were extracted from the reviewed studies. Standardized mean difference (SMD) was calculated for proportions (fixed-effect model) (Vogels, Scheltens, Schroeder-Tanka, et al., 2007). Calculations were performed using a fixed effects model. One comparison was made: cardiac rehabilitation versus control group. An α value of 0.05 was considered statistically significant. All analyses were conducted using Review Manager version 5.3.

III. Results

1. Description of studies

Seven hundred sixty-eight studies were identified using the database as described in the Methods section. After removal of duplicates and determined whether it met inclusion criteria, 68 full-text studies were assessed for eligibility. Sixty-one studies were excluded, leaving 7 studies that were eligible for review (Figure 1).



<Figure 1> Flowchart of study selection process

2. Characteristics of included studies

Characteristics of the studies that were included in the review are summarized in table 1 and table 2. A total of 7 studies were included in the analysis. Only two studies were RCT. The majority (n=5) were categorized as prospective studies. The median follow-up of 12 weeks, with 1 study reporting at least 2 weeks of follow-up, and 6 reporting follow-up of 12 weeks or more. The median age of participants across studies was 66.8 years. Most studies were small in sample size (median n=49; range 18 to 80). Most studies were conducted in a supervised hospital/university-based setting. Six studies were comprehensive CR, and 1 study included both CR and music intervention. The trail making test (TMT) A and B, which measures attention, perceptual speed, cognitive flexibility and visual memory was used in six studies. In two RCTs, participant groups were sedentary or had lightly active lifestyle with no cognitive impairment. In five prospective studies, all patient groups had CVD, heart failure(HF), coronary artery disease(CAD), or coronary heart disease(CHD) (table 1). All RCTs reported cognition was improved by performed CR. In 5 prospective studies, although these were conducted pre-post comparison in only intervention group, 3 studies were significantly improved global cognition, attention, executive function, and verbal fluency (table 2).

<Table 1> Design, methods, interventions and assessment, and outcome measures in included

Source and study design	Participants	Intervention	measurements
Randomized controlled trial(n=2)			
Iuliano et al (2015)	Eighty participants, 32 males and 48 females, aged 66.96 ± 11.73, volunteered for this study. Inclusion criteria was sedentary or they had lightly active lifestyle. The participants were randomly divided into the four following groups: Resistance group(n=20), Cardiovascular group(n=20), Postural group(n=20), Control group(n=20).	All exercise types were conducted in a local gym, 3 times per week for 12 weeks. Each session lasted 30 minutes. Resistance group performed high intensity strength training involving six muscle groups: shoulders, arms, chest, abdomen, back and legs. Cardiovascular group performed high intensity cardiovascular training on ergometer machines, including treadmills, cyclo-ergometers and step-ergometers. Postural group performed low intensity training based on postural and balance exercises. Control group did not perform any type of training.	<ul style="list-style-type: none"> Attentive matrices test(Attentive test) Raven's progressive matrices tests(Raven test) Stroop color word interference test(Stroop test) Trail making test A and B Drawing copy test
Vaughan et al (2014)	Forty-nine women aged 65 to 75 years, with no cognitive impairment. Inclusion criteria was they were doing <60min of formal exercise each week. The participants were randomly divided into the two groups: an intervention group(n=25) or a control group(n=23).	Exercise was conducted in a university campus and community-based halls. Intervention group attended a 60-min class, twice a week for 16 weeks. Each session included cardiovascular(aerobic), strength(resistance) and motor fitness(balance, co-ordination, flexibility and agility) training and a formal warm-up and cool-down routine. The control group was asked to continue with usual activities.	<ul style="list-style-type: none"> The California older adult stroop test (COAST) The controlled oral word association test (COWAT) The letter-number sequencing(LNS) test Trail making test A and B(TMT)
Prospective study(n=5)			
Alosco et al (2014)	Fifty two patients with HF completed a 12-week phase II CR program, 12-month follow-up(mean age=66.7 ±7.8years).	The majority of exercise sessions were conducted at hospital. The phase II CR program: 12 weeks with three exercise/education sessions per week. Each session consists of 1 hour of exercise and 1 half an hour of education. The session consisted of warm-up, cool down, stretching, and a 40-minute aerobic exercise such as rowers, treadmills, stationary cycles, elliptical trainers, stationary steppers, and arm exercises.	<ul style="list-style-type: none"> The mini mental state examination(MMSE) Trail making test A and B, Digit symbol coding The California verbal earning test-second edition(CVLT-II) The Boston naming test, the animal fluency test

Stanek et al (2011)	Fifty-one older adults with CVD: myocardial infarction, cardiac surgery, HF, CAD, and/or hypertension(mean age=67.8±9.1years).	Exercise was conducted in a hospital. Electrocardiogram-monitored exercise and education program is up to 12 weeks, with three sessions per week. Each CR session consists of 1 hour of exercise and 30 minutes of education. Individualized plans consist of warm-up, cooldown, stretching, and a 40-minute aerobic exercise including rowers, treadmills, stationary cycles, elliptical trainers, stationary steppers, and arm exercises.	<ul style="list-style-type: none"> • Modified MMSE(3MS) • Trail making test, Letter-number sequencing (LNS) subtest of Wechsler adult intelligence scale-III • Hopkins verbal learning test-revised learning, delayed recall, and recognition discrimination(HVLT-R), Brief visual memory test-revised learning, delayed recall, and recognition discrimination(BVMT-R) • Boston naming test-short form(BNT-15), Animal naming
Carles et al (2007)	Twenty-four male patients with CAD(n=12) or HF(n=12) who participated in a CR program(mean age=51.6 ±6.5years).	Patients underwent a standard CR program, including a 10-minute warm-up period followed by 35 minutes of exercise on a treadmill, a stair machine, and a leg ergometer, at an intensity ranging from 70% to 80% of heart rate reserve. Exercise was performed 5 times a week for 2 weeks and the program included 14.6±3.0 training sessions.	<ul style="list-style-type: none"> • Exclusively cognitive solicitation (COG): mental arithmetic test, trail making test, memory test • A tracking task (TRAC) with a mouse on a computer screen
Gunstad et al (2005)	A total of 18 persons with CHD(13 males, and 5 females, mean age=68.1±7.7years)	Exercise was conducted in a hospital. All participants received standard care as part of a phase II CR program. Exercise training began with 10- 50 15-minute intervals of activity, with a gradual increase to 30 to 45 minutes of continuous aerobic exercise 3 times per week for 75 minutes for 12 weeks.	<ul style="list-style-type: none"> • Trail making test A • Grooved pegboard • Category fluency • Digit symbol-coding • The Beck depression inventory • Animal naming
Emery et al (2003)	Thirty-three men and women (mean age=62.6±10.5 years) with CAD.	Exercise was conducted in a university center. During the one of the exercise sessions, participants listened to a taped musical selection through earphones attached to a personal cassette recorder. Each participant completed both 12-week exercise sessions, with the order of conditions determined by random assignment. Exercise sessions consisted of 10 minutes of gradual increase in slope and speed of the treadmill until reaching the equivalent of 85% of VO ₂ max.	<ul style="list-style-type: none"> • The verbal fluency test

Abbreviation: heart failure; HF, cardiovascular disease; CVD, coronary artery disease; CAD, coronary heart disease; CHD.

<Table 2> Results of included studies

Source and study design	Results
Randomized controlled trial (n=2)	
Iuliano et al (2015)	Significant differences were found among the four groups in the cognitive scores: Attentive test target (p=0.048), Raven test score (p=0.018), Raven test time (p=0.045) and Drawing copy test time (p=0.037). No significant differences in the scores of the other cognitive variables or in the interaction Time×Groups were found.
Vaughan et al (2014)	The neurocognitive performance scores showed between group differences for TMT A and B tests(p<0.05), COAST word(p<0.05), Interference and Total and the COWAT(p<0.01).
Prospective study(n=5)	
Alosco et al (2014)	Repeated measures analyses showed a significant time effect for both attention/executive function and memory(p<0.05). Attention/executive function performance increased from baseline to 12 weeks and these gains remained up to 12 months; memory was unchanged from baseline to 12 weeks, but then improved between the 12-week and 12-month time points.
Stanek et al (2011)	Repeated measures ANOVA showed improvements in global cognition, attention-executive-psychomotor function, and memory. Improvement in METs was related to improved verbal recall.
Carles et al (2007)	A significant effect was found for COG and TRAC at rest(p<0.05). During exercise, COG score significantly improved but TRAC score remained unchanged after training.
Gunstad et al (2005)	Posttests revealed significant improvement on Trail making test A(P=0.03) and Digit symbol-coding(p=0.03). No change from baseline to follow-up emerged for Grooved Pegboard(P=0.10) or Animal naming(p=0.47) performance.
Emery et al (2003)	Analysis of verbal fluency scores revealed a significant time × condition interaction(F(1,30)=4.92, p=0.03). The music condition was associated with significant improvements in verbal fluency, but the no-music control condition was not associated with cognitive change.

3. Risk of bias

The overall risk of bias across domains was judged to be low or unclear. In the sequence generation, a random number list and an independent randomization service were reported. In the allocation concealment and blinding of participants, personnel and outcome assessors, 1 study was assessed separately high risk of bias. In the incomplete outcome data, 1 study did not address missing outcome data. In the selective outcome reporting, both studies were assessed low risk of bias. In the other sources of bias, we could not figure out whether an important risk of bias exists or not.

<Table 3> The risk of bias of included RCT studies

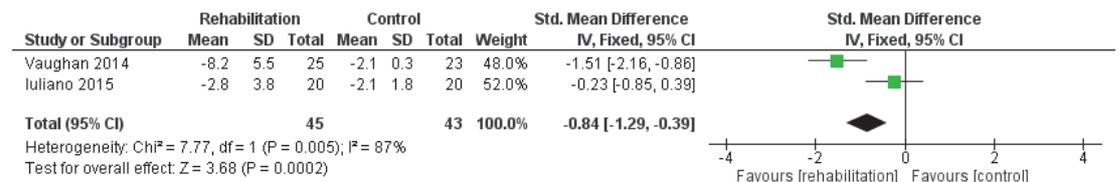
	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Iuliano et al(2015)	Low	High	Low	Unclear	Low	Unclear
Vaughan et al(2014)	Low	Low	High	Low	Low	Unclear

Low; Low risk of bias, Unclear; uncertain risk of bias, High; High risk of bias

4. Outcomes of included studies

1) Trail making test A

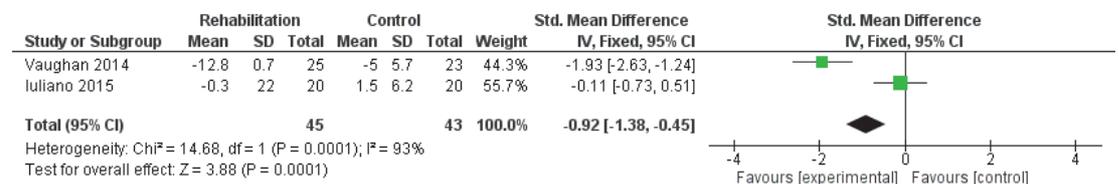
Both RCT studies assessed trail making test A as an outcome. The meta-analyses showed a significant improvement in trail making test A of -0.84 (95% confidence interval (CI):-1.29, -0.39, n=88) for participants in the rehabilitation group compared with controls.



<Figure 2> Trail making test A (TMTA) scores

2) Trail making test B

Both RCT studies assessed trail making test B as an outcome. The meta-analyses showed a significant improvement in trail making test B of -0.92(95% confidence interval (CI):-1.38, -0.45, n=88) for participants in the rehabilitation group compared with controls.



<Figure 3> Trail making test B (TMTB) scores

IV. Considerations and Conclusions

We conducted an updated systematic review and meta-analysis of CR on cognitive function in older adults. In the present review, a meta-analysis of two studies demonstrated that improved executive function in sedentary older adults after CR sessions when compared to controls.

CR is a multidimensional treatment designed to promote and facilitate physical activity and a healthful lifestyle in the context of known CVD, with tremendous relevance for older populations (Balady, Williams, Ades, et al., 2007). However, to date, no meta-analysis examined in effect of CR in older adults. This review is important because it analyzes CR as a potential modality in sedentary older adults.

Our meta-analysis showed 14.4% improvement in TMTA in the rehabilitation group. The mean TMTA in the two studies analyzed was 38.3 at baseline and 32.8 at the end of

the CR. In regard to TMTB, our meta-analysis showed 16.2% improvements in the rehabilitation group. The mean TMTB in the two studies analyzed was 71.4 at baseline and 59.9 at the end of the CR. The magnitude of change is similar to a previous analysis that evaluated the effect of different modalities of exercise in older adults (Vaucher, Herzig, Cardoso, et al., 2014).

CR is shown to be effective in the executive function of older adults. Recent meta-analysis examined the potential moderating effect of aerobic fitness on exercise-induced benefits on executive function. Ludyga and his colleagues reported that aerobic fitness is suggested to have an impact on executive function in older adults compared to other age groups (Ludyga, Gerber, Brand, et al., 2016). However, in this review, 3 of 9 studies were RCTs in older adults (6 studies were crossover studies (Córdova, Silva, Moraes, et al., 2009; Netz, Tomer, Axelrad, et al., 2007; Wang, Shih, Pesce, et al., 2015), the exercise duration was short range from 20 min to 35 min per session. One of these reports was concluded acute exercise does not broadly affect the entire family of executive functions, or its effect on a specific aspect of executive function may be task-dependent (Wang, Shih, Pesce, et al., 2015). Our results are very similar to previous study, one RCT was reported no significant improvement in cognitive function except for attentive and analytic tasks. Nevertheless, our meta-analyses showed a significant improvement in executive function.

Recent meta-analysis revealed that there was no clear evidence of benefit from exercise on cognitive functioning in dementia. The estimated standardized mean difference between exercise and control groups was 0.43(95% CI: -0.05 to 0.92, P value 0.08; 9 studies, 409 participants). There was very substantial heterogeneity in this analysis (I^2 value 80%), most of which they were unable to explain, and the quality of this evidence as very low (Forbes, Forbes, Blake, et al., 2015). In our results, there was significant improvement in executive function although we detected significant heterogeneities in both scales (TMTA: I^2 value 87%, TMTB: I^2 value 93%). It is possible that the physical exercise consisted of cardiac rehabilitation such as treadmills and cycle ergometer, and cognitive impairment was relatively higher than dementia patients. On the other hand, another recent RCT was reported that a 6-month lower limb aerobic exercise with a multicomponent cognitive intervention was associated with better cognitive function compared with only a multicomponent cognitive intervention. Aerobic exercise may enhance supportive care in individuals with moderate to severe cognitive impairment (Kim, Han, Min, et al., 2016).

Our review has several limitations. First, our search strategy only found two RCTs with small samples. Second, different variables may influence the effects of CR such as sex and culture. Nevertheless, CR appears to be an interesting means and deserves further investigation with better-controlled RCT. Third, it remains unclear how other exercise intensities influence executive control and if those effects are further moderated by the subjects' characteristics. Future meta-analyses are encouraged to address this

issue and are expected to benefit from a higher availability of effect sizes for exercise-induced changes in executive control after mild, moderate, and vigorous aerobic exercise. However, this requires an increase of the number of studies investigating possible benefits of different exercise modalities on executive function (Córdova, Silva, Moraes, et al., 2016).

In conclusion, considering the available data, our meta-analysis showed that CR improved executive function in sedentary older adults. However, our sample size was too small with only two RCTs. Future trials need to pay increased attention to recruitment of not only healthy older adults but also patients who are more representative of the broader CVD population.

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