Received Date : 06-Jan-2016

Revised Date : 05-Jul-2016

Accepted Date : 12-Jul-2016

Article type : Clinical Investigation

Cognitive function improvements are mediated by strength gains following resistance training in older adults with mild cognitive impairment: Outcomes of the SMART randomized controlled trial.

Yorgi Mavros^{1*}, Nicola Gates PhD², Guy C Wilson MSc¹, Nidhi Jain MPH¹, Jacinda Meiklejohn BS¹, Henry Brodaty DSc^{2,3}, Wei Wen PhD^{2,4}, Nalin Singh MBBS¹, Bernhard T Baune PhD⁵, Chao Suo PhD^{2,6,7}, Michael K Baker PhD^{1,8}, Nasim Foroughi PhD⁹, Yi Wang PhD¹⁰, Perminder S Sachdev PhD^{2,3}, Michael Valenzuela PhD⁶, Maria A Fiatarone Singh MD^{1,11‡}

¹Exercise Health and Performance Faculty Research Group, Faculty of Health Sciences, University of Sydney, Lidcombe, Australia

²Centre for Healthy Brain Ageing (CHeBA), School of Psychiatry, University of New South Wales, Sydney, Australia

³Dementia Collaborative Research Centre, University of New South Wales, Sydney, Australia

⁴Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, Australia.

⁵Department of Psychiatry, School of Medicine, University of Adelaide, Adelaide, Australia

⁶Regenerative Neuroscience Group, Brain and Mind Research Institute, University of Sydney, Sydney, Australia

⁷Monash Clinical and Imaging Neuroscience, School of Psychology and Psychiatry, Monash University, Australia

⁸School of Exercise Science, Australian Catholic University, Strathfield, Australia

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/jgs.14542](https://doi.org/10.1111/jgs.14542)

This article is protected by copyright. All rights reserved

⁹Clinical and Rehabilitation Research Group, Faculty of Health Sciences, University of Sydney,
Lidcombe, Australia

¹⁰Department of Medicine and the Diabetes Center, University of California, San Francisco, CA,
USA

¹¹Hebrew SeniorLife, Boston, MA, and Jean Mayer USDA Human Nutrition Research Center on
Aging at Tufts University, Boston, MA, USA

* Corresponding author:

Yorgi Mavros, PhD

Faculty of Health Sciences

University of Sydney

75 East Street, Lidcombe, NSW 2141, Australia

+612 9351 9279 (telephone)

+612 9351 9204 (fax)

yorgi.mavros@sydney.edu.au

‡ Alternate corresponding author:

Maria Fiatarone Singh, MD

Faculty of Health Sciences

University of Sydney

75 East Street, Lidcombe, NSW 2141, Australia

+612 9351 9755 (telephone)

+612 9351 9204 (fax)

maria.fiataronesingh@sydney.edu.au

Abbreviated Title: Strength gains mediate cognitive benefits

Word count: 3500

References: 37

Figures: 3

Tables: 2

Supplemental Files: 2

Supplemental Tables and Figures: 4

Trial Registration: Australian New Zealand Clinical Trials Registry

(ANZCTR1260800048932)

ABSTRACT

OBJECTIVES: Exercise has been shown to improve cognition in mild cognitive impairment (MCI). The purpose of this investigation was to determine whether improvements in cognitive function following resistance training (PRT) are mediated by improvements in aerobic capacity (VO₂peak) and/or strength.

DESIGN: Randomized, double-blind, double-sham controlled trial

SETTING: University research facility.

PARTICIPANTS: 100 community-dwelling older adults (>55 years) with MCI.

INTERVENTION: PRT and cognitive training (CT), 2–3 days/week for 6 months

MEASUREMENTS: Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog); global, executive and memory domain, peak strength (1RM) and VO₂peak.

RESULTS: PRT significantly increased upper [standardized mean difference (95% CI); 0.69 (0.47, 0.91)], lower [0.94 (0.69, 1.20)] and whole body [0.84 (0.62, 1.05)] strength and percent change in VO₂peak [8.0% (2.2, 13.8)] compared to sham exercise. Increases in strength scores, but not VO₂peak, were significantly associated with improvements in cognition ($p < 0.05$).

Increases in lower body strength significantly mediated the effect of PRT on improvements in ADAS-Cog [indirect effect $\beta = -0.64$ (-1.38, -0.004); direct effect $\beta = -0.37$ (-1.51, 0.78)] and global domain [indirect effect $\beta = 0.12$ (0.02, 0.22); direct effect $\beta = -0.003$ (-0.17, 0.16)] and approached statistical significance for executive domain [indirect effect $\beta = 0.11$ (-0.04, 0.26); direct effect $\beta = 0.03$ (-0.17, 0.23)].

CONCLUSION: High intensity PRT results in significant improvements in cognitive function, muscle strength, and aerobic capacity in older adults with MCI. Importantly, cognitive benefits following PRT are mediated by strength gains, but not aerobic capacity changes. Future investigations are warranted to determine the physiological mechanisms linking strength gains and cognitive benefits.

Key words: exercise, cognition, resistance training, dementia

INTRODUCTION

Globally, 135 million persons are projected to be affected by dementia by 2050¹, and attenuation of cognitive decline in those at elevated risk, such as individuals with Mild Cognitive Impairment (MCI), is paramount. Epidemiological evidence suggests that higher physical activity levels², maximal aerobic capacity (VO₂peak) and aerobic activity are associated with

preservation of cognitive function³, and a reduced risk of incident cognitive impairment or Alzheimer's disease (AD)^{4,5}. Similarly, lower muscle strength is associated with an increased risk of incident AD⁶. Experimental studies support and extend these observational data⁷.

Although less well studied than aerobic exercise, progressive resistance training (PRT) can also benefit cognition in older adults with MCI⁸⁻¹⁰ and dementia⁷, as well as improving strength and aerobic capacity¹¹. However, the extent and mechanisms of cognitive benefit by PRT require further study^{11,12}. Our recent SMART trial demonstrated that 6 months of PRT significantly improved global cognitive function in MCI, with benefits in global and executive domains maintained over 18 months⁹.

Thus, the purpose of this investigation was two-fold; a) to determine the effect of 6 months of PRT, cognitive training or sham versions of both interventions on fitness (VO₂peak and muscle strength) in individuals with MCI, and b) to determine if changes in aerobic capacity and strength over 6 months mediated changes in cognition. We hypothesized that:

1. PRT would significantly improve VO₂peak and muscle strength compared to sham-exercise (control).
2. Increases in VO₂peak and strength would be independently associated with improvements in cognition following the 6-month intervention.
3. Increases in VO₂peak and strength would significantly mediate the effects of PRT on improvements in cognition.

METHODS

The full protocol for the Study of Mental and Resistance Training (SMART) trial has been published¹³. The primary cognitive outcomes of the trial have been reported⁹. Informed consent was obtained from all participants. The study was approved by the Royal Prince Alfred Human Research Ethics Committee (X04-0064). The study was registered with the Australia New Zealand Clinical Trials Registry (ACTRN12608000489392).

Study population and eligibility criteria

100 community-dwelling adults (>55yrs, 32 men, 68 women) with MCI (by Peterson criteria¹⁴).

Randomization and study design

The SMART trial is a fully-factorial, double-blind, double-sham controlled trial. Participants were randomized into one of four groups, and received 6 months of either progressive resistance training (PRT) or sham-exercise (Sham-Ex), and cognitive training (CT) or sham-cognitive training (Sham-Cog), with follow-up over 78 months in progress.

Interventions

The complete study details have been published^{9, 13}. Interventions were fully supervised in small groups (size 1-10) over 60-100 min, and presented as potentially beneficial. Training was reduced from 3 to 2 days/week after the first 30 participants to minimize travel burden. Participant flow through the study has been previously reported⁹. The distribution of participants among intervention groups is presented in Figure 1.

Control group: Sham-Cog + Sham-Ex

Sham-Cog involved watching general documentary videos followed by simple questions about the material. Sham-Ex included stretching and seated calisthenics designed so as not to notably increase heart rate or enhance aerobic capacity or strength. No use of equipment or progression were included. A similar regimen has been shown to have no effects on brain volume in older adults¹⁵.

Progressive Resistance Training (+ Sham cognitive): (PRT+Sham-Cog)

High intensity PRT was supervised at a ratio of 1 trainer/4-5 subjects. Participants were progressed continuously throughout the 6-month intervention, with one-repetition maximums (1RMs) repeated every 3 weeks to maintain intensity between 80 to 92% of current strength.

Cognitive Training Intervention (+ Sham physical): (CT+Sham-Ex)

CT involved computer-based multimodal and multi-domain exercises targeting memory, executive function, attention and speed of information processing via the COGPACK program¹⁶ used in a previous MCI trial¹⁷.

Combined PRT and CT

This group received both PRT intervention and CT interventions, delivered sequentially in that order on the same day.

Assessment of cognitive outcomes

Details of the cognitive assessments have been published¹³. Global cognitive function was assessed via the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog). Global, executive and memory cognitive domain scores were also calculated (see Supplemental Appendix 1).

Assessment of VO₂peak

VO₂peak was determined via indirect calorimetry during a physician-administered, graded treadmill walking test with ECG monitoring to volitional fatigue (see Supplemental Appendix 1).

Assessment of Peak Strength

Testing was performed on Keiser pneumatic resistance machines (Keiser Sports Health Equipment, Ltd., Fresno, CA). Participants' 1RM was determined on the leg press (LP), knee extension (KE), hip abduction (HAb), chest press (CP) and seated row (SR).

Data Handling

Total tonnage over the intervention was calculated as the summed total of all weight lifted during all sessions. Changes in VO₂peak were expressed as absolute and percent changes. Due to varying magnitudes and units for strength tests, changes in strength were converted into percent changes for all 5 exercises. In order to combine strength test data into lower, upper, and whole body domains, all strength test data at both time-points were converted into z-scores⁶. The average z-scores for LP, KE and HAb were used for lower body strength, while the average z-scores for CP and SR were used for upper body strength. Whole body strength was calculated as the average z-score of all exercises. The standardized mean differences (SMD) for changes in strength were calculated as the difference between z-scores at 6 months and baseline.

Statistical analysis

All data were assessed for normality prior to use in parametric statistics. Baseline data are presented as mean (SD). Absolute and percent change scores are presented as adjusted marginal mean difference [95% confidence intervals (CIs)]. For composite strength scores, baseline data are presented as z-scores (SD), changes are presented as SMD (95% CI). All statistical models were adjusted for age and sex, plus education for models including cognitive outcomes, and the baseline score of the dependent variable for analysis of changes. Baseline comparisons were performed using a one-way ANOVA. Associations between continuous variables at baseline were explored using multiple linear regression models. General linear models were used to assess changes in VO₂peak and strength, with PRT and CT entered as factors. Relationships between changes in VO₂peak or strength and changes in cognitive outcomes were assessed using multiple linear regression models. Due to the association of PRT with strength, cognition and VO₂peak, multiple linear regression analyses were re-run stratified by group allocation to PRT. Stratification was decided upon *a priori* due to our previously reported improvements in cognitive function in individuals randomized to receive PRT⁹. Next the PROCESS macro for SPSS (version 2.13.2)¹⁸ was used to determine the indirect effect of PRT on cognitive function through increases in lower body strength. This method estimates the indirect effects of PRT (mediated through changes in lower body strength) on changes in cognitive function, while accounting for the direct effects PRT had on increases in lower body strength and cognitive function. This method provides unstandardized estimates of the direct and indirect pathways, along with corresponding 95% CIs. Bootstrapping was employed with 5000 resampling iterations. More information on the PROCESS macro can be found in Supplemental Appendix 1. Sequential models were created with changes in ADAS-Cog, global domain and executive domain as the dependent variables, and changes in lower body strength as the mediating variable. Models were repeated to include an interaction between PRT and lower body strength to determine if PRT moderated the mediating effect of lower body strength on cognition. Models were adjusted for age, sex, education and baseline score of the dependent variable. These variables were selected due to the significant associations between lower body strength and these dependent variables in multiple linear regression models. To determine reverse causality, a second model included change in lower body strength as the dependent variable, and change in cognition as the mediating variable. Results from mediation analysis are considered significant if the CIs do not include zero. While the primary outcomes paper examined the effect of the

combined intervention, it was not hypothesized that the combination of CT and PRT would have a significant effect on strength or fitness beyond that of PRT alone. Thus, models examining the effect of the combined intervention were not run. Finally, linear regressions were constructed to explore associations between total tonnage and strength gains within participants receiving PRT. A final model was constructed with changes in cognitive function as the dependent variable, and changes in strength and total tonnage as independent variables, to determine whether these associations were independent. All data were analyzed using SPSS (version 22). A $p < 0.05$ was considered statistically significant.

RESULTS

Participant characteristics

Participant flow through the study, and baseline characteristics have been previously reported, with no difference observed between groups for any cognitive outcome⁹. VO2peak data was unavailable for 1 participant at baseline due to incomplete collection. The same participant subsequently dropped out of the study, along with a further 7 participants. VO2peak data were unavailable in 3 of the remaining 92 participants. Therefore, 99 VO2peak tests were available at baseline; 89 tests at 6 months. Baseline values for VO2peak and peak strength are presented in Table 1. Participants in the PRT group tended to have higher LP strength ($p = 0.06$) compared to participants in the Sham-Ex group.

Associations between VO2peak and strength with cognition at baseline

At baseline, neither VO2peak nor strength were associated with cognition ($p > 0.05$). The data are presented and discussed in Supplemental Table 1.

Changes in cognitive function

The changes in cognitive function were presented in the primary outcomes paper⁹. Briefly, PRT significantly improved ADAS-Cog with normal cognitive scores achieved in 47% of all participants who received PRT, with a trend for improvements in executive function. Data are presented in Table 2.

Changes in VO2peak

PRT significantly improved absolute and relative VO₂peak compared to Sham-Ex [1.8ml/kg/min (95% CI 0.6, 3.0), p=0.003] and [8.0% (95% CI 2.2, 13.8), p=0.007], respectively.

Unexpectedly, participants receiving CT had a reduction in VO₂peak compared to Sham-Cog [-1.4ml/kg/min (95% CI -2.6, -0.2), p=0.02] and [6.6% (95% CI -12.6, -1.0), p=0.02].

Changes in strength

Data are presented in Table 1. PRT significantly improved all strength measures, with relative strength increases ranging from 23-52% and moderate to large z-score changes in upper, lower, and whole body strength of 0.69-0.94 (p<0.05).

Association of changes in VO₂peak with changes in cognitive function

Changes in VO₂peak were not associated with changes in ADAS-Cog, global domain, executive domain or memory domain scores in the whole cohort (p>0.05) nor after stratifying by exposure to PRT or Sham-Ex (Supplemental Table 2 - 4; p>0.05). Therefore mediation analysis was not performed.

Association of changes in strength with changes in cognitive function

Increases in lower body strength were associated with improvements in ADAS-Cog (r=-0.24, p=0.01), global (r=0.27, p=0.02) and executive domain (r=0.21, p=0.04), with a trend for memory domain scores (r=0.20, p=0.06). Changes in upper body and whole body strength were not associated with changes in cognitive outcomes (p>0.05), apart from a trend between increases in whole body strength and an increase in global (r=0.22, p=0.05) and executive domains (r=0.20, p=0.06) (See Supplemental Table 2). After stratifying by exposure to PRT or Sham-Ex, the associations between lower body strength and improvements in ADAS-Cog (r=-0.29, p=0.02), global (Figure 2a; r=0.38, p=0.01), executive (Figure 2b; r=0.31, p=0.05) and memory domains (r=0.33, p=0.05) were strengthened within those who received PRT.

Additionally, improvements in global and executive domain scores were now associated with increases in upper body (Figures 2c and 2d; r=0.28, p=0.07 and r=0.33, p=0.03, respectively) and whole body strength (Figures 2e and 2f; r=0.43, p<0.01 and r=0.41, p=0.01, respectively). No associations were observed in individuals randomized to receive Sham-Ex (Supplemental Table 4; p>0.05).

Mediation analysis of strength, PRT and cognitive function

As PRT improved both cognition⁹ and strength, we examined whether strength changes mediated the cognitive benefits of PRT. Mediation analysis revealed that there was a significant, indirect effect of PRT through increases in lower body strength on improvements in ADAS-Cog [Figure 3a; indirect effect $\beta=-0.64$ (95% CI -1.38, -0.0004); direct effect $\beta=-0.36$ (95% CI -1.51, 0.78)], and global domain [Figure 3b; indirect effect $\beta=0.12$ (95% CI 0.02, 0.22); direct effect $\beta=-0.003$ (95% CI -0.17, 0.16)]. Finally, the indirect effect of PRT through increases in lower body strength on executive function approached statistical significance [Figure 3c; indirect effect $\beta=0.11$ (95% CI -0.04, 0.26); direct effect $\beta=0.03$ (95% CI -0.17, 0.23)]. There was no moderating effect of PRT on the mediation of ADAS-Cog; $\beta=-0.55$ (95% CI -2.12, 1.10), global domain; $\beta=0.19$ (95% CI -0.36, 0.39) or executive domain; $\beta=0.08$ (95% CI -0.39, 0.55) by lower body strength change. These data suggest that the mediation of cognitive function by lower body strength was similar across all levels of strength gain. To investigate reverse causality, we examined change in lower body strength with PRT as the direct factor and change in ADAS-Cog and change global domain as mediators in sequential models, adjusted for age, sex and baseline lower body strength. Changes in ADAS-Cog and global domain did not significantly mediate the effect of PRT on changes in lower body strength [indirect effect $\beta=0.04$ (95% CI -0.01, 0.16); direct effect $\beta=0.89$ (95% CI 0.63, 1.14)] and [indirect effect $\beta=0.03$ (95% CI -0.01, 0.15); direct effect $\beta=0.89$ (95% CI 0.64, 1.14)] respectively, with a significant, and large direct effect of PRT on strength gains persisting. Thus, lower body strength changes mediated large portions of the cognitive benefits of PRT for the ADAS-Cog and global domain scores, with little evidence of reverse causality.

Factors associated with improvements in strength

Within the PRT group, total tonnage lifted during the intervention was associated with increases in upper ($r=0.48$, $p<0.01$), lower ($r=0.40$, $p=0.04$) and whole body strength ($r=0.50$, $p<0.01$). Total tonnage was also associated with improvements in global cognitive domain ($r=0.29$, $p=0.04$), but not changes in executive domain, memory domain, or ADAS-Cog ($p>0.05$). Finally, when total tonnage was entered into the same model as changes in strength, improvements in lower ($r=0.34$, $p<0.05$) and whole body ($r=0.38$, $p=0.03$) strength were

independently associated with improvements in global domain, with the effect of total tonnage attenuated and no longer significant ($p>0.05$).

DISCUSSION

As hypothesized, improvements in strength mediated the improvements in ADAS-Cog and global domain (Figures 3a-3c). We also observed a near significant mediating effect of strength on executive function, while no effect was observed on memory domain. This is consistent with the primary outcomes of the SMART trial, which showed that PRT significantly improved ADAS-Cog scores with a trend observed for executive function, and no effect on memory (Table 2)⁹. Similarly, Nagamatsu et al (2012) showed that twice-weekly PRT, but not aerobic training, significantly improved cognitive function in older women with probable MCI^{9, 19}. Thus, our empirical data extend epidemiological literature linking strength with rate of cognitive decline and incident dementia⁶. To our knowledge, this is the first study to examine the association between improvements in strength and cognition after PRT in MCI. Our results are in agreement with a 3-month uncontrolled study of PRT vs. multicomponent exercise (neuromuscular coordination, balance, agility, and cognitive executive control) in healthy older adults²⁰, where isokinetic knee flexor torque increased significantly in the PRT group, and mediated the significant effect of PRT on executive function. Thus, we provide novel data on the potential mechanistic effects between PRT and cognitive benefit in older adults with MCI that warrant further investigation.

Six months of PRT significantly improved strength ($SMD=0.69-0.99$), similar to effects reported previously in healthy elders ($SMD=0.84$)¹¹. Additionally, VO_{2peak} increased by 1.8ml/kg/min (8.0%) with PRT. This is the first study to report the effects of PRT on VO_{2peak} in older adults with MCI. Our improvements in VO_{2peak} are consistent with a Cochrane review of PRT in older adults [mean improvement of 1.5ml/kg/min (95% CI 0.49–2.51)] across 14 trials¹¹, comparable to the 7.78% increase reported after 1 year of aerobic training in healthy older adults²¹, and slightly less than the 11% increase reported after 6 months of aerobic training in older adults with MCI²². Thus, we have demonstrated that baseline cognitive impairment does not preclude robust physical adaptations to PRT, and some adaptations (muscle strength improvements) are linked to cognitive adaptations.

330

331 Analyses restricted to the PRT group enhanced the relationships between the magnitude of
332 strength gain and cognitive benefits (Figures 2a-2f), and revealed that strength gains were related
333 to the dose of PRT received, expressed as total tonnage. Collectively, these results suggest that
334 not only is PRT effective in improving cognitive function, but that PRT interventions should be
335 optimized to maximize strength gains, in order to maximize improvements in cognitive function.
336 For example, high intensity resistance training has been shown to be more effective than
337 moderate and low intensity resistance training interventions in improving strength in older
338 adults²³. Thus, higher intensity interventions may produce optimal outcomes for both strength
339 and cognition.

340

341 Given the novelty of our findings, future investigations should be directed towards identification
342 of potential mechanisms linking adaptations in strength and cognitive function after PRT. For
343 example, insulin like growth factor 1 (IGF-1) deficiency has been linked with cognitive
344 dysfunction in older adults^{24, 25} as well as incident dementia²⁶, while a 24-week resistance
345 training program in older adults was shown to increase IGF-1 concomitant with improvements
346 with cognitive function²⁷. Another possible mechanism is increases in BDNF. Previously,
347 increases in BDNF were shown to significantly mediate the effects of a 12-month walking
348 program in cognitively normal adults²⁸, consistent with previously reported animal data linking
349 voluntary exercise, BDNF and neuroplasticity²⁹. High levels of cortisol have been associated
350 with worse cognitive function and smaller brain volumes in older adults without dementia³⁰, as
351 well as memory impairments, hippocampal atrophy, and reduced hippocampal-dependent
352 memory tasks³¹. However, conflicting data exist on the effect of chronic resistance training on
353 basal cortisol levels, with studies showing reductions in cortisol, or no change³². Other possible
354 mechanisms include reductions in homocysteine³³⁻³⁵, insulin sensitivity and systemic
355 inflammation³⁶. Previously, worse cognition has been associated with greater declines in
356 strength, with reductions in strength potentially mediating the association between poor
357 cognition and subsequent ADL disability³⁷. However, our models do not suggest such reverse
358 causality following a PRT intervention. While these models did approach statistical significance,
359 changes in ADAS-Cog and global domain mediated very little of the change in strength (indirect

effect $\beta=0.03$ and $\beta=0.04$, respectively) in comparison with the direct effect of PRT on strength gains ($\beta=0.89$ for both). This suggests that improvements in cognition did not have any meaningful mediating effect on the changes in lower body strength following PRT.

Despite improvements in VO2peak, no associations were found between improvements in VO2peak and improvements in cognitive function. While epidemiological evidence shows an association between VO2peak and cognition³⁻⁵, the change in cognition and aerobic capacity after 1 year of aerobic training or stretching/toning/balance control activity were unrelated to each other in Erickson's study of healthy older adults²¹, suggesting that other pathways, such as increases in BDNF²⁸, might be operative. Additionally, in this same study, Forte²⁰ did not report mediation of executive function by changes in aerobic capacity. Thus, our findings support and extend existing experimental literature suggesting that improvements in VO2peak do not mediate improvements in cognition following exercise training in older adults, in contrast to the many epidemiological associations between aerobic fitness and cognitive function².

There are a few limitations to our study. Technical difficulties required the estimation of VO2 peak from indirect calorimetry up to 60 seconds after the cessation of treadmill exercise, which may have resulted in minor increases in VO2peak. While the ADAS-Cog represents a valid assessment tool for dementia and global cognition, it should not be considered a comprehensive neurocognitive battery. Finally, our mediation analyses depend on the assumption of no unmeasured confounders of the hypothesized mediators and outcomes. As it is not possible to randomize at the level of strength gains (mediator) to PRT, we cannot confirm this assumption.

CONCLUSION

Older adults with MCI are at high risk for further cognitive decline, along with physical frailty and disability. Anabolic exercise has clinically relevant benefits for cognitive function, muscle strength, and aerobic capacity in this cohort, a spectrum of benefits not observed with cognitive training or sham exercise, and the cognitive benefits observed are mediated in large part by strength gains. Future studies are required to understand the underlying physiological

mechanisms which link skeletal muscle physiology and function with brain morphology and neuroplasticity in this vulnerable cohort, as well as investigate the potential of exercise to reduce incident dementia itself.

ACKNOWLEDGMENTS

This work fulfilled a portion of the degree requirements for PhD for NG and CS. Donations for participant rewards were received from Gregory and Carr Funerals. We would also like to thank the extraordinary generosity and commitment of the participants and their families who devoted their time and continue to participate in the SMART study

Funding source: This study was funded by a National Health and Medical Research Council of Australia Dementia Research Grant (512672). Additional funding for a research assistant position was sourced from the NHMRC Program (568969), and the project was supported by the University of Sydney and University of New South Wales. YM is supported as a postdoctoral research associate by the CRN for Advancing Exercise and Sport Science. MV was supported by a University of New South Wales Vice Chancellor's Fellowship and a NHMRC Clinical Career Development Fellowship (1004156).

Conflict of Interest: MV has previously received honoraria for speaking at Pfizer and The Brain Department Pty Ltd sponsored events. HB has been an investigator for Pfizer, Novartis, Janssen, Lilly, Medivation, Sanofi and Servier; a sponsored speaker for Pfizer, Novartis, Janssen and Lundbeck; and is on advisory Boards for Pfizer, Novartis, Janssen, Lundbeck, Merck and Baxter. BB is a member of advisory boards and/or gave presentations for the following companies, for which he has received honoraria: AstraZeneca, Lundbeck, Pfizer, Servier, and Wyeth.

REFERENCES

- [1] Prince M, Guerchet M, Prina M. Policy Brief for Heads of Government: The Global Impact of Dementia 2013–2050. London: Alzheimer's Disease International, 2013.
- [2] Beydoun MA, Beydoun HA, Gamaldo AA, Teel A, Zonderman AB, Wang Y. Epidemiologic studies of modifiable factors associated with cognition and dementia: systematic review and meta-analysis. *BMC Public Health*. 2014;**14**: 643.

- [3] Barnes DE, Yaffe K, Satariano WA, Tager IB. A Longitudinal Study of Cardiorespiratory Fitness and Cognitive Function in Healthy Older Adults. *J Am Geriatr Soc.* 2003;**51**: 459-465.
- [4] Abbott RD, White LR, Ross G, Masaki KH, Curb J, Petrovitch H. Walking and dementia in physically capable elderly men. *JAMA.* 2004;**292**: 1447-1453.
- [5] Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. Physical activity and risk of cognitive impairment and dementia in elderly persons. *Arch Neurol.* 2001;**58**: 498-504.
- [6] Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Association of muscle strength with the risk of Alzheimer disease and the rate of cognitive decline in community-dwelling older persons. *Arch Neurol.* 2009;**66**: 1339-1344.
- [7] Colcombe S, Kramer AF. Fitness effects on the cognitive function of older adults a meta-analytic study. *Psychol Sci.* 2003;**14**: 125-130.
- [8] Gates N, Singh MAF, Sachdev PS, Valenzuela M. The effect of exercise training on cognitive function in older adults with mild cognitive impairment: a meta-analysis of randomized controlled trials. *Am J Geriatr Psychiatry.* 2013;**21**: 1086-1097.
- [9] Fiatarone Singh MA, Gates N, Saigal N, *et al.* The Study of Mental and Resistance Training (SMART) study—resistance training and/or cognitive training in mild cognitive impairment: a randomized, double-blind, double-sham controlled trial. *JAMDA.* 2014;**15**: 873-880.
- [10] Liu-Ambrose T, Nagamatsu LS, Graf P, Beattie B, Ashe MC, Handy TC. Resistance training and executive functions: A 12-month randomized controlled trial. *Arch Intern Med.* 2010;**170**: 170-178.
- [11] Liu Cj, Latham NK. Progressive resistance strength training for improving physical function in older adults. *Cochrane Database Syst Rev.* 2009;**3**: CD002759.
- [12] Gregory MA, Gill DP, Petrella RJ. Brain health and exercise in older adults. *Curr Sports Med Rep.* 2013;**12**: 256-271.
- [13] Gates NJ, Valenzuela M, Sachdev PS, *et al.* Study of Mental Activity and Regular Training (SMART) in at risk individuals: A randomised double blind, sham controlled, longitudinal trial. *BMC Geriatr.* 2011;**11**: 19.
- [14] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol.* 1999;**56**: 303-308.

- [15] Colcombe SJ, Erickson KI, Scalf PE, *et al.* Aerobic Exercise Training Increases Brain Volume in Aging Humans. *J Gerontol A Biol Sci Med Sci.* 2006;**61**: 1166-1170.
- [16] COGPACK. Heidelberg & Ladenburg: Marker Software, 1986.
- [17] Günther VK, Schäfer P, Holzner BJ, Kemmler GW. Long-term improvements in cognitive performance through computer-assisted cognitive training: A pilot study in a residential home for older people. *Aging Ment Health.* 2003;**7**: 200-206.
- [18] Hayes AF. *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach.* New York, NY: Guilford Press, 2013.
- [19] Nagamatsu LS, Handy TC, Hsu CL, Voss M, Liu-Ambrose T. Resistance training promotes cognitive and functional brain plasticity in seniors with probable mild cognitive impairment: A 6-month randomized controlled trial. *Arch Intern Med.* 2012;**172**: 666-668.
- [20] Forte R, Boreham CA, Leite JC, *et al.* Enhancing cognitive functioning in the elderly: multicomponent vs resistance training. *Clin Interv Aging.* 2013;**8**: 19-27.
- [21] Erickson KI, Voss MW, Prakash RS, *et al.* Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci.* 2011;**108**: 3017-3022.
- [22] Baker LD, Frank LL, Foster-Schubert K, *et al.* Effects of Aerobic Exercise on Mild Cognitive Impairment: A Controlled Trial. *Arch Neurol.* 2010;**67**: 71-79.
- [23] Steib S, Schoene D, Pfeifer K. Dose-response relationship of resistance training in older adults: a meta-analysis. *Med Sci Sports Exerc.* 2010;**42**: 902-914.
- [24] Toth P, Tarantini S, Ashpole N, *et al.* IGF-1 Deficiency Promotes Neurovascular Uncoupling: Implications for Cerebromicrovascular Aging and Age-Related Cognitive Decline. *The FASEB Journal.* 2015;**29**.
- [25] van Dam PS, Aleman A, de Vries WR, *et al.* Growth hormone, insulin-like growth factor I and cognitive function in adults. *Growth Hormone & IGF Research.* 2000;**10**, **Supplement 2**: S69-S73.
- [26] Westwood AJ, Beiser A, DeCarli C, *et al.* Insulin-like growth factor-1 and risk of Alzheimer dementia and brain atrophy. *Neurology.* 2014;**82**: 1613-1619.
- [27] Cassilhas RC, Viana VA, Grassmann V, *et al.* The impact of resistance exercise on the cognitive function of the elderly. *Med Sci Sports Exerc.* 2007;**39**: 1401-1407.
- [28] Leckie RL, Oberlin LE, Voss MW, *et al.* BDNF mediates improvements in executive function following a 1-year exercise intervention. *Front Hum Neurosci.* 2014;**8**: 985.

- [29] Gómez-Pinilla F, Feng C. Molecular Mechanisms for the Ability of Exercise Supporting Cognitive Abilities and Counteracting Neurological Disorders. In: Boecker H, Hillman CH, Scheef L, Strüder HK, eds. *Functional Neuroimaging in Exercise and Sport Sciences*: Springer New York, 2012, pp. 25-43.
- [30] Geerlings MI, Sigurdsson S, Eiriksdottir G, *et al.* Salivary cortisol, brain volumes, and cognition in community-dwelling elderly without dementia. *Neurology*. 2015;**85**: 976-983.
- [31] Lupien SJ, de Leon M, de Santi S, *et al.* Cortisol levels during human aging predict hippocampal atrophy and memory deficits. *Nat Neurosci*. 1998;**1**: 69-73.
- [32] Kraemer WJ, Ratamess NA. Hormonal responses and adaptations to resistance exercise and training. *Sports Med*. 2005;**35**: 339-361.
- [33] Vincent KR, Braith RW, Bottiglieri T, Vincent HK, Lowenthal DT. Homocysteine and Lipoprotein Levels Following Resistance Training in Older Adults. *Prev Cardiol*. 2003;**6**: 197-203.
- [34] Schafer JH, Glass TA, Bolla KI, Mintz M, Jedlicka AE, Schwartz BS. Homocysteine and Cognitive Function in a Population-Based Study of Older Adults. *J Am Geriatr Soc*. 2005;**53**: 381-388.
- [35] Seshadri S, Beiser A, Selhub J, *et al.* Plasma Homocysteine as a Risk Factor for Dementia and Alzheimer's Disease. *NEJM*. 2002;**346**: 476-483.
- [36] Yaffe K, Kanaya A, Lindquist K, *et al.* The metabolic syndrome, inflammation, and risk of cognitive decline. *JAMA*. 2004;**292**: 2237-2242.
- [37] Raji MA, Kuo Y-F, Snih SA, Markides KS, Kristen Peek M, Ottenbacher KJ. Cognitive Status, Muscle Strength, and Subsequent Disability in Older Mexican Americans. *J Am Geriatr Soc*. 2005;**53**: 1462-1468.

TABLES

Table 1: Baseline values and changes in maximal aerobic capacity and strength following progressive resistance training or cognitive training

	PRT	Sham-Ex	Mean Difference	p <i>GxT</i>	CT	Sham-Cog	Mean Difference	p <i>GxT</i>
VO2peak								
<i>Baseline (mL/kg/min)</i>	21.6 (5.0)	21.3 (6.4)			21.9 (5.8)	21.0 (5.8)		
<i>Change (mL/kg/min)</i>	1.4 (0.5, 2.3)	-0.4 (-1.2,0.4)	1.8 (0.6, 3.0)	0.003	-0.2 (-1.0, 0.6)	1.2 (0.3, 2.0)	-1.4 (-2.6, -0.2)	0.02
<i>Percent Change (%)</i>	7.3 (3.0, 11.5)	-0.7 (-4.7, 3.2)	8.0 (2.2, 13.8)	0.007	-0.1 (-4.0, 3.7)	6.6 (2.3, 10.9)	-6.6 (-12.6, -1.0)	0.02
LP 1RM								
<i>Baseline (N)</i>	1840 (566) ¹	1634 (538)			1751 (591)	1718 (528)		
<i>Percent Change (%)</i>	34.5 (26.6, 42.5)	2.5 (-5.1, 10.0)	32.1 (20.6, 43.5)	<0.0001	13.6 (6.4, 20.7)	23.4 (15.7, 31.1)	-10.0 (-20.4, 0.7)	0.07
KE 1RM								
<i>Baseline (Nm)</i>	123.2 (51.6)	107.8 (50.7)			1142.3 (53.9)	116.6 (49.3)		
<i>Percent Change (%)</i>	27.2 (14.9, 39.5)	-5.1 (-15.8, 5.5)	32.3 (15.7, 49.0)	<0.0001	12.4 (1.4, 23.4)	9.7 (-1.9, 21.3)	2.7 (-13.4, 18.7)	0.74
Hip Abd 1RM								

<i>Baseline (N)</i>	183.2 (80.8)	185.2 (91.2)			177.1 (82.8)	191.5 (89.0)		
<i>Percent Change (%)</i>	48.9 (37.6, 60.2)	-3.1 (-13.2, 6.9)	52.0 (36.8, 67.2)	<0.0001	25.0 (14.9, 35.0)	20.8 (9.5, 32.1)	4.2 (-11.1, 19.4)	0.59
CP 1RM								
<i>Baseline (N)</i>	272.6 (111.7)	265.7 (119.7)			264.7 (115.1)	273.3 (116.5)		
<i>Percent Change (%)</i>	18.3 (10.6, 26.0)	-5.1 (-11.8, 1.5)	23.4 (13.2, 33.8)	<0.0001	6.7 (-0.5, 13.8)	6.5 (-0.7, 13.7)	0.2 (-10.0, 10.3)	0.90
SR 1RM								
<i>Baseline (N)</i>	226.9 (91.0)	233.8 (86.2)			230.7 (96.5)	230.1 (80.7)		
<i>Percent Change (%)</i>	18.4 (8.7, 28.0)	-11.4 (-19.9, -3.0)	29.8 (16.8, 42.7)	<0.0001	0.2 (-8.7, 9.1)	6.7 (-2.4, 15.8)	-6.5 (-19.3, 6.3)	0.31
LB Strength								
<i>Baseline</i>	0.11 (0.88)	-0.11 (0.91)			-0.03 (0.93)	0.03 (0.88)		
<i>Change (z-score)</i>	0.86 (0.68, 1.05)	-0.08 (-0.25, 0.09)	0.94 (0.69, 1.2)	<0.0001	0.35 (0.18, 0.51)	0.44 (0.25, 0.63)	-0.09 (-0.35, 0.16)	0.46
UB Strength								
<i>Baseline (z-score)</i>	0.00 (0.96)	0.00 (0.96)			-0.02 (1.02)	0.02 (0.90)		
<i>Change (z-score)</i>	0.42 (0.26, 0.59)	-0.27 (-0.42, -0.12)	0.69 (0.47, 0.91)	<0.0001	0.02 (-0.13, 0.18)	0.13 (-0.03, 0.29)	-0.11 (-0.33, 0.11)	0.33
WB Strength								
<i>Baseline (z-score)</i>	0.09 (0.94)	-0.07 (0.91)			0.00 (1.00)	0.02 (0.86)		

<i>Change (z-score)</i>	0.65 (0.50, 0.81)	-0.18 (-0.33, -0.04)	0.84 (0.62, 1.05)	<0.0001	0.16 (0.02, 0.30)	0.31 (0.15, 0.46)	<u>-0.15 (-0.36, 0.07)</u>	0.17
-------------------------	-------------------	----------------------	-------------------	---------	-------------------	-------------------	----------------------------	------

Baseline data are presented as unadjusted mean (SD). ANCOVA models were used to determine differences between groups. The main effects of PRT and CT were entered as factors into the same model. Models were also adjusted by age, sex and the baseline value of the dependent variable. Change and percent change scores are presented as adjusted marginal means (95% CI). The improvements in VO2peak and strength seen within the CT and Sham-cog groups are driven by factorial design of the study, in which half of the participants in these groups also received PRT.

¹ p=0.08 between groups at baseline

Table 2: Mean scores for cognitive outcomes at baseline and following the progressive resistance training and cognitive training interventions

		PRT	Sham-Ex	p GxT	CT	Sham-Cog	p GxT
Global Function							
ADAS-Cog	<i>Baseline</i>	8.1 (3.2)	8.4 (3.2)		8.4 (3.2)	8.2 (3.2)	
	<i>6 months</i>	5.9 (3.3)	7.2 (3.2)	0.046	6.7 (3.2)	6.3 (3.3)	0.66
Global domain	<i>Baseline</i>	0.04 (0.6)	-0.04 (0.6)		-0.2 (0.6)	0.03 (0.6)	
	<i>6 months</i>	0.21 (0.6)	0.0 (0.6)	0.17	0.13 (0.6)	0.11 (0.6)	0.32
Executive Function							
WAIS-III Similarities	<i>Baseline</i>	19.4 (4.8)	18.5 (4.6)		8.4 (3.2)	8.2 (3.2)	
	<i>6 months</i>	21.4 (4.9)	20.3 (4.6)	0.77	6.7 (3.2)	6.3 (3.3)	0.89
WAIS-III Matrices	<i>Baseline</i>	12.6 (4.6)	11.7 (4.6)		12.0 (4.6)	12.4 (4.6)	
	<i>6 months</i>	14.1 (4.8)	11.5 (4.6)	0.06	12.5 (4.6)	13.1 (4.9)	0.79
Category Fluency	<i>Baseline</i>	18.3 (4.4)	19.5 (4.4)		19.2 (4.4)	18.5 (4.5)	
	<i>6 months</i>	19.5 (4.6)	19.3 (4.5)	0.06	19.6 (4.5)	19.3 (4.7)	0.62
COWAT	<i>Baseline</i>	38.6 (11.3)	37.7 (11.3)		38.2 (11.3)	38.0 (11.3)	

	<i>6 months</i>	41.5 (11.7)	42.4 (11.4)	0.29	40.8 (11.4)	43.1 (11.8)	0.14
Executive Domain	<i>Baseline</i>						
	<i>6 months</i>	0.03 (0.62)	-0.02 (0.62)		0.02 (0.62)	-0.01 (0.62)	
		0.32 (0.64)	0.14 (0.63)	0.09	0.21 (0.62)	0.25 (0.64)	0.39
Memory Function							
List Learning Memory Sum	<i>Baseline</i>	20.6 (3.8)	18.8 (3.8)		19.4 (3.8)	19.9 (3.8)	
	<i>6 months</i>	21.7 (4.0)	19.4 (3.9)	0.53	20.3 (3.8)	20.9 (4.1)	0.95
BVRT	<i>Baseline</i>	6.0 (1.7)	6.2 (1.7)		5.9 (1.7)	6.0 (1.7)	
	<i>6 months</i>	6.2 (1.8)	5.6 (1.7)	0.04	6.3 (1.7)	5.8 (1.8)	0.06
Immediate Memory I	<i>Baseline</i>	11.5 (3.8)	11.1 (3.8)		10.8 (3.8)	11.7 (3.8)	
	<i>6 months</i>	10.1 (4.0)	10.1 (3.9)	0.55	10.1 (3.8)	10.1 (4.1)	0.23
Delayed Memory II	<i>Baseline</i>	10.0 (4.1)	8.4 (4.2)		8.7 (4.2)	11.7 (4.1)	
	<i>6 months</i>	8.6 (4.3)	8.6 (4.2)	0.03	8.8 (4.2)	10.1 (4.4)	0.06
Memory Domain	<i>Baseline</i>	0.10 (0.65)	-0.09 (0.65)		-0.09 (0.65)	0.11 (0.65)	
	<i>6 months</i>	0.03 (0.67)	-0.17 (0.66)	0.88	-0.06 (0.66)	-0.09 (0.68)	0.02
Speed/Attention							
SDMT	<i>Baseline</i>	44.9 (9.4)	43.5 (9.4)		45.3 (9.4)	43.1 (9.4)	
	<i>6 months</i>	47.0 (9.7)	45.5 (9.5)	0.89	47.2 (9.5)	45.3 (9.7)	0.84

Data are presented as Mean (SD). Cognitive outcomes for the SMART trial were previously reported⁹.

ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive subscale; WAIS = Wechsler Adult Intelligence Scale; COWAT = Controlled Oral Word Association Test; BVRT= Benton Visual Retention Test; SDMT= Symbol Digit Modalities Test

N = 100 for all outcomes. All data were normally distributed and raw data used in analyses.

Domain scores represent the average of the z-scores of each component test.

Z-score at baseline = individual value at baseline minus mean value for baseline cohort/SD for baseline cohort.

Z-score at 6 = individual value at 6 months minus mean value for baseline cohort/SD for baseline cohort.

Memory Domain was calculated by averaging the z-scores of component memory tests: ADAS-Cog List Learning Memory Sum, Logical Memory I (Immediate), Logical Memory II (Delayed), and BVRT.

Executive Domain was calculated by averaging the z-scores of component executive function tests: WAIS-III Similarities, WAIS-III Matrices, COWAT, and Category Fluency.

Global Cognition Domain was calculated by averaging the z-scores of all tests except ADAS-cog Memory Sum, as this is a subscale within the ADAS-Cog and, therefore, already included. The sign was reversed on the ADAS-Cog z-score so that positive z-score changes indicate improvement for all tests and domains.

FIGURE LEGEND

Figure 1: Randomization chart

Participants received a combination of progressive resistance training (PRT) or sham-exercise with cognitive training or sham-cognitive training, in a 2x2 factorial design. Overall, 49 participants received PRT and 51 participants received sham-exercise, while 51 participants received cognitive training and 49 participants received sham-cognitive training.

Figure 2: Association between changes in lower, upper and whole body strength and changes in global and executive domain in the PRT group.

Regression analyses were performed within participants receiving PRT only. All analyses were adjusted for age, sex, education and baseline score of the dependent variable. Figure 2a ($r=0.38$, $p=0.01$), Figure 2b ($r=0.31$, $p=0.05$), Figure 2c ($r=0.28$, $p=0.07$), Figure 2d ($r=0.33$, $p=0.03$), Figure 2e ($r=0.43$, $p<0.01$) and Figure 2f ($r=0.41$, $p=0.01$)

Figure 3: Mediation model of lower body strength and global and executive domain.

ADAS-Cog: Alzheimer's Disease Assessment Scale-cognitive subscale

Solid lines indicate direct pathway while dashed lines indicate indirect pathway. Data are presented as unstandardized beta (β) coefficients and 95% CIs following bootstrapping with 5000 sampling iterations.

In each case, the models show the total effect of progressive resistance training on cognitive function (top), and the direct and indirect effects following mediation analysis with lower body strength (bottom).

*significant indirect effect of lower body strength

Figure 3a; The effect of PRT on ADAS-Cog was significantly mediated by gains in lower body strength [indirect effect $\beta=-0.64$ (95% CI -1.38, -0.004); direct effect $\beta=-0.37$ (95% CI -1.51, 0.78)]. Figure 3b; The effect of PRT on global domain was significantly mediated by gains in lower body strength [indirect effect $\beta=0.12$ (95% CI 0.02, 0.22); direct effect $\beta=-0.003$ (95% CI -0.17, 0.16)] Figure 3c; The mediating effect of lower body strength on executive domain

following PRT approached statistical significance [indirect effect $\beta=0.11$ (95% CI -0.04, 0.26); direct effect $\beta=0.03$ (95% CI -0.17, 0.23)].

SUPPLEMENTAL LEGENDS

Supplemental Appendix 1

Abbreviations

Supplemental Methods: Assessment of Cognitive Outcomes

Supplemental Methods: Assessment of maximal aerobic capacity (VO₂peak)

Supplemental Methods: SPSS Process Macro

Supplemental Tables

Supplemental Table 1: Supplemental Table 1. Association between maximal aerobic capacity and peak strength with cognitive function at baseline

Supplemental Table 2: Association between changes in maximal aerobic capacity and changes in peak strength with changes in cognitive function within the whole cohort

Supplemental Table 3: Association between changes in maximal aerobic capacity and changes in peak strength with changes in cognitive function within the PRT group only

Supplemental Table 4: Association between changes in maximal aerobic capacity with changes in cognitive function within the Sham-Ex group only

jgs_14542_f1.tif

Author Manuscript

jgs_14542_f3.tif

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Mavros, Y;Gates, N;Wilson, GC;Jain, N;Meiklejohn, J;Brodaty, H;Wen, W;Singh, N;Baune, BT;Suo, C;Baker, MK;Foroughi, N;Wang, Y;Sachdev, PS;Valenzuela, M;Singh, MAF

Title:

Mediation of Cognitive Function Improvements by Strength Gains After Resistance Training in Older Adults with Mild Cognitive Impairment: Outcomes of the Study of Mental and Resistance Training

Date:

2017-03-01

Citation:

Mavros, Y., Gates, N., Wilson, G. C., Jain, N., Meiklejohn, J., Brodaty, H., Wen, W., Singh, N., Baune, B. T., Suo, C., Baker, M. K., Foroughi, N., Wang, Y., Sachdev, P. S., Valenzuela, M. & Singh, M. A. F. (2017). Mediation of Cognitive Function Improvements by Strength Gains After Resistance Training in Older Adults with Mild Cognitive Impairment: Outcomes of the Study of Mental and Resistance Training. JOURNAL OF THE AMERICAN GERIATRICS SOCIETY, 65 (3), pp.550-559. <https://doi.org/10.1111/jgs.14542>.

Persistent Link:

<http://hdl.handle.net/11343/291870>