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Effect of resistance-type exercise training with or without protein supplementation on cognitive functioning in frail and pre-frail elderly: Secondary analysis of a randomized, double-blind, placebo-controlled trial

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ABSTRACT

Physical activity has been proposed as one of the most effective strategies to prevent cognitive decline. Protein supplementation may exert an additive effect. The effect of resistance-type exercise training with or without protein supplementation on cognitive functioning in frail and pre-frail elderly people was assessed in a secondary analysis. Two 24-week, double-blind, randomized, placebo-controlled intervention studies were carried out in parallel. Subjects performed a resistance-type exercise program of two sessions per week ($n = 62$) or no exercise program ($n = 65$). In both studies, subjects were randomly allocated to either a protein (2×15 g daily) or a placebo drink. Cognitive functioning was assessed with a neuropsychological test battery focusing on the cognitive domains episodic memory, attention and working memory, information processing speed, and executive functioning. In frail and pre-frail elderly, resistance-type exercise training in combination with protein supplementation improved information processing speed (changes in domain score 0.08 ± 0.51 versus -0.23 ± 0.19 in the non-exercise group, $p = 0.04$). Exercise training without protein supplementation was beneficial for attention and working memory (changes in domain scores 0.35 ± 0.70 versus -0.12 ± 0.69 in the non-exercise group, $p = 0.02$). There were no significant differences among the intervention groups on the other cognitive tests or domain scores.

1. Introduction

Current estimates indicate that 35.6 million people worldwide are living with dementia, and because of the aging population this number is predicted to double by 2030 and more than triple by 2050 (World Health Organization and Alzheimer's Disease International, 2012). Interventions targeted at risk factors for cognitive decline and Alzheimer's Disease (AD) may offer opportunities for the development of an optimal preventive strategy. Dementia is preceded by a decline in cognitive functioning; however, this decline in cognitive functioning is not uniform across all older individuals or across all cognitive domains. One of the factors that have been associated with cognitive decline is physical activity. Several meta-analyses and systematic reviews have summarized the evidence for the impact of physical activity on cognitive function in older individuals that are provided by either observational studies (Arab and Sabbagh, 2010; Sofi et al., 2010), randomized controlled trials (RCTs) (Angevaren et al., 2008; Colcombe and Kramer, 2003; Heyn et al., 2004; Hindin and Zelinski, 2012; O'Connor et al., 2010; Smith et al., 2010; van Uffelen

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et al., 2008), or both (Bherer et al., 2013; Rolland et al., 2008). Generally, it has been suggested that physical activity improves cognitive function and prevents cognitive decline, but results of observational as well as experimental studies are limited and inconsistent to draw firm conclusions.

The heterogeneous results may be explained not only by varying study populations and differences in study duration, but also by the different intensities and types of exercise employed. Beneficial effects, though not all significant, of various kinds of exercise programs were observed: aerobic, strength, balance, flexibility, or a combination of these. It is unclear which type of exercise program is most effective, for what aspect of cognition and for which specific population. The importance of resistance training is stressed in the meta-analysis by Colcombe et al. (2003) who showed that aerobic-based training exercises together with resistance training exercises had a greater beneficial effect on cognition than programs of aerobic-based exercise training alone, and is also postulated by a recent literature review of Bherer et al. (2013). In addition, the few RCTs that used resistance training alone were largely positive. Study durations ranged from 8 to 52 weeks and effects were mainly observed on the cognitive domains memory and executive functioning (Colcombe and Kramer, 2003; Liu-Ambrose et al., 2010; Nagamatsu et al., 2013; O'Connor et al., 2010; van Uffelen et al., 2008). A very recent study that was performed in frail older adults showed that 3 months of a combination of aerobic and strength exercise significantly improved several domains of cognitive performance (Langlois et al., 2013). Studies on different types of exercise in relation to brain function, structure, and connectivity assessed using magnet resonance imaging (MRI) have also started to emerge and the results are promising as has been summarized by Voelcker-Rehage and Niemann (2013).

In addition to exercise, dietary protein might improve cognitive functioning. Van de Rest et al. (2013) performed a literature review on the role of protein intake in relation to cognitive functioning and concluded that this has barely been studied. Five observational and three case-control studies were found, showing mixed results. However, all three RCTs that were performed showed some beneficial effects. A population of physically frail elderly would be a suitable target population for a combined exercise and protein supplementation intervention, since physical frailty has been identified as a risk factor for cognitive decline and AD (Boyle et al., 2010), frail elderly generally have a limited habitual physical activity level and moreover, they have a suboptimal protein intake (Tieland et al., 2012a).

We hypothesized that resistance-type exercise training would beneficially affect cognitive functioning, in particular in subjects supplemented with dietary protein, which would augment the exercise effect. Therefore, we examined the effect of 24-week resistance-type exercise training with or without protein supplementation on cognitive function in frail and pre-frail elderly.

2. Subjects and methods

2.1. Subjects

Individuals ≥65 years of age were recruited between December 2009 and October 2010, by using an existing database of volunteers, through distribution of information flyers, and by local information meetings. Potentially eligible elderly were screened for pre-frailty and frailty using the five criteria from Fried et al. (2001): (1) unintentional weight loss, (2) weakness, (3) self-reported exhaustion, (4) slow walking speed, and (5) low physical activity. Pre-frailty was classified when one or two criteria were present and frailty when three or more criteria were present. Individuals who were diagnosed with cancer, chronic obstructive pulmonary disease, muscle disease, type 2 diabetes (plasma glucose concentration ≥7.0 mmol/L) (Alberti and Zimmet, 1998), or renal insufficiency (estimated Glomerular Filtration Rate <60 mL/min/1.73 m^2 (Mandayam and Mitch, 2006) were excluded. For participants in the resistance-type exercise training program, a resting electrocardiogram was performed to exclude silent ischemia. The Wageningen University Medical Ethical Committee approved the study and all subjects gave their written informed consent.

2.2. Study design

For the current study, we used data of two randomized, placebo-controlled trials that were carried out in parallel. Both trials covered a 24-week intervention period and investigated the effect of protein versus placebo supplementation; in the absence or presence of additional resistance-type exercise training (Tieland et al., 2012b, c). Primary outcome in both studies was muscle mass, but one of the secondary outcome measures was cognitive functioning.

Sample size was calculated based on an expected difference in lean body mass of 1.1 kg between groups (Borsheim et al., 2008; Esmarck et al., 2001) with an SD of 1.4 kg, a minimum of 24 subjects per treatment group would be required to detect a difference (power = 80%, α = 0.05). With an expected dropout rate of 25% (Bonnefoy et al., 2003; Chin et al., 2002), a sample size of 30 subjects per treatment group was considered adequate.

After inclusion, 62 of the 127 subjects participated in a 24-week resistance-type exercise training program and 65 did not perform any exercise program. All subjects were randomly allocated to either protein or placebo supplementation for 24 weeks. Allocation was carried out independently for both trials by an independent person using a computer-generated random numbers in stratified permuted blocks of size 4 and was stratified by gender. All outcome measures were collected at baseline and after 12 (except most cognitive function tests) and 24 weeks of intervention.

2.3. Resistance-type exercise program

The supervised resistance-type exercise training was performed twice per week under personal supervision for a 24-week period. The sessions were performed in the morning and afternoon with at least 72 h between sessions. The training consisted of a 5-min warm-up on a cycle ergometer, followed by four sets on the leg-press and leg-extension machines and three sets on chest press, lat pulldown, pec-dec, and vertical row machines (Technogym, Rotterdam, the Netherlands). The workload started at 50% of 1-Repitition Maximum (1-RM) (10–15 repetitions per set) to 75% of 1-RM (8–10 repetitions) to stimulate muscle hypertrophy. Resting periods of 1 min were allowed between sets and 2 min between exercises. To evaluate changes in muscle strength, 1-RM was repeated after 4, 8, 12, 16, and 20 weeks of training. Workload intensity was adjusted based on the 1-RM outcomes.

2.4. Protein supplementation

Twice daily, the subjects received either a 250-mL protein-supplemented beverage containing 15 g protein (MPC80; milk protein concentrate), 7.1 g lactose, 0.5 g fat, and 0.4 g calcium, or a matching placebo supplement containing no protein, 7.1 g lactose, and 0.4 g calcium (FrieslandCampina Consumer Products Europe, Wageningen, the Netherlands). All beverages were vanilla flavored to mask the contents of the drinks, and the packages were non-transparent. The subjects consumed one beverage after breakfast and one beverage after lunch. Adherence to the protein and placebo drinks was judged by returned ticked calendars and non-