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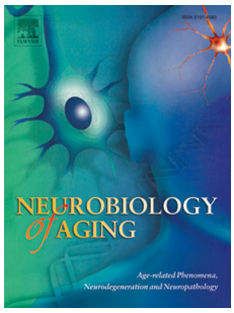


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# Impact of exercise training on physical and cognitive function among older adults: a systematic review and meta-analysis

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**Abstract**

Exercise plays a key role in healthy aging by promoting both physical and cognitive function. Physical function and cognitive function appear to be interrelated and may share common mechanisms. Thus, exercise-induced improvements in physical function and cognitive function may co-occur and be associated with each other. However, no systematic review has specifically assessed and compared the effects of exercise on both physical function and cognitive function in older adults, and the association between changes in both outcomes following exercise training. Thus, we conducted a systematic review and meta-analysis (N= 48 studies) among older adults (60+ years). These data suggest exercise training has a significant benefit for both physical function ($g$= 0.39; $p$< 0.001) and cognitive function ($g$= 0.24; $p$< 0.001). At the study level, there was a positive correlation between the size of the exercise-induced effect on physical function and on cognitive function ($b$= 0.41; $p$= 0.002). Our results indicate exercise improves both physical and cognitive function, reiterating the notion that exercise is a panacea for aging well.

## 1. Background

Maintaining older adult physical and cognitive function are critical for healthy aging (Morley, 2016; Morley et al., 2015). The loss of both physical and cognitive function leads to functional dependence and increases morbidity and mortality (Njegovan et al., 2001; Panza et al., 2018). Forty-four percent of older adults have physical disability (i.e., physical weakness if aged 65 years and older) which increases the risk of activities of daily living impairment by 54% (Duchowny et al., 2017). Furthermore, one new case of dementia is detected every four seconds (World Health Organization and Alzheimer's Disease International, 2012), for which there is no pharmaceutical cure. Given that the number of older adults worldwide is increasing (Vincent and Velkoff, 2010), strategies that maintain older adult physical and cognitive health are imperative to relieve an already overburdened healthcare system.

Aging is associated with both impaired physical and cognitive function. Moreover, evidence suggests that impaired physical and cognitive function are linked (Clouston et al., 2013). For example, lower cognitive performance predicts declines in gait speed (Best et al., 2016), and slower gait speed precedes cognitive decline (Mielke et al., 2012). These data appear to indicate that age-related changes in both domains are driven by a unifying process (Christensen et al., 2001); that is, declines in both physical and cognitive function may be due to age-associated changes in brain circuitry (Baillieux et al., 2008), brain pathology (Penke et al., 2010), and molecular fidelity (Farooqui and Farooqui, 2009). Given the apparent link between age-associated declines in physical and cognitive function, it is important to investigate strategies which may promote improvements in both physical and cognitive health.

One important strategy which benefits both physical and cognitive health is exercise training (Nagamatsu et al., 2014). Physical exercise is a demonstrated effective intervention for

improving older adult cognitive performance independent of baseline cognitive ability (Northey et al., 2018). Indeed, current guidelines suggest that all older adults should engage in exercise training as a means of promoting both physical and cognitive health (Nelson et al., 2007). Although the molecular pathways through which exercise training impacts physical and cognitive function remain unknown (Rea, 2017), it is plausible that exercise-induced improvements in physical function and cognitive function may be related due to shared biological pathways and neural substrates targeted by exercise training. For example, exercise training stimulates growth markers which positively influence physical and cognitive function (e.g., insulin-like growth factor-1 [IGF-1]) in both the periphery and the central nervous system (Cotman et al., 2007; Pedersen and Febbraio, 2012). Although exercise training demonstrates benefit to both physical and cognitive function, the precise prescription of exercise (i.e., training intensity, frequency, time, and type) for obtaining optimal benefits of exercise training remains unknown (Oberg, 2007). Briefly, *intensity* is the level of exertion during the exercise (e.g., heart rate, repetition maximum, etc.), *frequency* refers to how often the exercise occurs (i.e., days/week), and *time* refers to the duration (in minutes) of the exercise bout with the *volume* of training consisting of the combined frequency and duration of exercise (i.e., frequency*duration). *Type* refers to the modality of exercise training, with the three most common types of exercise training being: 1) aerobic training (AT); 2) resistance training (RT) and 3) multicomponent training (MT; Baechle and Earle, 2008). As such, the precise implementation of these variables is critical to effectively elicit improvements in both physical and cognitive function (Nagamatsu et al., 2014).

While the benefits of exercise training on both physical function and cognitive function are thus well established, several important questions remain. Specifically: 1) Are exercise-

induced improvements in physical function and cognitive function related? 2) What are the exercise-related (e.g., type, volume, intensity) and individual-level moderators (e.g., sex, health status) of exercise effects for physical and cognitive outcomes? While previous meta-analyses have examined the effects of exercise training on older adult cognitive function (Colcombe and Kramer, 2003) and physical function (Chou et al., 2012), and also the exercise related and individual-level moderators of exercise effects on cognitive performance (Northey et al., 2018), no study has yet explored the concurrent effects of exercise training on physical and cognitive function and whether these exercise-induced improvements are related. Hence, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) of exercise in older adults to examine the effects of exercise training on physical and cognitive function and the association between changes in both outcomes.

## 2. Materials and Methods

### 2.1. Summary of search strategy

We conducted this systematic review and meta-analysis in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analysis* and the *Cochrane Handbook for Systematic Reviews and Interventions* statements (Moher et al., 2009; Higgins and Green, 2011). We searched Cochrane Central Register of Controlled Trials (CENTRAL), PsychINFO, EMBASE, and Web of Science between January 1, 1990-November 1, 2018. A sample of the search strategy is provided in Appendix A.

### 2.2. Study Selection

We selected peer reviewed, published RCTs which examined the effect of an exercise intervention (i.e., AT, RT, or MT) on both physical and cognitive function. We defined 1) AT as exercise with the intent of improving cardiovascular fitness including walking, running, or dance; 2) RT as exercise with the intent of increasing muscular strength, power, or endurance using bands, weight-machines, or free-weights; and 3) MT as either exercise which incorporated both AT and RT, or AT and/or RT which also included other forms of exercise training such as balance or agility training. Articles that mentioned exercise, physical function, and cognitive function in the title or abstract were included for full-text review. In addition, we searched the bibliographies of relevant reviews (Northey et al., 2018; Zheng et al., 2016; Levin, Netz and Ziv, 2017; Young et al., 2015) for articles which appeared to meet our inclusion criteria.

### 2.3. Inclusion and exclusion criteria

We included peer-reviewed studies if they met the following criteria: 1) RCTs; 2) published in the English language between January 1, 1990-May 22, 2017; 3) participants were 60 years and older without any neurodegenerative diseases or clinical disorders including metabolic syndrome (i.e., at least three of the following simultaneous conditions: central obesity, high blood pressure, high blood sugar, high serum triglycerides or low serum high-density lipoprotein), stroke (i.e., TIA, lacunar infract), depression (moderate/severe), diabetes (Type 1/Type II); 4) the intervention was AT, RT, or MT that was at least 2 months in duration and occurred at least once weekly; 5) included performance-based measures of physical function related to cardiovascular fitness, muscle strength, flexibility, mobility, and balance; and 6) included global and domain specific performance-based cognitive outcomes. Studies reporting

outcomes of combined physical function and cognitive function (i.e., choice stepping or dual task) were also included.

To ensure no studies were excluded which measured both physical function and cognitive function, we reviewed all bibliographies of papers initially excluded for "not including both physical function and cognitive function measures". If another paper from the same parent study included the missing type of measure (i.e., physical function or cognitive function measures), we included both papers within our analyses; these data were treated as a single study within our analysis.

### 2.4. Data extraction

Two authors (RSF and RAC) initially screened and identified studies based on the study title and abstract. Duplicates and articles failing to meet inclusion criteria were removed. The remaining full-text articles were reviewed by RSF and RAC to determine eligibility. Any disagreements were resolved by a third reviewer (JCD). Two raters (RSF and RAC) independently extracted data from all articles included and any discrepancies were discussed and reviewed by a third party (JCD). There were five studies which included non-exercise interventions (Barnes et al., 2013; Brown et al., 2009; Desjardins-Crépeau et al., 2016; Lord et al., 2003a; Middleton et al., 2018). In these instances, we only extracted data for the exercise intervention and the control group.

In this review, physical function is defined as the ability to execute and complete objectively measured performance-based tasks which assessed cardiovascular fitness, muscle strength, flexibility, mobility, and/or balance (Freiberger et al., 2012). For data extraction purposes, we classified physical function measures into four categories: 1) functional capacity;

2) gait speed and composite falls risk as assessed by the Physiological Profile Assessment (Lord et al., 2003b); 3) body strength; and 4) balance and flexibility. Functional capacity was used as a descriptor if the task assessed multiple aspects of physical function (e.g., the task assessed both body strength and gait speed, such as the Short Physical Performance Battery [Guralnik et al., 1994] or Timed Up and Go [Guralnik et al., 1989]) and/or the task measured cardiovascular fitness (e.g., 6 Minute Walk [Enright, 2003], or a $VO_2$max test). We provide our specific classification criteria in Appendix B.

We defined cognitive function as a broad set of thinking abilities which can be measured using performance-based tasks. Measures of cognitive function were classified into four domains: 1) global cognitive function (e.g., Mini Mental State Exam [Folstein et al., 1975]); 2) executive function; 3) memory; and 4) processing speed. We provide our specific classification criteria in Appendix B. We excluded studies that did not include measures of both physical function and cognitive function, or did not measure combined physical and cognitive outcome measures.

### 2.6. Assessment of bias

Two authors (RSF and RAC) independently assessed the risk of bias of included studies in accordance with the Cochrane Collaboration Guidelines as *low*, *high*, or *unclear* (Higgins and Green, 2011). Discrepancies in data extraction were resolved by a third party (JCD).

### 2.7. Effect size calculation

In the meta-analysis, we used Hedges' *g* effect sizes and variances for all outcomes, which provides a small sample bias correction to Cohen's *d* (Hedges, 1981). Cohen's *d* and its

variance was computed first using the pre- and post-test mean scores for the treatment and control groups, the pretest standard deviation for each group, and the sample size for each group:

$$d = \frac{(M_{PostTreat} - M_{PreTreat}) - (M_{PostCtrl} - M_{PreCtrl})}{\sqrt{((n_{Treat} - 1) \times SD^2_{PreTreat} + (n_{Ctrl} - 1) \times SD^2_{PreCtrl}) \times 1/(n_{Treat} + n_{Ctrl} - 2)}}$$

76% of physical outcomes and 84% of cognitive outcomes provided the necessary data to compute Cohen's *d* in this way. Two studies provided median data (Pichierri et al., 2012; Schättin et al., 2016), for which we estimated mean and standard deviation according to the method of Hozo and colleagues (2005); we then calculated effect sizes according to the formula above. One study computed Cohen's *d* for each outcome of interest (Taylor-Piliae et al., 2010), and another study computed $\eta^2$ for each outcome of interest which we then transformed into Cohen's *d* (Malliot et al., 2012). Eight papers (Ansai et al., 2015; Antunes et al., 2015b; Cassilhas et al., 2007; Hu et al., 2014; Barnes et al., 2013; Middleton et al., 2018; Nascimento et al., 2015; Tsutsumi et al., 1997) provided change scores which were used to compute Cohen's *d*. Cohen's *d* calculation method was included as a moderator variable to determine whether this influenced the summary effect size estimate. For studies with multiple treatment groups (e.g., separate AT and RT groups), effect sizes were computed separately in comparison to the control group. Separate effect sizes were computed for each outcome measure reported in the study. Effect sizes were coded such that positive estimates indicate a favorable change for the intervention group in comparison to the control group.

### 2.8. Statistical Analysis

Our meta-analysis protocol was guided by a recent meta-analysis on the effects of self-control training (Friese et al., 2017). Analyses were conducted in the statistical package R

version 3.4.3 using the primary packages of *robumeta* and *clubSandwich* (Fisher et al., 2017; Pustejovsky, 2017; R Core Team, 2017). Meta-analyses were conducted using random effects models to account for the heterogeneity between studies. Traditional meta-analytic packages assume that effect sizes are statistically independent; however, the inclusion of multiple effect sizes from the same study sample (even if those effect sizes are published in separate manuscripts) violates this assumption. Robust variance estimation (RVE) implemented in *robumeta* accounts for the dependency of within-study effect sizes by weighting those effect sizes based on a pre-specified within-study correlation. We used a within-study correlation of 0.8 (the default setting for this statistical package) and then conducted sensitivity analyses in which we varied the correlation from 0.0 to 1.0 by increments of 0.2. A complete summary of our analytic procedure, as well as a copy of our statistical code, is provided in Appendices C and D.

The overall summary effect was computed for performance-based measures of physical function (i.e., measures of functional capacity, body strength, gait speed and falls risk, and balance and flexibility) and global cognition as well as the specific domains of cognition (including executive function, memory, processing speed) and separately by fitting intercept-only random-effects RVE models to the set of dependent effect sizes. Because only 9 studies examined combined physical and cognitive function measures, we did not calculate effect sizes for combined physical and cognitive measures. Next, we conducted analyses to determine whether exercise-induced effects on physical function correlated with exercise-induced effects on cognitive function. To mitigate the possibility any observed correlation may be confounded by variance in study quality or precision, we limited this analysis to the 20 studies (25 articles) identified as high quality and also included the effect size standard error as a covariate in the model.

We tested several potential moderators using mixed-effects RVE models. A separate model was constructed for each potential moderator. For these moderation analyses, we conducted approximate Hotelling-Zhang tests (*HTZ*) for categorical moderators with 3 or more levels, and *t* tests for continuous moderators and binary moderators (Tipton and Pustejovsky, 2015). For these statistical tests, $\alpha$ was set at 0.05. Importantly, *t* tests derived from RVE models with $df < 4$ have been shown to be untrustworthy (Hedges et al., 2010); thus, we did not calculate *p* values and confidence intervals in these instances and estimates should be interpreted cautiously. We then examined potential publication bias using 1) funnel plots, (Sterne and Egger, 2005); 2) Egger's regression test, (Sterne and Egger, 2005); and 3) precision effect estimation with standard error (Stanley and Doucouliagos, 2014).

## 3. Results

### 3.1. Search Results and Study Characteristics

Appendix E describes the results of the search strategy for articles examining the effect of exercise training on both physical function and cognitive function. Of the initial 7551 articles title and abstract identified, our final systematic review included 58 articles; 48 original parent studies and 10 secondary outcome papers (Appendix A).

A total of 6281 participants took part in these studies. Sample sizes ranged from 14-1635 participants with samples from United States, Canada, Brazil, France, Germany, Finland, Spain, Italy, China, Taiwan, Japan, Australia and Republic of Korea. Overall mean participant age was 73 years (SD= 5) with 69% (SD= 22%) of all participants were female. Across all studies, 30 samples (63%) included participants with healthy cognition, 9 samples (19%) included participants with Mild Cognitive Impairment, and 10 (21%) were composed of participants with

mixed cognitive status. There were 28 studies (58%) of participants with healthy physical status, six studies (13%) with participants who were categorized as frail physical status, and 14 studies (29%) with participants who had a heterogeneous mix of healthy and frail physical status. Across all studies, we examined 19 AT interventions (N= 1652), 9 RT interventions (N= 567), and 24 MT interventions (N= 4062).

### 3.2. Main Analyses

For physical function, the 44 included studies produced 233 effect sizes (40 for balance and flexibility; 84 for body strength; 25 for gait speed and falls risk; and 84 for functional capacity) with a Hedges' *g* range of -0.97 to 3.19. A forest plot with all the effect sizes is provided in Appendix F. The meta-analytic summary effect was $g$= 0.39 (95% CI: 0.23, 0.54; $p$< 0.001), which is representative of a medium effect. More than four-fifths of the variance was estimated to be true effect size heterogeneity ($I^2$ = 80.94%, $T^2$ = 0.15).

For cognitive function, the 47 included studies produced 409 effect sizes (174 for executive function; 84 for global cognitive function; 82 for memory; and 69 for processing speed) with a Hedges' *g* range of -1.89 to 3.41. A forest plot with all the effect sizes is provided in Appendix F. The meta-analytic summary effect was $g$= 0.24 (95% CI: 0.15, 0.33; $p$< 0.001), which is representative of a small effect (Cohen, 1992). Nearly two-thirds of the variance was estimated to be true effect size heterogeneity ($I^2$= 65.87%, $T^2$= 0.08).

We describe our sensitivity analyses and our tests for publication bias in Appendices G and H. The results suggest some degree of publication bias for both physical and cognitive outcomes.

Among the 20 high quality studies, the average physical effect size predicted the average cognitive effect size ($b_{SE}$= 0.41, *SE*= 0.14, *p*= 0.002). Figure 1 depicts the association, with each point size being proportionate with the study's weight in the meta-regression. The solid line represents the slope estimate from the meta-regression.

### 3.3. Moderator analyses

Table 1 provides a summary of the main outcomes for moderator analyses of categorical moderators and Table 2 provides a summary of the continuous moderators. A complete summary of our categorical moderator analyses is in Appendix I. For the cognitive outcomes, three moderators were statistically significant. Effect sizes with *df*< 4 should be interpreted with caution due to the small number studies included. First, the cognitive status of participants moderated the cognitive outcome effect size (*HTZ* [15.26]= 5.97; *p*= 0.012). The estimated effect size was largest for older adults with healthy cognition (Hedge's *g*= 0.31) and Mild Cognitive Impairment (Hedge's *g*= 0.25), and smallest for samples with mixed cognitive status (Hedge's *g*= 0.06). Second, the physical status of participants moderated the cognitive outcome effect size (*HTZ* [14.45]= 3.89; *p*= 0.044). The estimated effect size was largest for adults with healthy physical status (Hedge's *g*= 0.32) and for frail older adults (Hedge's *g*= 0.29), and smallest for samples with mixed mobility status (Hedge's *g*= 0.10). Third, the type of outcome (i.e., primary versus secondary outcomes) moderated the cognitive outcome effect size (*HTZ* [38.58]= 6.67; *p*= 0.014). Primary outcomes (Hedge's *g*= 0.36) had a larger estimated effect size than secondary outcomes (Hedge's *g*= 0.15).

For the physical outcomes, two moderators were statistically significant. Effect sizes with *df*< 4 should be interpreted with caution due to the small number studies included. First, the

physical domain moderated the physical outcome effect size (*HTZ* [19.19]= 3.13; *p*= 0.0498). The estimated effect size was largest for the domains of functional capacity (Hedge's *g*= 0.49) and body strength (Hedge's *g*= 0.42), and smallest for the domains balance and flexibility (Hedge's *g*= 0.20) and gait speed and falls risk (Hedge's *g*= 0.09). Second, mean age of the participants moderated the physical outcome effect size such that increasing mean sample age was associated with smaller physical outcome effect sizes (*b*= -0.044; *SE*= 0.017; *p*= 0.023).

## 4. Discussion

The results of this meta-analysis support the efficacy of exercise training in promoting both physical and cognitive function in late life. In addition, we observed a significant association between exercise-induced improvements in physical function and cognitive function, such that studies with large effects on physical function tended to show large effects on cognitive function.

Our review provides five important updates to our current understanding of the effects of exercise training on physical and cognitive function. First, we provide an update to the exercise recommendations of Northey and colleagues (2018). We now suggest that multimodal exercise programs (i.e., those with both AT and RT) are beneficial for both cognitive function and physical function (with the greatest benefits appearing to impact functional capacity and body strength) in older adults aged 60+ years.

Second, by distinguishing between primary versus secondary outcomes of cognitive function, our current systematic review and meta-analysis suggest that the effects of exercise on cognition may be smaller than that reported in previous meta-analyses. Colcombe and Kramer (2003) first reported a standardized mean difference 0.31. More recently Northey and colleagues

(2018) determined that the effect of exercise on cognitive function was a standardized mean difference of 0.29. These two estimates are higher than the effect size which we calculated (Hedge's *g*= 0.24). When one considers that the meta-analysis by Young and colleagues (2015) found that exercise training does not lead to improvements in cognitive performance,[1] our results appear to provide a tempered and conservative estimate of the effects of exercise training on cognitive function. Our lower estimate can be attributed to our finding that the effect of exercise on primary cognitive outcomes (Hedge's *g*= 0.36) are larger compared with secondary cognitive outcomes (Hedge's *g*= 0.15). Many randomized controlled trials have and report a number of outcomes. However, it is critical that the primary outcome is identified and differentiated from secondary outcomes as randomized controlled trials are sampled to detect an effect in the primary outcome. Thus, systematic reviews and meta-analyses that treat primary and secondary outcomes equally may result in errors in estimates of effect.

Third, we determined that the effects of exercise training on cognitive performance are moderated by physical status and cognitive status. Briefly, cognitively and physical healthy older adults demonstrated the largest effect sizes for cognitive outcomes (Hedge's *g*= 0.31 and 0.32, respectively), and smaller effect sizes were observed in older adults with Mild Cognitive Impairment (Hedge's *g*= 0.25) and physically frail older adults (Hedge's *g*= 0.29). Moreover, the estimated cognitive outcome effect sizes for samples with mixed cognitive status and mixed physical status were much smaller (Hedge's *g*= 0.06 and Hedge's *g*= 0.10, respectively). These studies which used mixed samples also tended to be lower quality. Specifically, a majority of the studies which included participants with mixed cognitive status (80%) or mixed physical status (63%) we rated as low quality studies. Including participants with either mixed cognitive status or mixed physical status can also potentially lead to deviations from the initial exercise protocol,

[1]Young and colleagues (2015) only included studies that measured the effects of exercise training on cognitively and physically healthy older adults over the age of 60.

as most studies which included participants with mixed cognitive status (13%) or physical status (44%) did not include information on exercise intensity, and included only nominal information on volume of training (i.e., days/week and duration of each exercise session). Based on these results, we suggest that future research to determine the optimal dose of exercise for cognitive health should 1) carefully consider their target population; and 2) report the specific dose and type of exercise training performed.

Fourth, our meta-analysis also provides new insight on moderators of exercise efficacy on physical function. Specifically, we found that age attenuates the effects of exercise training on physical function, such that studies with younger participants demonstrated greater improvements in physical function than studies with older participants.

Fifth, we suggest that exercise training has greater impact on markers of frailty, such as functional capacity and body strength, than other measures of physical function, such as gait speed, falls risk, and balance and flexibility. A meta-analysis by Chou and colleagues (2012) determined that exercise training improved gait speed (n= 4 studies) and balance (n= 3 studies); however, our much larger review did not find that gait speed ($n_{study}$= 13) improved with exercise training, and exercise training yielded only small improvements in balance and flexibility ($n_{study}$= 16). By comparison, our review suggests exercise training leads to moderate-to-large improvements in functional capacity (g= 0.49) and body strength (g= 0.42), which may have important implications on reducing the risk of frailty and disability (Theou et al., 2011; Liu and Fielding, 2011).

Our paper therefore provides an important update to the current understanding of how exercise training can effect physical and cognitive function, and suggests that exercise training can have important implications on maintaining physical and cognitive function in older

adulthood. We discuss these findings in detail and provide practical recommendations based on our results.

### 4.1. Effects of exercise training on physical function

Exercise training can have positive benefits on older adult physical function (Nelson et al., 2007). The current American College of Sports Medicine (ACSM) exercise guidelines suggest a combination of AT, RT, flexibility, and balance training—which when performed together constitute MT. While our moderation analyses do not indicate that there is one type of training modality which leads to substantially larger improvements in physical function, there is still reason to think that adhering to the ACSM guidelines (i.e., performing MT, rather than just one type of exercise training) can lead to the greatest benefits on physical function. MT likely has a more potent effect on physical function due to the complementary and diverse benefits of performing different types of exercise training (Nelson et al., 2007). For example, AT specifically improves cardiovascular fitness (Fleg, 2012), while RT specifically improves muscle strength, power, mobility, and balance (Hunter et al., 2004; Orr et al., 2008). Performing each of these types of training in an exercise program will thus likely have the largest benefit on physical function.

Our analyses also demonstrated that the largest effects of exercise training (i.e., AT, RT or MT), regardless of modality, are on functional capacity and body strength. Exercise training led to only small improvements in balance and flexibility ($g$= 0.20), and there was no significant benefit of exercise training on gait speed and falls risk ($g$= 0.09). These findings are quite different than what has been previously suggested in a meta-analysis by Chou and others (2012), where the authors found that exercise training improved both gait speed and balance but Timed

Up and Go performance—which we included as a measure of functional capacity—did not significantly improve with exercise training. By comparison, our review which included more studies (48 studies vs. 8 studies) suggests that exercise training does not lead to improvements in gait speed, has a small benefit on balance and flexibility, and has moderate-to-large benefits for body strength and functional capacity. This finding is not altogether surprising since, as we mentioned before, AT and RT (or when amalgamated in some fashion as MT) each lead to specific improvements in functional capacity (e.g., cardiovascular fitness or mobility) and body strength.

Our findings also appear to indicate the importance of exercise training for maintaining independence in later life, since functional capacity and body strength are each important indicators of frailty (Dayhoff et al., 1998; Misic et al., 2007). While our data suggest that the effects of exercise training on physical function attenuate with increasing age, we did not determine that physical status (i.e., healthy, frail, or mixed sample) at baseline moderated the effect of exercise training. Hence, it is plausible that exercise training is both a preventive strategy for maintaining physical function in healthy older adults, and also an intervention to improve independence and physical function in frail older adults (Dayhoff et al., 1998; Misic et al., 2007; Theou et al., 2011; Liu and Fielding, 2011). Future research should determine the most effective combination and dosing of exercise training (i.e., how much AT, how much RT, how much balance training, etc.) needed to maximize benefits on older adult physical function.

### 4.2. Effects of exercise training on cognitive function

Exercise training is important for maintaining cognitive health in older adults (Northey et al., 2018), although we do not know which aspects of cognitive function are most responsive to

exercise training, or which types of exercise training are most potent. Currently, evidence suggests that the benefits of exercise training are greatest for executive function and memory (Colcombe and Kramer, 2003; Northey et al., 2018)—a broad term used to define planning and problem-solving capability (Brennan et al., 1997; Perry and Hodges, 1999). Further, recent evidence suggests the effects of exercise training on executive function are dependent on training type, such that AT appears to have the largest effect (Barha et al., 2016). The effects of exercise training on cognitive function appear to be more robust for older adult females than for males—for both animal and human studies (Barha et al., 2017a; Barha et al., 2017b). By comparison, our results do not appear to indicate that exercise training has domain-specific benefits on cognitive function. Furthermore, our results do not suggest that training type (i.e., AT, RT, or MT) moderates the efficacy of exercise training on cognitive function.

One possible explanation for this finding is that our statistical analysis, as compared to past meta-analyses, accounted for within-study correlations between effect sizes. As noted previously, traditional meta-analysis packages assume that effect sizes are statistically independent; however, the inclusion of multiple effect sizes from the same study sample (even if those effect sizes are published in separate manuscripts) violates this assumption. By using robust variance estimation (RVE), we accounted for the dependency of within-study effect sizes by weighting these effect sizes based on a pre-specified within-study correlation. Hence, it is plausible that the previous meta-analyses determined stronger effect sizes for aerobic training (as compared to MT or RT) because of within-study correlations among effect sizes. More recently, Northey and colleagues (2018) did perform RVE, but did not determine that AT has stronger effects on the cognitive domains of memory and executive function. In fact, Northey and colleagues found that RT (but not AT) had a significant interaction effect on executive function

and memory. The authors rightly pointed out that this does not indicate that RT is better than other modes of exercise, and instead suggest that performing both AT and RT may provide the greatest benefit for cognitive health. Our results align with this finding, and thus we suggest that all adults should engage in both AT and RT for cognitive health.

It is unclear why AT should target one (or some) areas of cognitive function, while RT should benefit other areas of cognitive function. A recent hypothesis is that the benefits of AT on memory and executive function were an evolutionary adaptation which increased future hunter-gathering success (Raichlen and Alexander, 2017). While this appears plausible, exercise training either in the form of AT, RT, or MT are each beneficial to multiple aspects of cognitive health, including memory and executive function (Northey et al., 2018; Barha et al., 2017b). It is unknown whether these different modalities act simultaneously, synergistically, or in silos to impact cognitive health. Animal models consistently demonstrate that exercise training—specifically AT—improves cognitive health through three distinct mechanisms: 1) hippocampal neurogenesis, or the creation of new neurons; 2) cerebral angiogenesis or the creation of new blood vessels in the brain; and 3) changes in inflammatory markers (Cotman et al., 2007). Only recently have animal models been developed to investigate how RT impacts cognitive health (Cassilhas et al., 2012). These data suggest that RT increases IGF-1 signalling, which stimulates hippocampal neurogenesis (Gomes et al., 2014). In contrast, AT triggers the production of brain derived neurotrophic factor (BDNF) which also stimulates neurogenesis (Van Praag et al., 1999). Upregulation of IGF-1 and BDNF are integral (i.e., sufficient *and* necessary) to the mechanism of neurogenesis (Ding et al., 2006), and thus it appears that both AT and RT may stimulate neurogenesis through independent mechanisms. However, human trials indicate that both AT and RT can increase functional plasticity (Best et al., 2015; Erickson and Kramer, 2009; Voss et

al., 2013) and improve functional connectivity (Suo et al., 2016; Voss et al., 2010). Hence, AT and RT may promote different substrates within the same neurogenesis mechanism—leading to improvements in cognitive function, neuroplasticity, and functional connectivity irrespective of the type of exercise training performed. We posit that AT, RT and MT each elicit positive benefits on multiple, unexclusive, aspects of cognitive function. Our results thus provide initial support for this hypothesis: 1) the efficacy of exercise training on cognitive function are both global and domain-specific and 2) exercise training can elicit improvements in cognitive function that are similar in effect size irrespective to which type of exercise training is performed.

The role of sex as a potential moderator of the efficacy of exercise also needs further inquiry. Unlike past meta-analyses which examined sex differences in exercise efficacy (Barha et al., 2017a; Barha et al., 2017b; Colcombe and Kramer, 2003), we performed our analyses with sex as a continuous variable (i.e., %female). It may thus be that while exercise-induced improvements in cognitive function are moderated by sex, the extent of this moderation effect is small. Indeed, while acknowledging exercise training may have different efficacy on cognitive function for males and females, the public health message should continue to recommend similar guidelines for males and females (Nelson et al., 2007).

The optimal modality-specific exercise dosing remains unclear — more precisely, the *volume* and *intensity* for each type of exercise training (i.e., AT, RT, or MT). The effect of exercise training on cognitive function was not moderated by any exercise dose variable. There was also inconsistency in how exercise dose variables were reported. For example, only 9 (47%) AT interventions reported exercise intensity (Albinet et al., 2016; Blumenthal et al., 1989; Hsu et al., 2017; Kuo et al., 2018; Liu-Ambrose et al., 2016; Moul et al., 1995; Muscari et al., 2009; Nagamatsu et al., 2012; Varela et al., 2011; Whitehurst, 1991). Exercise intensity was only

reported in three (33%) RT intervention (Cassilhas et al., 2007; Tsutsumi et al., 1997, Yoon et al., 2017), and only 11 (46%) MT interventions reported exercise intensity (Albinet et al., 2016; Barnes et al., 2013; Desjardins-Crépeau et al., 2016; Eggenberger et al., 2016; Langlois et al., 2013; Linde et al., 2014; Middleton et al., 2018; Pahor et al., 2014; Pichierri et al., 2012; Napoli et al., 2014; Nascimento et al., 2014; Nascimento et al., 2015; Sink et al., 2015; Villareal et al., 2011). This exercise intensity reporting heterogeneity impeded our ability to determine the intensity of exercise providing greatest benefit.

Nonetheless, the effects of exercise training on cognitive function appear to be smaller than has been previously reported by other meta-analyses (Northey et al., 2018; Colcombe and Kramer, 2003). As we mentioned earlier, one possible reason for why we determined a smaller effect size than these previous studies is that, unlike previous meta-analyses, we investigated whether the type of outcome (i.e., primary or secondary) moderated the calculated cognitive outcome effect size. Our results suggest that the calculated effect size for primary cognitive outcomes is more than twice the effect size of secondary cognitive outcomes.

We also determined that both baseline cognitive status and physical status appear to moderate the cognitive outcome effect size. The largest effect sizes for cognitive outcomes were calculated for cognitively ($g$= 0.31) and physically healthy older adults ($g$= 0.32), and only slightly smaller for older adults with Mild Cognitive Impairment ($g$= 0.25) and frail older adults ($g$= 0.29). However, the estimated cognitive outcome effect sizes for samples with mixed cognitive status and mixed physical status were much smaller ($g$= 0.06 and $g$= 0.10, respectively). While at face value a heterogeneous sample of older adults with mixed cognitive statuses and/or physical statuses may appear to be more generalizable, and thus preferable, in practice this heterogeneity is indicative of lower quality study design. Indeed, a majority of the

studies which included participants with mixed cognitive status (80%) or mixed physical status (63%) we rated as low quality studies. Including participants with either mixed cognitive status or mixed physical status can also potentially lead to deviations from the initial exercise protocol. Most studies which included participants with mixed cognitive status (87%) or physical status (56%) did not include information on exercise intensity, and included only nominal information on volume of training (i.e., days/week and duration of each exercise session). We therefore think it prudent to suggest that while determining the optimal dose of exercise for cognitive health is an important line of inquiry, it is imperative that future investigations should 1) carefully consider who their target population is; 2) report the specific dose and type of exercise training performed; and 3) a priori determine the primary outcome and the sample size necessary to achieve adequate power.

### 4.3. The relationship between improvements in physical function and cognitive function

Exercise-induced improvements in physical function were associated with improvements in cognitive function at the study level, providing further support that exercise-induced improvements in physical function are associated with improvements in cognitive function (Figure 1). However, the temporal aspect and the neural underpinnings of this relationship are not yet established. Physical function and cognitive function are linked through common growth factors that exercise targets (e.g., IGF-1), and as such both improve in response to exercise. Our results appear to provide further evidence that exercise-induced improvements in cognitive function and physical function are linked (Hsu et al., 2017). One potential explanation for our findings, as suggested by the Central Benefit Model (Liu-Ambrose et al., 2012), is cognitive and neural plasticity may be an important mechanism by which exercise training promotes mobility.

While our meta-analysis provides further evidence suggesting that exercise training promotes cognitive function, we cannot conclude from our results if improvements in cognitive function from exercise training are the mechanism by which physical function improves. Future research should focus on understanding the biological links between how physical function and cognitive function are impacted by exercise training.

### 4.4. Practical Applications and Recommendations

This study provides initial evidence supporting the following recommendations: 1) the largest effects of exercise training appear to impact functional capacity, body strength, and global cognitive function; 2) MT likely provides the greatest benefit for the maintenance of older adult physical health; and 3) exercise training regardless of modality is beneficial for maintaining older adult cognitive health.

Given the above findings, we suggest an update to the recommendations provided by Northey and colleagues (2018). Specifically, an exercise program with components of both aerobic training and resistance training is beneficial for both physical function (with the greatest benefits being towards improving functional capacity and body strength) and cognitive function in older adults aged 60+ years. We also contend that the greatest benefits of exercise training are that it helps to maintain older adult physical and cognitive function, and thus reduces the risk of physical and cognitive frailty. As such, continued efforts should be made to encourage all adults to exercise regularly as this may help reduce the risk of physical and cognitive impairment in later life.

### 4.5. Limitations

Our inclusion criteria, although necessary, result in two distinct limitations: 1) they reduce the strength of our moderation analyses by limiting our sample size and 2) they reduce the generalizability of our findings due to the exclusion of individuals with metabolic syndrome, stroke, depression and diabetes given that individuals with these chronic conditions represent a proportion of our aging population. For example, the cognitive effects of exercise among older adults may be associated with improvements in mood (Arent, Landers, and Etnier, 2000). We were not able to explore this association in this manuscript due to the exclusion of individuals with depression, and the fact that only 12 studies which we included measured mood prospectively. These inclusion criteria were applied in order to improve the homogeneity of the sample studies such that meta-analyses and moderation analyses were possible. Thus, we suggest future meta-analyses address how exercise training may improve older adult mood.

Our findings are also limited by the approach we used to categorize different cognitive measures into cognitive domains. First, some cognitive measures could fall into multiple cognitive domains. For example, digit symbol coding can be categorized as a measure of executive function, global cognitive function, or processing speed (Jaeger, 2018). Second, our classification scheme included a breadth of cognitive processes under single domains of cognition. For example, under the cognitive domain of memory, we included immediate memory, interference list performance, delayed recall subtests involving verbal and non-verbal. While each of these cognitive processes are broadly related to memory, they could be categorized under more specific cognitive domains (e.g., verbal memory, visual-spatial memory) that may (or may not) be impacted differentially by exercise.

In this meta-analysis we found that exercise training had greater impact on functional capacity and body strength than gait speed, falls risk, balance, and flexibility. However, our

results should be treated with caution due to our broad categorization of physical function domains. For example, we categorized the six minute walk and 400 meter walk as measures of functional capacity, however these tests could also be categorized as measures of gait speed. It is thus plausible that our results may differ according to how physical function measures are classified.

While our results suggest that exercise training can improve markers of frailty, frailty is a complex condition that does not have a single definition (Chen, Mao, & Leng, 2014). For example, the frailty phenotype model suggests that frailty is defined as having at least three of the following: unintentional weight loss, self-reported exhaustion, weak grip strength, slow walking speed, and low physical activity (Fried et al., 2001). By comparison, the frailty index model defines frailty based on a comprehensive geriatric assessment by counting the number of deficits accumulated, including: diseases, physical and cognitive impairments, psychosocial risk factors, and common geriatric syndromes other than frailty (Jones et al., 2004). It is thus plausible that our results may indicate that exercise may improve markers of frailty according to one definition, but may not reduce the risk of frailty according to other definitions. Although current evidence indicates exercise training is an important strategy for reducing the risk of frailty (Chen et al., 2014), future research is needed to determine the extent to which exercise training can reduce the risk of frailty, and what aspects of frailty syndrome are improved by exercise training.

Our meta-analysis also only included nine RT interventions, and we did not include studies which used other types of exercise training such as yoga or tai chi. We were unable to examine the association of exercise-induced improvements in physical function and in cognitive function at the participant level, and instead, could only examine the association at the study

level. Future research should report participant-level correlations between these two domains so that these findings can be incorporated into future meta-analyses. It is also possible that the moderating effect of sex is mediated by hormonal factors (e.g., the number of years post-menopause or the use of hormone replacement therapy) since a growing body of literature indicates that menopause and hormone replacement therapy can influence cognitive changes in women (Hogervorst et al., 2000; Yaffe et al., 1998); however no study which we examined reported these variables. Finally, there was considerable publication bias for the effect size generated for cognitive outcomes. Studies reporting larger effect sizes are more likely to be published; therefore, the efficacy of exercise training on cognitive function may be smaller than what we estimated. However, our estimated effect size is in accordance with previous meta-analyses (Barha et al., 2017a; Barha et al., 2017b; Chou et al., 2012; Colcombe and Kramer, 2003; Northey et al., 2018; Sherrington et al., 2011; Zheng et al., 2016).

### 4.6. Conclusion

In summary, our study suggests that exercise training improves physical and cognitive function, and that exercise-induced improvements in physical function and cognitive function are associated with each other. In order for future research to draw meaningful conclusions on exercise prescription: 1) cognitive function and physical function outcomes should be measured longitudinally and concomitantly, 2) volume and intensity need to be consistently measured and reported and 3) mechanistic research is needed to delineate the pathways that exercise training exerts its impact of cognitive and physical function.

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Table 1. Results of moderation analyses for categorical moderators

| **Cognitive Domain** | Summary effect | | | | | | | | Test of moderation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Moderator | *g* | LL | UL | *t* | *df* | *p* | $n_{study}$ | $n_{effects}$ | Statistic | *df* | *p* | $I^2$ |
| ***Treatment-level Moderators*** | | | | | | | | | | | | |
| Type of Intervention | | | | | | | | | *HTZ* = .45 | 17.95 | .643 | 66.54% |
| Type of Control | | | | | | | | | *HTZ* = .05 | 19.63 | .954 | 66.68% |
| Exercise Intensity | | | | | | | | | *HTZ* = .85 | 3.94 | .493 | 62.93% |
| ***Study-level Moderators*** | | | | | | | | | | | | |
| Study Quality | | | | | | | | | *HTZ* = .05 | 37.62 | .827 | 65.41% |
| Type of Study | | | | | | | | | *HTZ* = .45 | 6.45 | .527 | 65.38% |
| Effect Size Calculation Method | | | | | | | | | *HTZ* = .04 | 1.22 | .986 | 66.47% |
| Cognitive Status | | | | | | | | | *HTZ* = 5.97 | 15.26 | .012 | 65.86% |
| *Healthy* | .31 | .20 | .43 | 5.48 | 25.89 | <.001 | 29 | 253 | | | | |
| *Mild Cognitive Impairment* | .25 | -.03 | .54 | 2.11 | 6.76 | .074 | 9 | 79 | | | | |
| *Mixed* | .06 | -.04 | .17 | 1.38 | 7.52 | .207 | 9 | 77 | | | | |
| Physical Status | | | | | | | | | *HTZ* = 3.89 | 14.45 | .044 | 64.46% |
| *Healthy* | .32 | .19 | .45 | 5.12 | 25.00 | <.001 | 28 | 250 | | | | |
| *Frail* | .29 | .05 | .64 | 2.21 | 4.78 | .081 | 6 | 25 | | | | |
| *Mixed* | .10 | -.01 | .21 | 2.04 | 11.10 | .066 | 13 | 134 | | | | |

| **Cognitive Domain** | Summary effect | | | | | | | | Test of moderation | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Moderator | *g* | LL | UL | *t* | *df* | *p* | $n_{study}$ | $n_{effects}$ | Statistic | *df* | *p* | $I^2$ |
| ***Outcome-level Moderators*** | | | | | | | | | | | | |
| Cognitive Domain | | | | | | | | | *HTZ* = .93 | 27.18 | .440 | 64.91 % |
| Type of outcome | | | | | | | | | *HTZ* = 6.67 | 38.58 | .014 | 64.29% |
| *Primary* | .36 | .21 | .52 | 4.81 | 21.20 | <.001 | 23 | 143 | | | | |
| *Secondary* | .15 | .07 | .23 | 3.74 | 25.60 | <.001 | 24 | 266 | | | | |

| **Physical Domain** | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Summary effect | | | | | | | | Test of moderation | | | |
| Moderator | *G* | LL | UL | *t* | *df* | *p* | $n_{study}$ | $n_{effects}$ | Statistic | *df* | *p* | $I^2$ |
| ***Treatment-level Moderators*** | | | | | | | | | | | | |
| Type of Intervention | | | | | | | | | *HTZ* = .92 | 17.17 | .418 | 81.28% |
| Type of Control | | | | | | | | | *HTZ* = .55 | 18.77 | .587 | 80.96% |
| Exercise Intensity | | | | | | | | | *HTZ* = .42 | 3.64 | .684 | 69.34% |
| ***Study-level Moderators*** | | | | | | | | | | | | |
| Study Quality | | | | | | | | | *HTZ* = .99 | 38.47 | .325 | 80.41% |
| Type of Study | | | | | | | | | *HTZ* = 9.24 | 1.07 | .190 | 81.15% |
| Effect Size Calculation Method | | | | | | | | | *HTZ* = .62 | .91 | .714 | 80.43% |
| Cognitive Status | | | | | | | | | *HTZ* = 2.99 | 12.72 | .086 | 81.28% |
| Physical Status | | | | | | | | | *HTZ* = 3.58 | 13.76 | .056 | 79.71% |
| ***Outcome-level Moderators*** | | | | | | | | | | | | |
| Physical Domain | | | | | | | | | *HTZ* = 3.13 | 19.19 | .0498 | 80.47 % |
| *Balance and Flexibility* | .21 | .03 | .38 | 2.53 | 12.02 | .026 | 16 | 40 | | | | |
| *Body Strength* | .42 | .10 | .75 | 2.73 | 17.28 | .014 | 25 | 84 | | | | |
| *Functional Capacity* | .56 | .29 | .83 | 4.30 | 26.38 | <.001 | 39 | 84 | | | | |
| *Gait Speed and Falls Risk* | .09 | -.12 | .30 | 1.01 | 7.17 | .344 | 13 | 25 | | | | |
| Type of Outcome | | | | | | | | | *HTZ* = .16 | 31.76 | .689 | 81.00% |

***Note:*** *Only significant categorical moderating effect size estimates are shown*

Table 2. Results of moderation analyses for continuous moderators.

| **Cognitive Domain** | | | | | | |
|---|---|---|---|---|---|---|
| | Meta-regression | | Test of moderation | | | |
| Moderator | Intercept | Slope | *t* | *df* | *p* | $I^2$ |
| ***Study-level Moderators*** | | | | | | |
| Mean age | .254 | -.012 | 1.67 | 16.70 | .114 | 63.63% |
| Percent female | .236 | -.002 | 1.39 | 8.10 | .202 | 65.56% |
| Intervention length | .251 | -.001 | .79 | 3.40 | -- | 64.73% |
| Training volume (hrs) | .262 | .000 | .59 | 2.09 | -- | 65.25% |
| **Physical Domain** | | | | | | |
| | Meta-regression | | Test of moderation | | | |
| Moderator | Intercept | Slope | *t* | *df* | *p* | $I^2$ |
| ***Study-level Moderators*** | | | | | | |
| Mean age | .381 | -.044 | 2.55 | 14.10 | .023 | 77.22% |
| Percent female | .388 | -.005 | .73 | 8.90 | .486 | 80.75% |
| Intervention length | .400 | -.001 | .53 | 4.40 | .624 | 80.40% |
| Training volume (hrs) | .408 | .000 | .04 | 2.32 | -- | 80.95% |

**Figures**

**Figure 1.** Meta-regression of the relationship between the effects of exercise training on physical function (x-axis), and the effect of exercise training on cognitive function (y-axis). Each point size is proportionate with the study's weight in the meta-regression. Among the 20 high quality studies, the average physical effect size predicted the average cognitive effect size ($b_{SE}$= 0.41, *SE*= 0.14, *p*= 0.002).

**Appendices**

**Appendix A.** A) Simplified search strategy. B) Flow chart of study selection.

**Appendix B.** Physical and Cognitive Domain Criteria and Classifications

**Appendix C.** Complete summary of meta-analytic procedure

**Appendix D.** Statistical code for R version 3.4.3

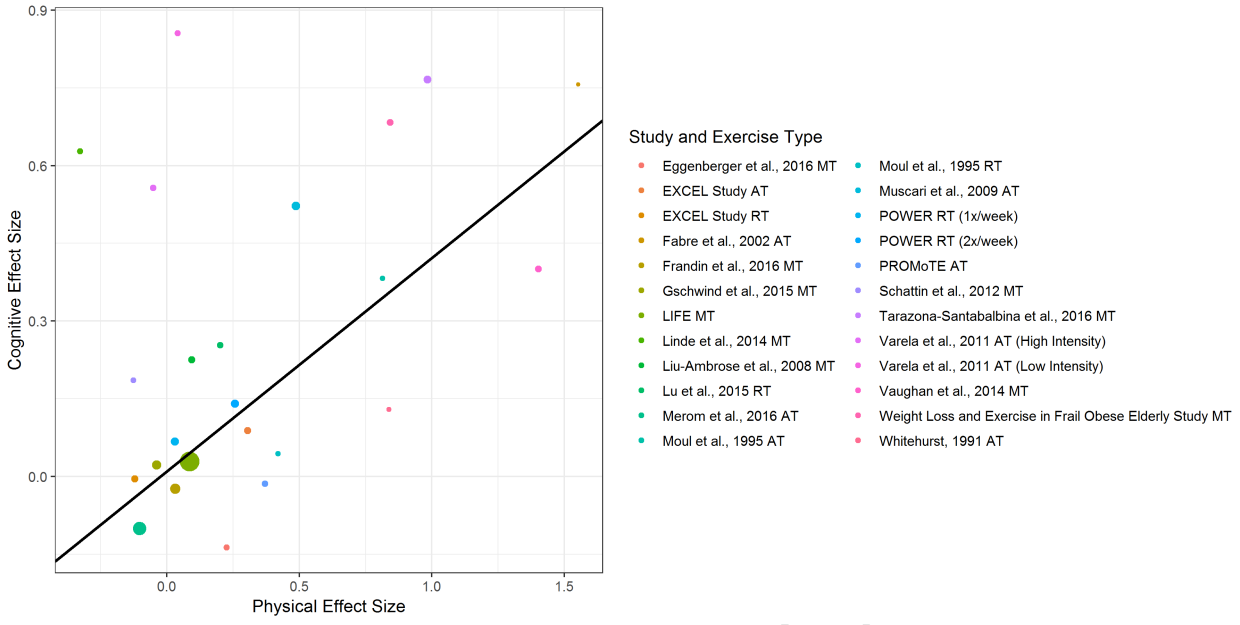
**Appendix E.** Study characteristics

**Appendix F.** 1) Forest plot for all the estimated effects of exercise training on different domains of physical function: i) Balance and Flexibility; ii) Body Strength; iii) Gait Speed and Falls Risk; iv) Functional Capacity. 2) Forest plot for all the estimated effects of exercise training on different domains of cognitive function: i) Executive Function; ii) Memory; iii) Processing Speed; iv) Global Cognitive Function. Dotted lines indicate the effect size needed to reach statistical significance.

**Appendix G.** Sensitivity analyses and publication bias

**Appendix H.** A) Funnel plots for physical function outcomes; B) Funnel plots for cognitive function outcomes

**Appendix I.** Complete summary of categorical moderator analyses



## Highlights

- Maintaining physical and cognitive function are critical for healthy aging
- Physical function and cognitive function are linked and share common mechanisms
- Exercise training improves physical function and cognitive function
- Exercise-induced improvements in physical and cognitive function are associated