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Commentary OMICS International

Commentary on "Group-Based Exercise Combined with Dual-Task Training Improves Gait but not Vascular Health in Active Older Adults without Dementia" - Missed Opportunities for Mediation Analyses

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Abstract

This commentary considers the implications of the findings related to the effect of a community-based, multiple modality and dual-task exercise training program in the Archives of Gerontology and Geriatrics. Findings from this study suggest that participants who performed the multiple modality and dual-task exercise intervention experienced greater improvements in global cognition, greater elevations in dual-task gait speed and dual-task step-length and greater reductions in dual-task stride time variability when compared to participants who did not perform the dual-task component of the exercise training program. The ability of exercise to impart cognitive and other physiological benefits has been long understood; however, the mechanisms that facilitate these training-induced improvements remain elusive. Mediation analyses provide a unique avenue to investigate the relationship between various physiological measures and can provide insight related to the causal sequence that drives the beneficial physiological and psychological response to an intervention. Recent works have incorporated mediation analyses within their study designs and the insight provided therein has revealed a number of intriguing intricacies with respect to cognition in aging and the effect of exercise on the body and brain. Mediation analyses are rarely utilized in neurophysiological research; however, the complex phenomenological relationships that can be revealed using this method will be crucially required for the identification of factors responsible for improvements in cognition following pharmacological or lifestyle-based interventions, and the development of effective management strategies for older adults with cognitive impairment.

This commentary considers the implications of the findings related to the effect of a community-based, multiple modality and dual-task exercise training program previously described by Gregory et al. [1] in the Archives of Gerontology and Geriatrics. The authors report that participants who performed the multiple modality and dual-task exercise intervention experienced greater elevations in dual-task gait speed and dual-task step-length and reductions in dual-task stride time variability when compared to participants who did not perform the dual-task component of the exercise training program. These results were secondary to the primary analysis concerning change in cognition post-exercise training [2], which suggested that participants performing the multiple modality and dual-task exercise training program experienced greater elevations in global cognitive functioning when compared to those who performed the multiple modality exercise program alone; these improvements were driven by improvements in verbal learning and memory and verbal fluency scores.

Although this study was a well-designed randomized controlled trial (RCT) that collected a number of physiological, psychological and behavioural outcomes, the primary limitation to the interpretation of these results lies within the absence of an investigation in to the mediators of cognitive change post-exercise training. Mediation analyses are complex, experimental and theory-driven regression analyses that investigate the effect of an intervention on a mediator and a specific outcome of interest [3]. Mediators represent the causal sequence between and intervention and a specific outcome; these analyses can provide insight related to the mechanistic facilitators of post-training improvements in cognition. Mediation analyses are considerably absent from RCT designs [3] and this absence has resulted in the development countless ill-informed experimental studies that are not properly situated to identify the mechanisms that mediate improvements in cognition and mobility following exercise training.

A number of recent RCTs have incorporated mediation analyses within their study designs, and the insights provided by these analyses have been quite intriguing. For example, the mediation analysis performed by Forte et al. [4] suggest that the mechanisms that drive improvements in cognition differ according to the specific exercise modality used; multicomponent training directly benefits inhibitory control, while resistance training indirectly benefits cognition through gains in muscular strength. Additionally Yates et al. [5] found that subjective memory complaints partially mediate the relationship between anxiety and cognition, as well as depression and cognition. These results suggest that mood disturbances among those with cognitive impairment are primarily reserved for those who concomitantly perceive memory difficulties rather than being ubiquitously present among all those with objective cognitive impairment and the management of subjective memory complaints may be an effective method to mitigate mood disturbances in these individuals. A final example of the utility of mediation analyses can be found from Leckie et al. [6], who identified a moderating role of age on the exercise-induced elevation in serum brain-derived neurotrophic factor (BDNF) (i.e., participants in the highest age quartile had the largest elevations in serum BDNF), and implicated elevations in serum BDNF as a mediator of improved executive function (EF) among these older following the exercise intervention. This analysis highlights the importance of considering the effect of age on the cognitive response to an exercise intervention, and suggests that age also influences the BDNF response to exercise training programs. These few

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instances highlight the utility of mediation analyses and the intricate insight that these techniques can provide with respect to furthering our understanding of complex, systems-level phenomenon such as the physiological response to exercise training.

There are a number of missed opportunities in which Gregory et al. failed to attempt to identify the mediators responsible for the observed improvements in cognition and gait. For instance, vascular risk factors appear to be mediators of pathological cognitive decline and vascular risk factor management may be a key strategy to improve cognitive function in aging [7]. Despite this suggestion, the results from Gregory et al. call to question the pivotal role of vascular risk management for the improvement of cognition and gait outcomes in older adults; cognition improved independent of changes in vascular health outcomes. It is important to note that other potential mediators could facilitate improvements in cognition improvements in cognition following exercise training, including changes in social interaction [8], depressive symptomatology [9], cortical volume [10] and potentially many others; however, the authors failed to investigate this relationship within their study. Furthermore, the authors chose to use a predictive cardiorespiratory fitness outcome measure to determine evaluate changes in cardiorespiratory fitness following the exercise intervention. Although this estimate tool (i.e., the STEP test tool [11]) is pragmatic and easily employed, standardized graded exercise testing would provide a more reliable measure of cardiorespiratory fitness. The lack of an observed change in cardiorespiratory fitness reported in the primary study [12] could have been due to a lack of sensitivity of the predictive cardiorespiratory fitness measure that was used, as well as the relatively short (50 min of aerobic exercise per week), non-progressive nature of the aerobic component of their intervention. Second, the authors speculate that the lack of an observed within- or between-group difference in usual gait performance following the intervention was due to the limited impact of the exercise program on EF [2]. This interpretation was based on previous studies, which implicated improvements in EF as a potential mediator of exercise-induced improvements in usual gait [13,14]. However, the results from the primary outcome paper suggest otherwise, as the between-group difference in the cognitive response to the exercise programs was driven by improvements in verbal fluency, a cognitive process that is heavily dependent upon frontal lobe integrity and EF [15]. Although the authors arguably observed exercise-induced improvements in certain aspects of EF (i.e., verbal fluency but not set-shifting), this was not accompanied by improvements in usual gait performance following exercise training. Despite this oversight, the dissociation between improvements in EF and usual gait performance in this study can likely be partially attributed to specific characteristics of the participants; they were active, highly educated older adults with relatively preserved mobility and cognitive function at baseline. The gait speed required for safe community ambulation is 1.0 m/s [16] and the participants within both study groups demonstrated baseline gait speed well beyond this pathological threshold (i.e., 1.13 m/s for controls; 1.22 m/s for intervention). The preserved gait function of these participants likely contributed to a diminished potential to observe changes in these usual gait outcomes, despite having imparted a beneficial impact on EF.

Nevertheless, the work of Gregory et al. does indeed provide some important insight in to the relationship between exercise, cognition, and mobility. It appears that vascular risk factor reduction is not necessarily required to observe improvements in cognition or gait following exercise training; other factors can also facilitate these benefits. Evidence suggests that the neural networks responsible for the control of gait are plastic and can be modified [17] and improved gait without concomitant reductions in vascular risk factor burden have been previously observed following exercise training [18-20]. The mechanisms associated with these improvements appear to be dependent upon the specific exercise training modality employed, and only preliminary evidence related to these mechanisms within each exercise training have been investigated. However, dual-task exercise interventions appear to be appropriately situated to facilitate these improvements, as successful dual-task performance is heavily dependent upon and reflective of EF [21]. Thus, dual-task training programs like those reported by Gill et al. [2], Gregory et al. [1] and more recently Gregory et al. [22] exploit this relationship, and appear to be specifically tailored to impart a direct benefit EF following exercise training. Further work is required to identify the specific characteristics of a dual-task exercise training program that are required to impart the greatest benefit to cognition and gait and to investigate the importance of potential physiological and behavioural mediators in the relationship between exercise, cognition and mobility in older adults.

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