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Original Research Article

Effects of Exercise Intervention on Vascular Risk Factors in Older Adults with Mild Cognitive Impairment: A Randomized Controlled Trial

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Key Words
Cholesterol · Rehabilitation · Cognitive impairment · Metabolic profiles · Dementia · Vascular risk factors · Physical activity

Abstract
Aims: The purpose of this study is to clarify the effects of exercise intervention on vascular risk factors in older adults with mild cognitive impairment (MCI). ***Methods:*** Community-dwelling older adults who met the definition of MCI using the Petersen criteria (n = 100; mean age = 75.3 years) were randomly allocated to the exercise (n = 50) or education control group (n = 50). Participants in the exercise group exercised under the supervision of physiotherapists for 90 min/day, 2 days/week, 80 times for 12 months. Anthropometric profiles, blood markers, blood pressure, and physical fitness (the 6-min walking test) were measured. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and TC/HDL-C risk ratio measurements were taken from blood samples. ***Results:*** The exercise group showed significantly reduced TC and TC/HDL-C risk ratio after training compared with baseline levels ($p < 0.001$, $p = 0.004$). However, no significant reduction was found for the control group ($p = 0.09$, $p = 0.09$). Physical fitness also significantly improved after exercise intervention compared with the control group ($p < 0.0001$). ***Conclusion:*** Exercise intervention was associated with positive changes in important vascular risk factors related to cognitive decline and vascular disease in older adults with MCI.

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Introduction

Cognitive problems in older adults range from mild impairment to severe dementia. The transitional stage between normal aging and dementia has been designated as mild cognitive impairment (MCI) [1, 2]. Individuals with MCI have been found to have a 10–15 times higher risk of developing Alzheimer's disease (AD), although up to 40% will not develop dementia [3]. It is of great importance to recognize and treat patients at the earliest stage of the disease [4]. Recent studies have reported beneficial effects of physical activity or exercise on cognitive health, such as cognitive function [5–7], brain volume, and activation [8, 9], in older adults with and without cognitive impairment.

Vascular risk factors, such as hypertension, hypercholesterolemia, and diabetes mellitus, are associated with both the occurrence and progression of AD dementia [10–13]. It has also been found that vascular risk factors increase the risk of MCI [14, 15] and the risk of conversion from MCI to AD [16]. Li et al. [16] also reported that treatment (i.e., medication) of vascular risk factors was associated with a reduced risk of AD dementia, which suggests that active interventions for vascular risk factors might reduce the progression from MCI to AD dementia.

There is a growing body of evidence showing that regular physical activity has therapeutic and protective effects against dementia [17, 18] and cardiovascular disease [19] in older adults. Several studies have suggested that aerobic or resistance exercises have positive effects on vascular risk factors in healthy older adults, for example increases in high-density lipoprotein cholesterol (HDL-C) [20] as well as decreases in total cholesterol (TC), TC/HDL risk ratio, and triglyceride (TG) [21–23]. It is possible that improvements of metabolic profiles by exercise may lead to a decrease in the risk of dementia or vascular disease. However, it remains unclear whether exercise intervention affects vascular risk factors in older adults with MCI.

The identification and subsequent management of risk factors at the MCI stage could be an important strategy for preventing and delaying progression to AD. Considering the observed influence of the cardiovascular system and metabolic profile on the risk of developing dementia, it is important to know the potential benefits derived from exercise in terms of metabolomics. The purpose of this study was to investigate the effects of exercise intervention on vascular risk factors in older adults with MCI.

Participants and Methods

Participants

In this 12-month randomized controlled trial, subjects were randomly allocated to the exercise or education control group at the end of a baseline assessment. Study personnel involved in the collection of outcome measures were blinded to the randomization assignment. The Ethics Committee of the National Center for Geriatrics and Gerontology (Obu, Japan) approved the study protocol. The purpose, nature, and potential risks of the experiments were fully explained to the subjects, and all subjects gave written informed consent before participating in the study.

Subjects in this study were recruited from our volunteer databases, which included elderly individuals (65 years and over). Participants had to be community-dwelling adults aged 65 years and older to be included in the study. A total of 528 prospective subjects with a Clinical Dementia Rating (CDR) of 0.5 [24] or who complained of memory impairment were recruited in the first eligibility assessments. A total of 135 subjects responded to the second eligibility assessments. Thirty-five out of 135 subjects were excluded, and the 100 subjects

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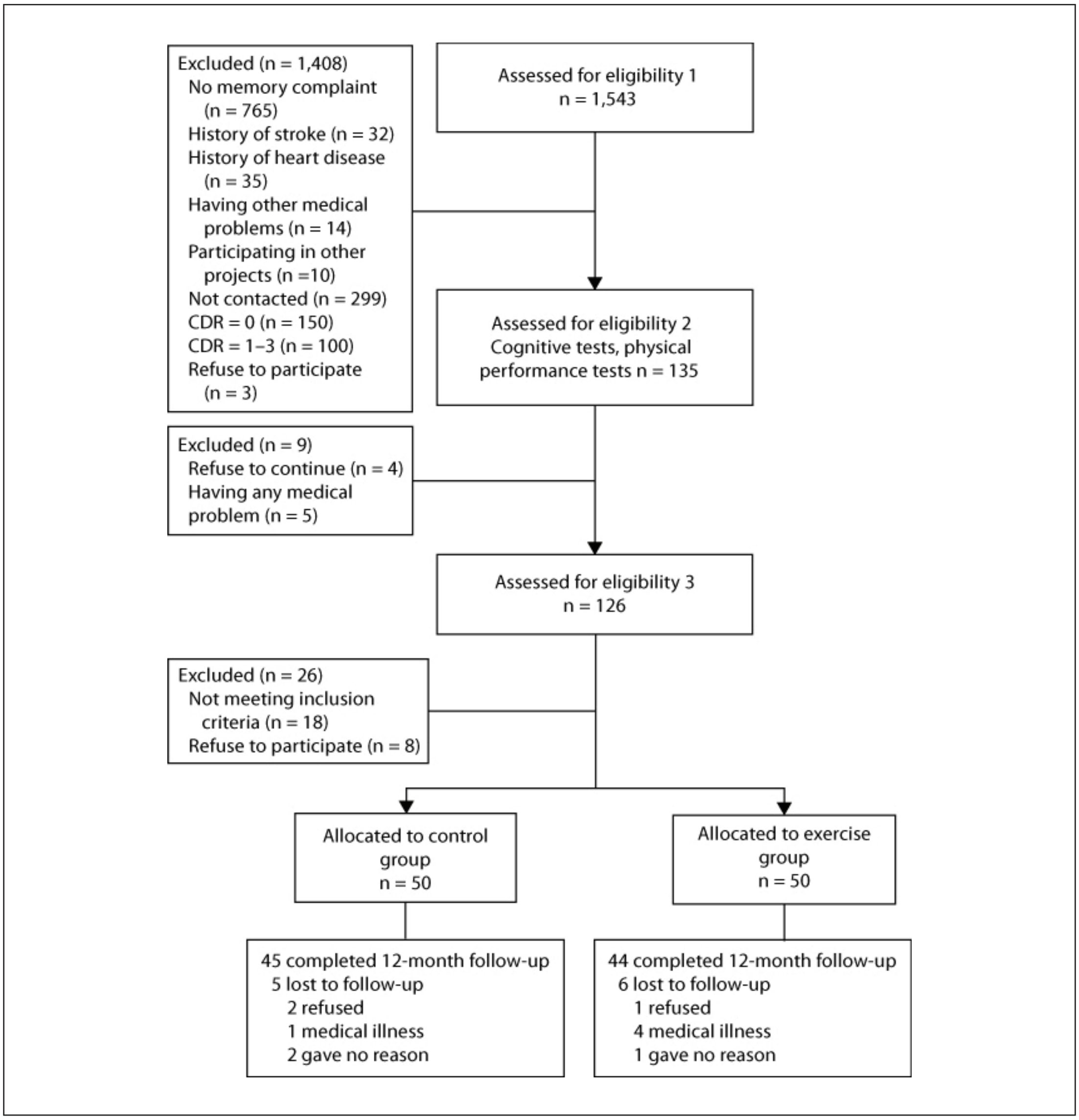

Fig. 1. Subject flow diagram from the initial contact through to study completion.

who remained met the definition of MCI using the Petersen criteria [3]. Exclusion criteria included a CDR of 0 or 1–3, a history of neurological, psychiatric, and cardiac disorders, and other severe health issues (i.e., recent myocardial infarction and unstable angina), uncontrolled hypertension, use of donepezil, impairments in basic activities of daily living, and participation in other research projects.

The Consolidated Standards of Reporting Trials (CONSORT) [25] diagram outlining the subject flow from the first contact to the study completion is shown in figure 1.

Interventions

The 12-month exercise program involved biweekly 90-min sessions with aerobic exercise, muscle strength training, postural balance retraining, and combined training. In addition, the exercise program included a focus on promoting exercise and behavior change. Two

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trained physiotherapists involved in geriatric rehabilitation conducted each intervention. Each supervised session began with a 10-min warm-up period and stretching exercise, followed by 20 min of muscle strength exercise. Then, the participants practiced aerobic exercise, postural balance retraining, and combined training for 60 min. For the aerobic exercise, participants underwent stair stepping and endurance walking. The mean intensity of the aerobic exercise was approximately 60% of the maximum heart rate.

Before and after each session of the program, the physiotherapists conducted a physical check of each participant. The participants were required to carry out daily home-based muscle strength exercises and walking, which were self-monitored using a booklet and pedometer based on the concept of promoting exercise and behavior change.

Subjects in the education control group attended three education classes about health promotion during the 12-month study period. The classes provided information regarding aging, healthy diet, oral care, brain image diagnosis, prevention of urinary incontinence, and health checks. However, the group did not receive specific information regarding exercise, physical activity, or cognitive health.

Anthropometry

Anthropometric measurements were obtained while the subjects were dressed in light clothing without shoes. Height (to the nearest 0.1 cm) and body weight (to the nearest 0.1 kg) were recorded. The body mass index (BMI) was calculated using the standard formula: weight (kg)/[height (m)^2].

Blood Markers and Blood Pressure

TC, HDL-C, TG, and glycosylated hemoglobin (HbA1c) were measured from blood samples, which were collected between 11 a.m. and 4 p.m. in a non-fasting state. The blood samples were kept at room temperature for 30 min to allow for clotting, then the samples were centrifuged for 15 min. Serum was harvested and stored at –25°C until analysis. Analyses were carried out centrally in one laboratory (Special Reference Laboratories, Tokyo, Japan). Serum samples were analyzed for TC, HDL-C, TG, and HbA1c. The TC/HDL-C ratio [26] was calculated as an index of lipid-associated coronary heart disease risk and is supported by both its superior predictive power compared with TC, LDL-C, or HDL-C levels and lower within-person variability [27]. Systolic and diastolic blood pressures were measured using a standard sphygmomanometer in the sitting position after a 5-min rest.

Physical Fitness

The participants' exercise capacity was quantitatively measured using the 6-min walking test (6MWT). The 6MWT is used to measure the maximum distance that a person can walk in 6 min [28]. Participants were instructed to walk as far as possible in 6 min along a 10-meter course, performed under the supervision of a physiotherapist. This study used the distance (in meters) in the 6MWT as a measure of physical fitness.

Statistical Analysis

Baseline characteristics were compared among groups using Student's t test for quantitative variables and the χ^2 test for qualitative variables. The intervention effects on all outcome measures were determined using two-way repeated measures ANOVA, with group (exercise, control) as a between-subjects factor and time (before training, after training) as a within-subjects factor. A probability of $p < 0.05$ was considered statistically significant. Post hoc comparisons were performed to test the differences in physical function variables between before and after the training in each group. The significance level of multiple comparisons was adjusted using the Bonferroni correction ($p < 0.025$; 0.05/2), and analyses were

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Table 1. Baseline characteristics of the study subjects

	Exercise (n = 50)	Control (n = 50)	p value (t test)
Age, years	74.8 ± 7.4	75.8 ± 6.1	0.46
Men	25 (50)	26 (52)	0.84[a]
BMI	23.4 ± 3.4	22.9 ± 3.1	0.52
Educational level, years	10.9 ± 2.8	10.3 ± 2.3	0.29
Number of medications	2.5 ± 2.3	2.4 ± 2.2	0.89
GDS score	3.8 ± 3.1	3.3 ± 2.8	0.38
Physical performance			
Grip strength, kg	24.7 ± 8.1	23.5 ± 7.3	0.47
Timed up & go, s	8.8 ± 2.5	9.2 ± 2.1	0.37
Cognitive function			
MMSE score	26.8 ± 2.3	26.3 ± 2.7	0.30
ADAS-cog score	6.0 ± 2.7	6.5 ± 2.8	0.37

Values are means ± SD or n (%). GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination; ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive subscale. [a] χ^2 test.

performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, Ill., USA). To perform the intention-to-treat analysis, a single imputation was used for all outcome measures. Missing data values were estimated using mean values for each corresponding group [29].

Results

There were no significant differences in baseline characteristics between the exercise and control groups (table 1). Figure 1 shows the flow of participants from the time of screening to study completion at 12 months. Eighty-nine (exercise group, n = 44) subjects completed the 12-month follow-up. The mean adherence to the exercise program was 78.6%, and 34 subjects (68.0%) in the exercise group attended our intervention program with more than 80% adherence.

Table 2 depicts all fitness-related variables for the exercise and control groups before and after the training. No interaction effects between group and time were detected for body weight and BMI [$F(1, 98) = 0.6$, $p = 0.43$; $F(1, 98) = 0.4$, $p = 0.51$, respectively]. Both the exercise and control groups showed reduced body weight and BMI after the intervention compared with before the intervention (exercise, $p < 0.001$; control, $p = 0.01$).

No interaction effects between group and time were detected for systolic and diastolic blood pressure [$F(1, 98) = 1.0$, $p = 0.31$; $F(1, 98) = 3.7$, $p = 0.06$, respectively]. Both the exercise and control groups showed reduced systolic blood pressure after intervention (exercise, $p = 0.02$; control, $p = 0.001$), but no significant change in diastolic blood pressure between before and after the intervention was observed in both groups (exercise, $p = 0.09$; control, $p = 0.9$).

A statistically significant interaction effect between group and time was found for the TC level [$F(1, 98) = 5.1$, $p = 0.03$; fig. 2a]. Post hoc comparisons revealed that the exercise group had significantly reduced TC levels compared with baseline levels ($p < 0.001$); however, no significant reduction was found for the control group ($p = 0.09$). There were no interaction effects between group and time for other blood markers [TC/HDL-C risk ratio, $F(1, 98) = 0.77$, $p = 0.38$; HDL-C, $F(1, 98) = 0.6$, $p = 0.25$; TG, $F(1, 98) = 0.2$, $p = 0.78$; HbA1c, $F(1, 98) = 0.05$, $p = 0.36$]. Post hoc comparisons revealed that the exercise group had a significantly reduced TC/HDL-C risk ratio after exercise training compared with before exer-

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Table 2. Fitness-related measurements according to group before and after the intervention (mean ± SD)

		Before	After	F-value 1. time effect 2. time × group	Partial η^2 1. time effect 2. time × group
Anthropometry					
Body weight, kg	exercise group	56.2 ± 9.6	55.2 ± 8.9**	19.7††	0.17
	control group	54.2 ± 8.8	53.5 ± 8.7*	0.6	0.006
BMI	exercise group	23.4 ± 3.3	22.9 ± 3.1**	19.7††	0.17
	control group	22.8 ± 3.1	22.5 ± 3.0*	0.4	0.004
Blood pressure					
Systolic, mm Hg	exercise group	144.6 ± 21.6	138.4 ± 20.3*	17.8††	0.15
	control group	142.4 ± 19.4	132.5 ± 17.5**	1.0	0.01
Diastolic, mm Hg	exercise group	74.6 ± 11.7	77.9 ± 11.1	0.24	0.014
	control group	75.1 ± 11.2	74.3 ± 9.2	3.7	0.036
Blood markers					
TC, mg/dl	exercise group	211.7 ± 36.2	193.6 ± 28.1**	19.3††	0.16
	control group	200.5 ± 34.6	194.7 ± 31.0	5.1†	0.05
TC/HDL-C risk ratio	exercise group	3.9 ± 1.0	3.7 ± 1.0**	10.8††	0.1
	control group	3.8 ± 0.9	3.7 ± 0.8	0.38	0.008
HDL cholesterol, mg/dl	exercise group	57.5 ± 16.0	55.6 ± 14.6	0.3	0.01
	control group	55.1 ± 13.2	55.2 ± 12.5	0.25	0.01
TG, mg/dl	exercise group	129.2 ± 64.7	131.8 ± 57.4	0.007	0
	control group	138.5 ± 91.5	134.7 ± 69.9	0.21	0.002
HbA1c, %	exercise group	5.6 ± 0.8	5.6 ± 0.9	1.1	0.01
	control group	5.4 ± 0.5	5.4 ± 0.4	0.05	0.001
Physical fitness					
6MWT distance, m	exercise group	378.0 ± 78.4	445.9 ± 97.8**	81.5††	0.45
	control group	363.5 ± 63.0	402.9 ± 70.7**	5.7†	0.06

* Significant difference between before and after the training within the group (Bonferroni, p < 0.025).
** Significant difference between before and after the training within the group (Bonferroni, p < 0.005).
†† p < 0.01; † p < 0.05.

cise training (p = 0.004), but no significant reduction was found for the control group (p = 0.09). There were no significant changes in HDL-C, TG, and HbA1c between before and after the intervention in both the exercise and control groups.

6MWT, our measure of physical fitness, showed significant interaction effects between group and time [F(1, 98) = 5.7, p = 0.02; fig. 2b] and was significantly increased in both the exercise and control groups compared with before the intervention (exercise, p < 0.001; control, p < 0.001).

Discussion

This study found that exercise intervention resulted in positive changes of blood markers, namely TC and TC/HDL-C levels, among older adults with MCI. Our baseline values were normal for TG and HDL-C, and borderline high for TC [30]. Numerous studies have shown that exercise improves lipid profiles among older adults. Indeed, a meta-analysis concluded that exercise could improve lipid profiles, including reducing TC and TC/HDL-C levels [31]. The multicomponent exercises in our intervention involved mainly aerobic exer-

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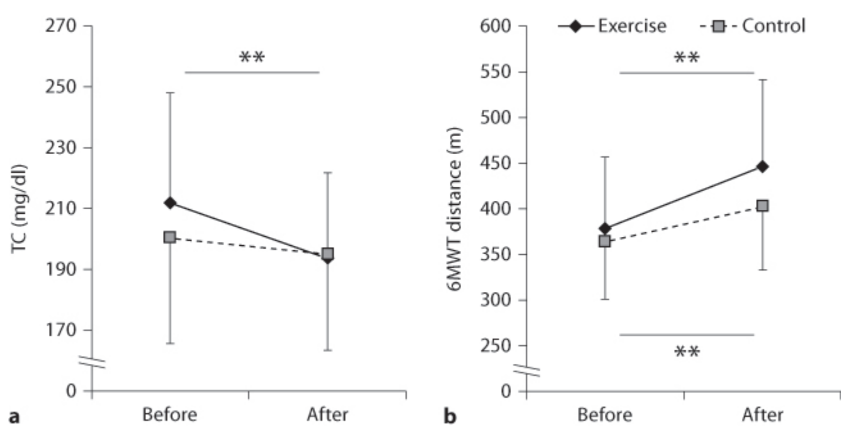

Fig. 2. The average values of TC (**a**) and 6MWT distance (**b**) in the exercise and control groups before and after the intervention. ** Significant difference between before and after the training within the group (Bonferroni post hoc test, $p < 0.005$).

cise. This type of exercise has been suggested to have positive effects on lipid profiles among older adults with coronary artery disease [32] or type 2 diabetes [33] as well as among healthy older adults [34]. Our study is the first to reveal the effectiveness of exercise intervention on vascular risk factors in older adults with cognitive impairment. Moreover, cardiorespiratory fitness also improved as a result of the increase in the 6MWT distance after exercise intervention, which is in line with previous studies reporting that exercise intervention improved cardiorespiratory functionality in healthy older adults, potentially counteracting the documented age-related decline in peak oxygen uptake [22, 23]. Previous studies have reported associations between habitual physical activity levels, increased endurance capacity, and/or chronic exercise programs and improvements in lipoprotein profiles in elderly subjects [35, 36]. In the present study, improved cardiorespiratory fitness might contribute to increased physical activity and positive changes in lipid metabolism.

From a metabolomic point of view, exercise intervention may be useful for dementia prevention in older adults with MCI. It has been reported that higher serum levels of TC lead to future cognitive decline and risk of cognitive impairment [37, 38]. It has also been reported that hypercholesterolemia independently increases the risk of conversion from MCI to AD [16]. Improved cardiorespiratory fitness and lipid metabolism may prevent vascular pathologies such as atherosclerosis. Furthermore, cholesterol is known to interact with, and modulate the generation of, Aβ, which alters cholesterol dynamics in neurons leading to tauopathy [39]. In addition, hypercholesterolemia promotes Aβ production by activating the activity of β- and γ-secretases [40]. The increased Aβ burden resulting from hypercholesterolemia may ultimately promote the development of AD [16]. The Aβ-modulating role of cholesterol may contribute to cognitive dysfunction, although conclusive evidence of the pathophysiological mechanism in dyslipidemias has not been provided yet [39]. In the current study, we also found that decreased TC levels were associated with an improvement in logical memory scores after exercise intervention [unpubl. data]. Therefore, exercise intervention may prevent cognitive decline and the incidence of dementia in older adults with MCI by improving cholesterol metabolism and risk factors (i.e., TC and TC/HDL-C levels) in older adults with MCI.

Cholesterol is not only a risk factor for cognitive impairment, but is also regarded as a vascular risk factor in such diseases as coronary heart disease and cerebrovascular disease [41]. It has been reported that TC is positively associated with ischemic heart disease mortality in both middle- and old-aged patients [42]. Independent of the mechanism underlying lipid changes, a reduction of 1% in TC level has been shown to reduce the risk for coronary artery disease by 2% [43], which implies that our exercising participants have reduced their risk of coronary artery disease by approximately 17%. Additionally, there is a growing body of evidence showing that regular physical activity has therapeutic and protective effects against cerebrovascular disease in older adults [19]. Exercise intervention may have the potential to prevent incidences of vascular disease and related mortality in older adults with MCI. Overall, exercise is a beneficial and inexpensive practice that is associated with numerous benefits for cognitive and metabolic health with minimal adverse effects.

Study Limitations

There are several limitations to the current study. First, blood samples were collected in a non-fasting state. Although it has been reported that lipoprotein and apolipoprotein levels are not considerably different between fasting and non-fasting states, with the exception of TG, a fasting sample is preferred for precise assessment and management of cardiovascular risk [44]. Second, the intervention of this study lacked nutrient intake assessment and dietary control. It is possible that changes in nutrient intake contributed to decreases in body weight, systolic blood pressure in both groups, and unchanged HDL-C levels, which have been shown to decrease with low total and saturated fat diets [45]. To ascertain that the observed changes were due to exercise rather than other possible factors, a randomized controlled trial with control of nutrient intake in older adults with cognitive impairment and abnormal metabolic profiles, such as metabolic syndrome, should be conducted.

Conclusions

We investigated the effects of exercise intervention on vascular risk factors in older adults with MCI. The main finding of this study is that exercise intervention reduced TC levels and TC/HDL-C risk ratios among older adults with MCI. Reduction of these vascular risk factors may contribute to reduced cognitive decline and prevention of dementia, vascular disease, and related mortality in the future.

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Disclosure Statement

The authors have no conflict of interest to declare.

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