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Effects of multicomponent exercise on cognitive function in older adults with amnestic mild cognitive impairment: a randomized controlled trial

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Abstract

Background: To examine the effects of a multicomponent exercise program on the cognitive function of older adults with amnestic mild cognitive impairment (aMCI).

Methods: Design: Twelve months, randomized controlled trial; Setting: Community center in Japan; Participants: Fifty older adults (27 men) with aMCI ranging in age from 65 to 93 years (mean age, 75 years); Intervention: Subjects were randomized into either a multicomponent exercise (n = 25) or an education control group (n = 25). Subjects in the multicomponent exercise group exercised under the supervision of physiotherapists for 90 min/d, 2 d/wk, for a total of 80 times over 12 months. The exercises included aerobic exercises, muscle strength training, and postural balance retraining, and were conducted using multiple conditions to stimulate cognitive functions. Subjects in the control group attended three education classes regarding health during the 12-month period. Measurements were administered before, after the 6-month, and after the 12-month intervention period; Measurements: The performance measures included the mini-mental state examination, logical memory subtest of the Wechsler memory scale-revised, digit symbol coding test, letter and categorical verbal fluency test, and the Stroop color word test.

Results: The mean adherence to the exercise program was 79.2%. Improvements of cognitive function following multicomponent exercise were superior at treatment end (group × time interactions for the mini-mental state examination (P = 0.04), logical memory of immediate recall (P = 0.03), and letter verbal fluency test (P = 0.02)). The logical memory of delayed recall, digit symbol coding, and Stroop color word test showed main effects of time, although there were no group × time interactions.

Conclusions: This study indicates that exercise improves or supports, at least partly, cognitive performance in older adults with aMCI.

Keywords: Aerobic exercise, MCI, Elderly, Alzheimer's disease, Prevention

Background

Population-based studies in older adults performed in North America, Europe, and Asia report a prevalence of mild cognitive impairment (MCI) ranging from 11% to 17% [1-5], and a prevalence of the amnestic MCI (aMCI) subtype between 3 and 5% [2,6]. Evidence from both neuropsychological and neuroimaging studies have suggested that MCI represents a clinical prodrome to degenerative dementias such as Alzheimer's dementia (AD) [7,8]. This is particularly the case with aMCI, which is likely to progress to AD [9]. Early treatment of mild to moderate AD is associated with better responses than later treatment [10], so it is conceivable that treating MCI may be particularly effective in delaying the progression to AD.

Clinical aspects have been widely examined as possible biomarkers for MCI to detect subjects at greater risk of conversion to dementia. Neuropsychological predictors of conversion include performance on specific cognitive

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tests, particularly those assessing delayed recall and executive functions [11-14]. Reducing or recovering from identified risk factors is important in the prevention of the conversion from MCI to AD or to delay the progression of the prodromal symptoms of dementia.

Epidemiological data suggests that moderate exercise and physical activity, such as walking, are associated with a lower risk of dementia [15]. According to these findings, epidemiological studies and randomized controlled trials examining the effects of exercise have proposed it is associated with various cognitive benefits [16-25], and a meta-analysis reported that physical activity or exercise is associated with improvements in attention, processing speed, and executive function in older adults with or without cognitive impairments [26-28]. RCT have been conducted to determine the effects of exercise or physical activity on cognitive functions in older adults with MCI. These studies identified the effects of exercise or physical activity on cognitive function including general cognitive function, executive function and glucometabolic and hypothalamic-pituitary-adrenal axis responses in older adults with MCI [16,19,22,23]. However, because the results of these studies differed largely due to differences in methodology, sufficient evidence has not been garnered regarding the relationship between exercise and cognitive function in aMCI.

We designed the present randomized trial to test whether 12 months of supervised multicomponent exercise improved cognitive function among older adults with aMCI. The multicomponent exercise included aerobic exercise, muscle strength training, and postural balance retraining. We adopted the multicomponent regimen because a previous review suggested that participants in combined aerobic and strength training regimens improved cognitive function to a reliably greater degree than those in aerobic training alone (0.59 vs. 0.41, SE = 0.043, n = 101, $p < 0.05$) [29].

Methods

Participants

In this 12-month randomized controlled trial, the subjects were divided into a multicomponent exercise or an education control group at the end of the baseline assessment. Study personnel involved in collection of outcome measures were unaware of each subject's assigned group. The Ethics Committee of the National Center for Geriatrics and Gerontology 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). The inclusion criteria we used were dwelling in the community and being 65 years or age or older. 528 prospective subjects with a Clinical Dementia Rating (CDR) [30] of 0.5, or who complained of memory impairments, were recruited for the initial eligibility assessments. 135 subjects participated in the secondary eligibility assessments, including neuropsychological tests and magnetic resonance imaging. 35 of these 135 subjects were excluded and the remaining 100 subjects met the definition of MCI using the Petersen criteria [31]. The objective memory impairment was defined as having a lower memory in the Logical Memory II subtest of the Wechsler memory scale-revised (WMS-LM II) [32]. The cut-off score to define the aMCI was adjusted by educational history (0–9 years: <7 points, 10–15 years: <10 points, more than 16 years: <12 points) [33]. The exclusion criteria we used included having a CDR = 0, 1, 2, and 3, a history of neurological, psychiatric, and cardiac disorders or other severe health issues, use of donepezil, loss of independence in basic activities of daily living (ADL), and current participation in other research projects. A diagram consistent with the Consolidated Standards of Reporting Trials (CONSORT) [34] that outlines the subject flow from first contact to study completion is shown in Figure 1. Fifty older adults (mean age 76.0 ± 7.1 years, range 65–92 years, male = 27 (54 %), mean education level 10.9 ± 2.5 years) with aMCI who had objective memory disabilities and who completed the neuroimaging assessments were selected as the subjects in the study.

Intervention

Subjects in the multicomponent exercise group exercised under the supervision of physiotherapists for 90 min/d, 2 d/wk, for a total of 80 times over 12 months. Two physiotherapists involved in geriatric rehabilitation and three well-trained instructors conducted each intervention. The exercise class consisted of 16–17 participants, and each supervised session began with a 10-min warm-up period, followed by 20 min of muscle strength exercise. The subjects then practiced aerobic exercise, postural balance retraining, and dual-task training for 60 min. In the aerobic exercises and postural balance retraining, subjects completed circuit training including stair stepping, endurance walking, and walking on balance boards. The mean intensity of the aerobic exercises was approximately 60% of maximum heart rate. Heart rate was monitored after aerobic exercise each session to take their pulse. One out of every four classes during the intervention period included outdoor walking during approximately 20–30 minutes. These exercises or training were also conducted under multitask conditions. For example, the subjects in the exercise group were asked to invent their own poem while walking. In the ladder training, subjects memorized a step pattern in

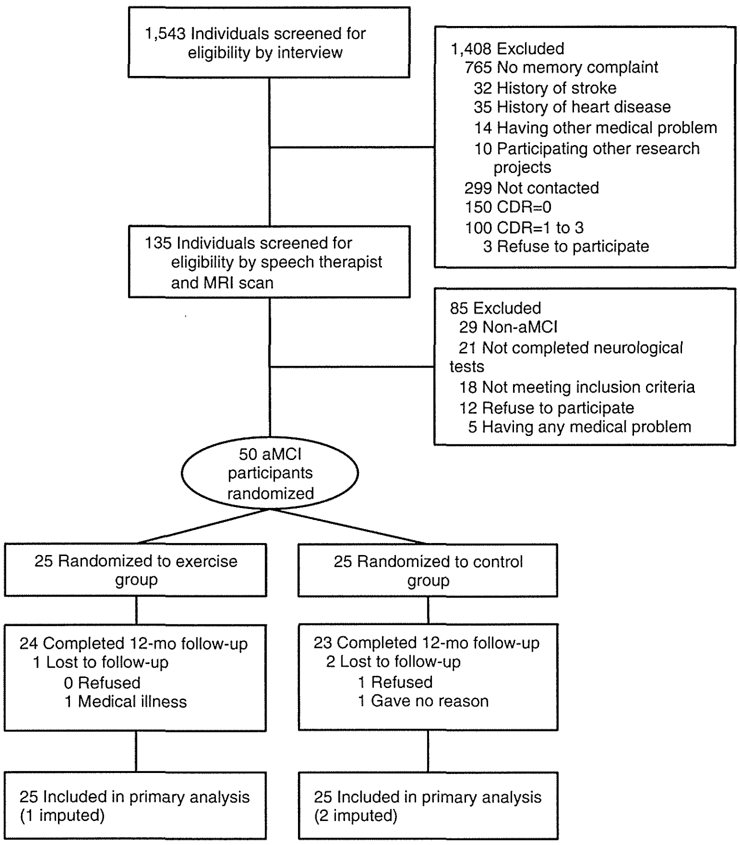

Figure 1 Subject flow diagram from the initial contact through the study completion.

consecutive square segments, and were instructed to step as quickly and accurately as possible. Before and after each session of the program, physiotherapists conducted a health check of each subject. The physiotherapists and well-trained instructors provided ongoing safety monitoring to prevent adverse accidents such as falling during the program. Daily home-based exercise in addition to structured program and outdoor walking was recommended to the exercise group. The subjects allocated the exercise group were asked to recording the amount of time spent on daily home-based exercise and the daily total steps for pedometer in a notebook. The subjects made graphs from the records of amount of time and steps to promote active lifestyle through a self-monitoring. Attendance at each session was recorded and a transportation service was provided for the participants, if necessary, to help the subjects maintain their participation in the program.

Subjects in the education control group attended three education classes regarding health promotion during the 12-month study period. The class 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.

Outcomes

The cognitive function before, after 6-month, and after 12-month intervention period was measured by speech therapists. Prior to the commencement of the study, all staff received training from the authors in the correct protocols for administering all of the assessment measures included in the study. The assessors introduced and demonstrated the assessments to facilitate understanding of the tests by the participants before they conducted the tests. A speech therapist calculated all of the results of the cognitive function tests.

The mini-mental state examination (MMSE) was measured as a general cognitive function [35]. The WMS-LM I and II [32] was used to assess logical memory function. In the WMS-LM, two short stories (story A and B) were read aloud to the subjects, who were then instructed to recall details of the stories immediately (WMS-LM I) and after 30 min (WMS-LM II) (total recall score = 50) [32]. The digit symbol-coding (DSC) subset of the Wechsler Adult Intelligence Scale III was used to assess processing speed [36]. Verbal fluency

[37,38] was measured by the number of words generated across 60-second trials [37]. The subject's listed words began with a letter composed of Japanese characters for the three trials (letter verbal fluency test: LVFT) and that belonged to a semantic category (category verbal fluency test: CVFT). The total number of correct responses was used for the analysis. The Stroop Color and Word Test (SCWT) [39] was used to assess executive function. For the Stroop test, we used two conditions. First, the subjects were instructed to read out words printed in black ink (e.g., *blue*) (SCWT-I). Second, they were shown a page with color words printed in incongruent colored inks (e.g., the word *blue* printed in red ink). The subjects were asked to name the ink color in which the words were printed (while ignoring the word itself) (SCWT-III). There were 24 trials for each condition, and we recorded the time the participants took to read each condition.

Analysis

The statistical analyses were conducted using SPSS software (Version 20; SPSS Inc., Chicago, IL, USA). The independent samples *t*-test or Chi-square test was used to compare the basic characteristics between the exercise and education control group. The effect of intervention (exercise vs control) over time on the cognitive functions was investigated in intention-to-treat (ITT) analyses. Measurements were analyzed using linear mixed models; analyses assumed missing at random with missingness allowed to be driven by variables included in the analyses. All models included random intercepts to account for correlations between the repeated measures for each participant. The fixed components of the models included effects of group and time and a group × time interaction. To assess the presence of a group and time effect, where this may change over time, we first determined the existence of time, group, and group × time interactions. The post hoc analyses were made between times and groups using the Bonferroni method. All statistical significance tests were two-sided, and an alpha-level of 0.05 was considered statistically significant.

Table 1 Baseline characteristics of the subjects

Characteristic	Exercise (n=25)	Control (n=25)
Age, mean ± SD, y	75.3 ± 7.5	76.8 ± 6.8
Men, No. (%), n	13 (52.0)	14 (56.0)
Educational level, mean ± SD, y	11.1 ± 2.4	10.8 ± 2.7
Blood pressure, mean ± SD, mmHg		
Diastolic	77.3 ± 11.1	74.3 ± 10.1
Systolic	152.2 ± 21.0	143.7 ± 21.3
Diagnosis, No. (%), n		
Hyper tension (1*)	13 (52.0)	11 (44.0)
Heart disease (1*)	2 (8.0)	0 (0)
Diabetes Mellitus	5 (20.0)	3 (12.0)
Medication, 3 and over	10 (40.0)	11 (44.0)
Blood test, mean ± SD		
Total cholesterol, mg/dL	212.6 ± 36.9	202.8 ± 32.2
Triglyceride, mg/dL	146.8 ± 73.7	130.4 ± 112.3
Glucose, mg/dL	116.3 ± 27.1	110.4 ± 23.4
HA1c, %	5.6 ± 0.6	5.4 ± 0.5
Cognitive functions, mean ± SD		
MMSE, score	26.8 ± 1.8	26.6 ± 1.6
WMS-LM I, score	12.5 ± 5.9	12.0 ± 4.9
WMS-LM II, score	8.2 ± 5.4	6.9 ± 5.0
DSC, s	47.5 ± 15.4	44.3 ± 16.3
LVFT, score	16.0 ± 5.3	16.9 ± 6.0
CVFT, score	33.1 ± 6.9	31.2 ± 7.7
SCWT-I, s	22.6 ± 9.7	23.4 ± 11.1
SCWT-III, s	42.0 ± 13.7	41.5 ± 17.7
TMIG index, mean ± SD, score		
IADL	5.0 ± 0.2	4.9 ± 0.3
Intellectual activity	3.8 ± 0.4	3.8 ± 0.4
Social role	3.6 ± 0.9	3.6 ± 0.8
Total	12.3 ± 1.1	12.3 ± 0.9
GDS, mean ± SD, score	3.0 ± 2.1	2.6 ± 2.0

SD; standard deviation, MMSE; mini-mental state examination, WMS-LM II; Logical Memory II subtest of the Wechsler memory scale-revised, LVFT; letter verbal fluency test, CVFT; category verbal fluency test, DSC; digit-symbol cording, SCWT; Stroop Color and Word Test, TMIG index; Tokyo Metropolitan Institute of Gerontology index, GDS; Geriatric Depression Scale. * missing value.

Results

Adherence to intervention

There were no significant differences in the baseline characteristics between the exercise and education control groups (Table 1). Figure 1 shows the flow of the participants from the time of screening to study completion at 12 months. 47 (exercise group, n = 24) subjects completed the 12-month follow-up. Two of the twenty-five subjects in the exercise group (1 man and 1 woman) did not attend a single session, but were included in the following analyses. The mean adherence to the exercise program, including these subjects, was 79.2%, and 17 subjects (68.0%) in the exercise group attended our intervention program with more than 80% adherence.

Changes in cognitive function

Table 2 shows changes in cognitive scores over the 12 months across the groups. On the MMSE, there was a group × time interaction (P = 0.04) indicated benefit of the exercise over time (Figure 2). Although there were no main effects of group or time, the control group showed significant decline in the MMSE score after 6

Table 2 Comparison of cognitive functions between exercise and control groups

	Mean difference (95% CI) between before and after 6 months		Mean difference (95% CI) between before and after 12 months		Time			Group			Group × time		
	Exercise (n=25)	Control (n=25)	Exercise (n=25)	Control (n=25)	df	F value	P value	df	F value	P value	df	F value	P value
MMSE	0.32 (−0.96–1.60)	−1.37 (−2.66–−0.07)	−0.47 (−1.75–0.81)	−0.44 (−1.74–0.86)	92.1	1.17	0.32 [d]	48.0	2.2	0.14 [g]	92.1	3.4	0.04
WMS-LM I	3.83 (1.40–6.25)	0.60 (−1.87–3.06)	4.62 (2.19–7.05)	5.00 (2.53–7.46)	90.9	23.0	<0.01 [a, b, e, f]	47.8	0.9	0.34 [g]	90.9	3.9	0.03
WMS-LM II	3.79 (1.49–6.10)	2.09 (−0.25–4.43)	5.13 (2.82–7.43)	6.20 (3.86–8.54)	91.1	35.4	<0.01 [a, b, e, f]	48.1	1.1	0.30	91.1	2.1	0.13
DSC	−0.19 (−4.20–3.81)	3.27 (−0.80–7.34)	3.64 (−0.36–7.64)	3.73 (−0.34–7.80)	90.4	5.0	<0.01	48.0	0.2	0.65	90.4	1.4	0.25
LVFT	2.87 (0.57–5.17)	−0.97 (−3.31–1.37)	2.99 (0.69–5.30)	1.61 (−0.73–3.95)	91.2	5.9	<0.01	48.3	0.3	0.59	91.2	4.1	0.02
CVFT	1.54 (−1.27–4.35)	−1.81 (−4.67–1.04)	1.33 (−1.48–4.14)	−1.61 (−4.46–1.25)	91.2	0.02	0.98	48.5	3.1	0.08	91.2	2.5	0.09
SCWT-I	−3.30 (−7.56–0.96)	−0.98 (−5.30–3.34)	−3.68 (−7.94–0.58)	−3.20 (−7.52–1.12)	91.5	3.9	0.02	47.7	0.73	0.40	91.5	0.5	0.62
SCWT-III	−4.70 (−12.72–3.33)	0.15 (−8.00–8.30)	−2.61 (−10.64–5.42)	−4.57 (−12.72–3.58)	92.0	1.2	0.31	48.8	0.009	0.92	92.0	1.1	0.34

MMSE; mini-mental state examination, WMS-LM; Logical Memory subtest of the Wechsler memory scale-revised, DSC; digit-symbol cording, LVFT; letter verbal fluency test, CVFT; category verbal fluency test, SCWT; Stroop Color and Word Test, TMIG; Tokyo Metropolitan Institute of Gerontology index.
[a] P < .05; significant differences between before and after 6 months in the exercise group, [b] P < .05; significant differences between before and after 12 months in the exercise group, [c] P < .05; significant differences between after 6 months and 12 months in the exercise group, [d] P < .05; significant differences between before and after 6 months in the control group, [e] P < .05; significant differences between before and after 12 months in the control group, [f] P < .05; significant differences between after 6 months and 12 months in the control group, [g] P < .05; significant differences between the exercise and control groups at after 6 months, [h] P < .01; significant differences between the exercise and control groups at after 12 months.

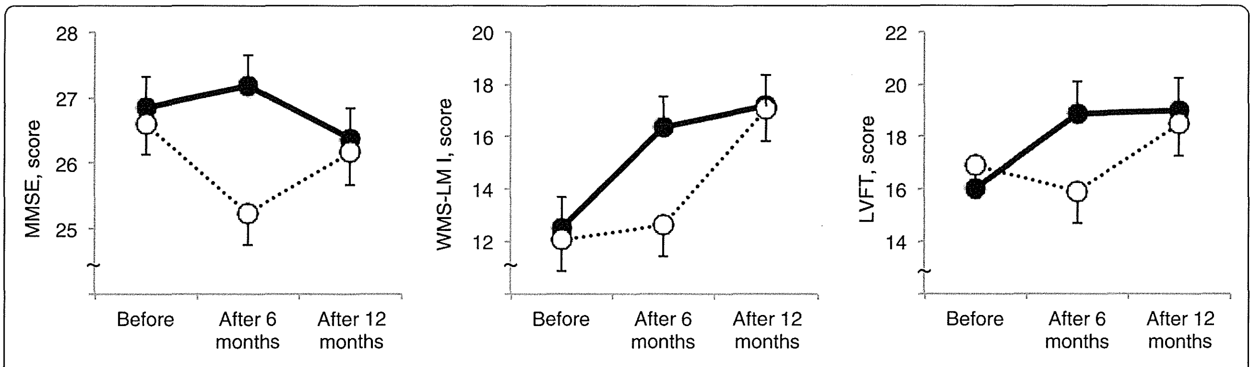

Figure 2 Changes in the MMSE, WMS, and LVFT scores. MMSE; mini-mental state examination, WMS-LM I; Logical Memory I subtest of the Wechsler memory scale-revised, LVFT; letter verbal fluency test. Panels showed change in MMSE, WMS-LM I, and LVFT scores before, after 6 months, and after 12 months intervention. Solid and dashed lines indicate the exercise and control groups, respectively. Group mean and standard errors are shown in older adults with amnestic mild cognitive impairment. The linear mixed models revealed significant group × time interactions in MMSE (P = 0.04), WMS-LM I (P = 0.03), and LVFT (P = 0.02).

months compared to before intervention ($P < 0.05$) and there was significant differences between the groups at after 6 months ($P < 0.05$).

For the WMS-LM I, there was a group × time interaction ($P = 0.03$); there were an overall effect of time and no main effect of group (Figure 2). In the post hoc analysis, the exercise group showed significant increase in the WMS-LM I score after 6 and 12 months compared to before intervention ($P < 0.05$) and the control group showed significant increase after 12 months compared to before intervention and after 6 months ($P < 0.05$). There was a significant difference between the groups at 6 months ($P < 0.05$).

On the LVFT, there was a group × time interaction ($P = 0.02$); there were an overall effect of time and no main effect of group (Figure 2). In the post hoc analysis, There were no significant differences between the times and groups.

The WMS-LM II, DSC, and SCWT-I showed main effect of time, although there were no group × time interaction and main effect of group. In the post hoc analysis, the exercise group showed significant increase in the WMS-LM II score after 6 and 12 months compared to before intervention ($P < 0.05$) and the control group showed significant increase after 12 months compared to before intervention and after 6 months ($P < 0.05$). There were no significant differences between the groups at each timepoints (Table 2).

Discussion

There was a significant group × time interaction on the MMSE, WMS-LM I, and LVFT scores. Twelve months of multicomponent exercise improved cognitive function in older adults with aMCI relative to the education control group. In particular, positive effects were observed for general cognitive function, immediate memory, and language ability, which is consistent with findings in cognitively intact adults [28]. A recent randomized controlled trial has been described as providing verification of the benefits of exercise in elderly adults with MCI [23]. In that study, 152 participants were randomly assigned to an aerobic exercise group and a non-aerobic exercise group, and to a vitamin B group and a placebo group, and a one-year intervention was carried out. The participants exercised twice weekly for 60 minutes each time. For the aerobic exercises, they walked together in groups. The results showed that aerobic exercise has no significant effect in improving cognitive function. However, these results were based on an intention-to-treat analysis, which included 30 participants who did not attend the exercise sessions. Had those elderly adults who had a high attendance rate among the aerobic exercise group been included in the analysis, then the results would have shown increased memory and attention, confirming the effectiveness of aerobic exercise in elder adults with MCI, though only to a limited extent. In another recent report, when elderly adults with MCI (a mean age of 70 years) engaged in aerobic exercise four times every week over the course of six months with a heart rate reserve of 75% to 85%, executive function significantly improved [16].

The present study shows that significant interactions were observed in general cognitive function, immediate memory, and verbal fluency between the groups, although intervention effects on delayed memory, processing speed, and executive control did not reach significance. Lautenschlager et al. reported that physical activity and behavioral interventions improve general cognitive function [19]. The multicomponent exercise training used in the current study also included aerobic exercise and behavioral interventions, such as self-monitoring of home-based exercise. Our results further supported the idea that a composite approach including aerobic exercise and behavioral interventions can have beneficial effects on cognitive function in aMCI patients.

Older adults with aMCI exhibit greater decreases in memory function than in other cognitive functions, relative to healthy older adults [40]. The cognitive deficits in aMCI increase the risk of conversion from MCI to AD [11,12]. Enhancing cognitive function, especially memory, in MCI may prevent conversion from MCI to AD in older adults. Our multicomponent exercise program involved cognitive loads during exercise. In other words, exercise was conducted under multitask conditions such as dual-task stimulation or while learning tasks during the exercises [41]. Our multicomponent exercise program, involving aerobic exercise, muscle strength, and additional cognitive demand, has some advantages for improving cognitive function over aerobic exercise alone, including possibly increasing logical memory in older adults with aMCI. The WMS-LM I scores in the education control group increased significantly at 12 months compared to before and after 6 months. The education control group received reports of the results of the three assessments and lectures regarding health. We suggest that these educational approaches may be useful in maintaining healthy behavior, such as starting cognitive training or intellectual activities. In fact, the subjects in the control group had fewer cessations of intellectual activity, e.g. culture lessons, than the exercise group during the 12-month period (−9% vs. −19%).

Baker et al. reported that high intensity aerobic exercise increased VFT scores in older women with MCI [16]. Early in the dementia process, the ability to consciously access lexical information about a target word is impaired while the overall semantic system is intact [42], whereas later in the disease, the integrity of the entire system is compromised, resulting in impaired name recall in structured tasks and spontaneous conversation [42,43]. Fluency tests tap into lexical and semantic retrieval operations and may be able to measure these specific aspects of language breakdown in aMCI patients. In a functional neuroimaging study using near infrared spectroscopy, patients with AD showed decreased brain activation patterns compared with healthy controls during the conduct of VFT. Significant correlations between brain activation and performance in the LVFT for dementia patients were found [44]. In the present study, multicomponent exercise provided positive effects on LVFT scores in the aMCI subjects, who had a higher risk of dementia [45].

The present study has several limitations. The small sample size means that replication with a larger group of adults with MCI would be beneficial. Other limitations include unknown group differences in the risk factors of cognitive decline and AD, such as apolipoprotein E ε4 genotypes [46], and inflammation [47], although there were no significant differences between the groups in hypertension, diabetes mellitus, medications, biomarkers of lipid metabolism, physical performance, instrumental ADL functioning, and depressive moods. In addition, it is possible that the improvement in the exercise group resulted from the social contact that the intervention group received. This possibility cannot be completely excluded with the present design and should be addressed in future studies.

Conclusions

Twelve months of exercise improved cognitive function in older adults with aMCI relative to the education control group. In particular, positive effects were observed for general cognitive function, immediate memory, and language ability. A future follow-up investigation is required to determine whether the effect is associated with prevention or delayed onset of dementia in older adults with aMCI.

Abbreviations

aMCI: Amnestic mild cognitive impairment; AD: Alzheimer's dementia; CDR: Clinical dementia rating; WMS-LM: Wechsler memory scale-logical memory; ADL: Activities of daily living; CONSORT: Consolidated standards of reporting trials; MMSE: Mini-mental state examination; DSC: Digit symbol-coding; LVFT: Letter verbal fluency test; CVFT: Category verbal fluency test; SCWT: Stroop color and word test; ITT: Intention-to-treat.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Conception of the idea for the study: TS and HS. Development of the protocol and organization: TS, HS, HM, TD, and DY. Acquisition of participants, study management, and statistical analysis: HS, HM, TD, DY, KT, YA, KU, SL, and HP. All authors contributed to the interpretation of the data and drafting the article and provided final approval of the version to be published. All authors read and approved the final manuscript.

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References

1. Ganguli M, Dodge HH, Shen C, DeKosky ST: **Mild cognitive impairment, amnestic type: an epidemiologic study.** *Neurology* 2004, **63**(1):115–121.
2. Lopez OL, Jagust WJ, DeKosky ST, Becker JT, Fitzpatrick A, Dulberg C, Breitner J, Lyketsos C, Jones B, Kawas C, *et al*: **Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1.** *Arch Neurol* 2003, **60**(10):1385–1389.
3. Ritchie K, Artero S, Touchon J: **Classification criteria for mild cognitive impairment: a population-based validation study.** *Neurology* 2001, **56**(1):37–42.
4. Di Carlo A, Baldereschi M, Amaducci L, Maggi S, Grigoletto F, Scarlato G, Inzitari D: **Cognitive impairment without dementia in older people: prevalence, vascular risk factors, impact on disability. The Italian Longitudinal Study on Aging.** *J Am Geriatr Soc* 2000, **48**(7):775–782.
5. Graham JE, Rockwood K, Beattie BL, Eastwood R, Gauthier S, Tuokko H, McDowell I: **Prevalence and severity of cognitive impairment with and without dementia in an elderly population.** *Lancet* 1997, **349**(9068):1793–1796.
6. Manly JJ, Bell-McGinty S, Tang MX, Schupf N, Stern Y, Mayeux R: **Implementing diagnostic criteria and estimating frequency of mild cognitive impairment in an urban community.** *Arch Neurol* 2005, **62**(11):1739–1746.
7. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B: **Current concepts in mild cognitive impairment.** *Arch Neurol* 2001, **58**(12):1985–1992.
8. Palmer K, Wang HX, Backman L, Winblad B, Fratiglioni L: **Differential evolution of cognitive impairment in nondemented older persons: results from the Kungsholmen Project.** *Am J Psychiatry* 2002, **159**(3):436–442.
9. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, *et al*: **Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment.** *J Intern Med* 2004, **256**(3):240–246.
10. Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, Wetterholm AL, Haglund A, Zhang R, Schindler R: **3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy.** *Dement Geriatr Cogn Disord* 2006, **21**(5–6):353–363.
11. Amieva H, Letenneur L, Dartigues JF, Rouch-Leroyer I, Sourgen C, D'Alchee-Biree F, Dib M, Barberger-Gateau P, Orgogozo JM, Fabrigoule C: **Annual rate and predictors of conversion to dementia in subjects presenting mild cognitive impairment criteria defined according to a population-based study.** *Dement Geriatr Cogn Disord* 2004, **18**(1):87–93.
12. Tabert MH, Manly JJ, Liu X, Pelton GH, Rosenblum S, Jacobs M, Zamora D, Goodkind M, Bell K, Stern Y, *et al*: **Neuropsychological prediction of conversion to Alzheimer disease in patients with mild cognitive impairment.** *Arch Gen Psychiatry* 2006, **63**(8):916–924.
13. Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M: **Cognitive tests that best discriminate between presymptomatic AD and those who remain nondemented.** *Neurology* 2000, **55**(12):1847–1853.
14. Visser PJ, Verhey FR, Hofman PA, Scheltens P, Jolles J: **Medial temporal lobe atrophy predicts Alzheimer's disease in patients with minor cognitive impairment.** *J Neurol Neurosurg Psychiatry* 2002, **72**(4):491–497.
15. Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W: **Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older.** *Ann Intern Med* 2006, **144**(2):73–81.
16. Baker LD, Frank LL, Foster-Schubert K, Green PS, Wilkinson CW, McTiernan A, Plymate SR, Fishel MA, Watson GS, Cholerton BA, *et al*: **Effects of aerobic exercise on mild cognitive impairment: a controlled trial.** *Arch Neurol* 2010, **67**(1):71–79.
17. Hamer M, Chida Y: **Physical activity and risk of neurodegenerative disease: a systematic review of prospective evidence.** *Psychol Med* 2009, **39**(1):3–11.
18. Kramer AF, Hahn S, Cohen NJ, Banich MT, McAuley E, Harrison CR, Chason J, Vakil E, Bardell L, Boileau RA, *et al*: **Ageing, fitness and neurocognitive function.** *Nature* 1999, **400**(6743):418–419.
19. Lautenschlager NT, Cox KL, Flicker L, Foster JK, Van Bockxmeer FM, Xiao J, Greenop KR, Almeida OP: **Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial.** *JAMA* 2008, **300**(9):1027–1037.
20. Masley SC, Weaver W, Peri G, Phillips SE: **Efficacy of lifestyle changes in modifying practical markers of wellness and aging.** *Altern Ther Health Med* 2008, **14**(2):24–29.
21. Okumiya K, Matsubayashi K, Wada T, Kimura S, Doi Y, Ozawa T: **Effects of exercise on neurobehavioral function in community-dwelling older people more than 75 years of age.** *J Am Geriatr Soc* 1996, **44**(5):569–572.
22. Scherder EJ, Van Paasschen J, Deijen JB, Van Der Knokke S, Orlebeke JF, Burgers I, Devriese PP, Swaab DF, Sergeant JA: **Physical activity and executive functions in the elderly with mild cognitive impairment.** *Aging Ment Health* 2005, **9**(3):272–280.
23. van Uffelen JG, Chinapaw MJ, van Mechelen W, Hopman-Rock M: **Walking or vitamin B for cognition in older adults with mild cognitive impairment? A randomised controlled trial.** *Br J Sports Med* 2008, **42**(5):344–351.
24. Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F: **Physical activity, including walking, and cognitive function in older women.** *JAMA* 2004, **292**(12):1454–1461.
25. Yaffe K, Barnes D, Nevitt M, Lui LY, Covinsky K: **A prospective study of physical activity and cognitive decline in elderly women: women who walk.** *Arch Intern Med* 2001, **161**(14):1703–1708.
26. Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L: **Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment.** *Cochrane Database Syst Rev* 2008, (3):CD005381.
27. van Uffelen JG, Chin APMJ, Hopman-Rock M, van Mechelen W: **The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review.** *Clin J Sport Med* 2008, **18**(6):486–500.
28. Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, Browndyke JN, Sherwood A: **Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials.** *Psychosom Med* 2010, **72**(3):239–252.
29. Colcombe S, Kramer AF: **Fitness effects on the cognitive function of older adults: a meta-analytic study.** *Psychol Sci* 2003, **14**(2):125–130.
30. Morris JC: **The Clinical Dementia Rating (CDR): current version and scoring rules.** *Neurology* 1993, **43**(11):2412–2414.
31. Petersen RC: **Mild cognitive impairment as a diagnostic entity.** *J Intern Med* 2004, **256**(3):183–194.
32. Wechsler D, Stone C: *Wechsler Memory Scale manual*. New York: Psychological Corp; 1973.
33. Aisen PS, Petersen RC, Donohue MC, Gamst A, Raman R, Thomas RG, Walter S, Trojanowski JQ, Shaw LM, Beckett LA, *et al*: **Clinical Core of the Alzheimer's Disease Neuroimaging Initiative: progress and plans.** *Alzheimers Dement* 2010, **6**(3):239–246.
34. Schulz KF, Altman DG, Moher D: **CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.** *BMJ* 2010, **340**:c332.
35. Folstein MF, Folstein SE, McHugh PR: **"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician.** *J Psychiatr Res* 1975, **12**(3):189–198.
36. Wechsler D: *Wechsler Adult Intelligence Scale—III*. San Antonio: The Psychological Corporation; 1997.
37. Nutter-Upham KE, Saykin AJ, Rabin LA, Roth RM, Wishart HA, Pare N, Flashman LA: **Verbal fluency performance in amnestic MCI and older adults with cognitive complaints.** *Arch Clin Neuropsychol* 2008, **23**(3):229–241.
38. Lonie JA, Herrmann LL, Tierney KM, Donaghey C, O'Carroll R, Lee A, Ebmeier KP: **Lexical and semantic fluency discrepancy scores in aMCI and early Alzheimer's disease.** *J Neuropsychol* 2009, 3(Pt 1):79–92.
39. Stroop JR: **Studies of interference in serial verbal reactions.** *J Exp Psychol* 1935, **18**:643–662.
40. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E: **Mild cognitive impairment: clinical characterization and outcome.** *Arch Neurol* 1999, **56**(3):303–308.
41. Woollacott M, Shumway-Cook A: **Attention and the control of posture and gait: a review of an emerging area of research.** *Gait Posture* 2002, **16**(1):1–14.
42. Chenery HJ, Murdoch BE, Ingram JCL: **An investigation of confrontation naming performance in Alzheimer's dementia as a function of disease severity.** *Aphasiology* 1996, **10**:423–441.
43. Nicholas M, Obler LK, Au R, Albert ML: **On the nature of naming errors in aging and dementia: a study of semantic relatedness.** *Brain Lang* 1996, **54**:184–195.
44. Herrmann MJ, Langer JB, Jacob C, Ehlis AC, Fallgatter AJ: **Reduced prefrontal oxygenation in Alzheimer disease during verbal fluency tasks.** *Am J Geriatr Psychiatry* 2008, **16**(2):125–135.
45. Gao S, Hendrie HC, Hall KS, Hui S: **The relationships between age, sex, and the incidence of dementia and Alzheimer disease: a meta-analysis.** *Arch Gen Psychiatry* 1998, **55**(9):809–815.

46. Hsiung GY, Sadovnick AD, Feldman H: **Apolipoprotein E epsilon4 genotype as a risk factor for cognitive decline and dementia: data from the Canadian Study of Health and Aging.** *CMAJ* 2004, 171(8):863–867.
47. Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, Tylavsky FA, Newman AB: **The metabolic syndrome, inflammation, and risk of cognitive decline.** *JAMA* 2004, 292(18):2237–2242.

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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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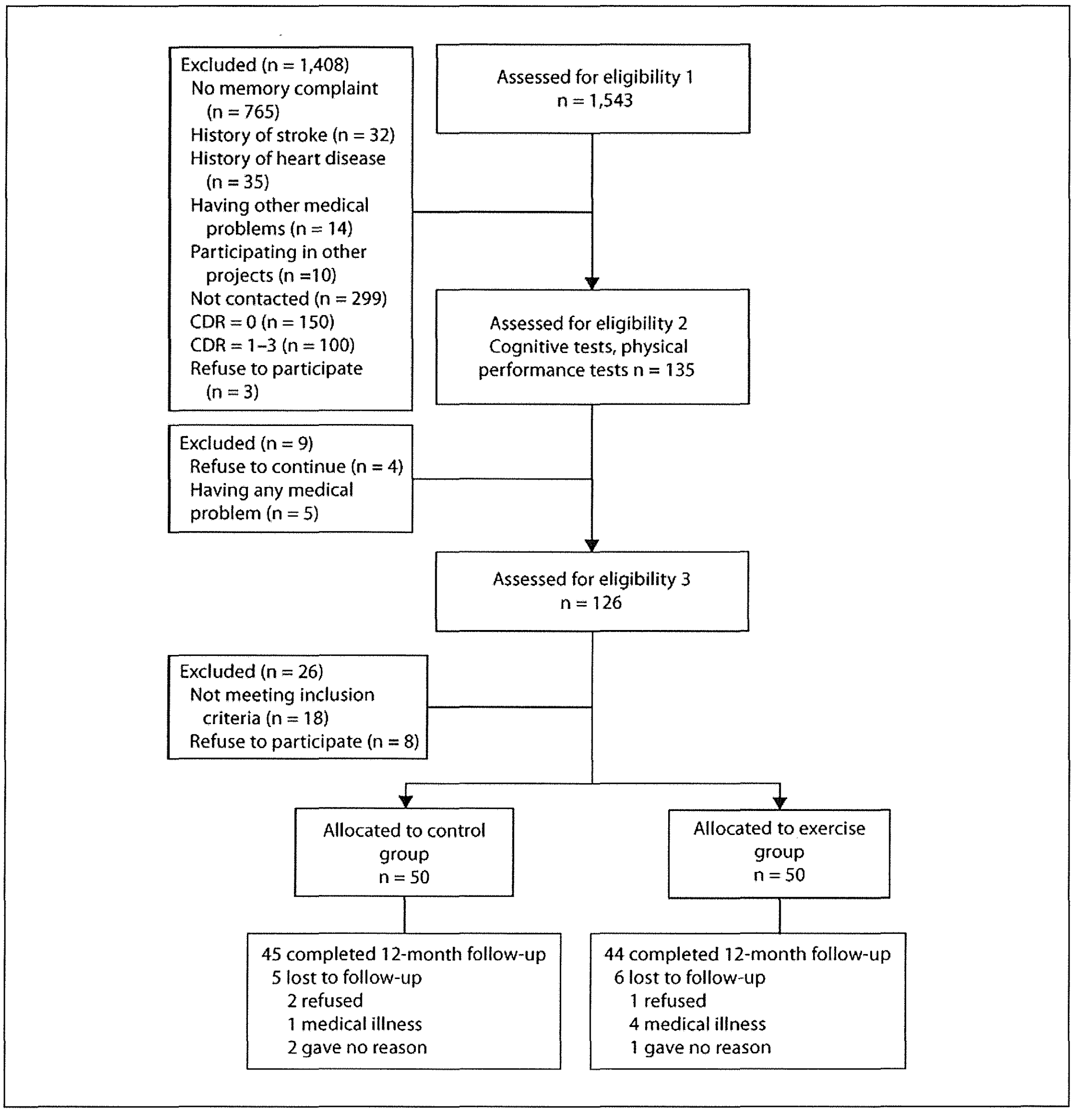

Fig. 1. Subject flow diagram from the initial contact through to study completion.

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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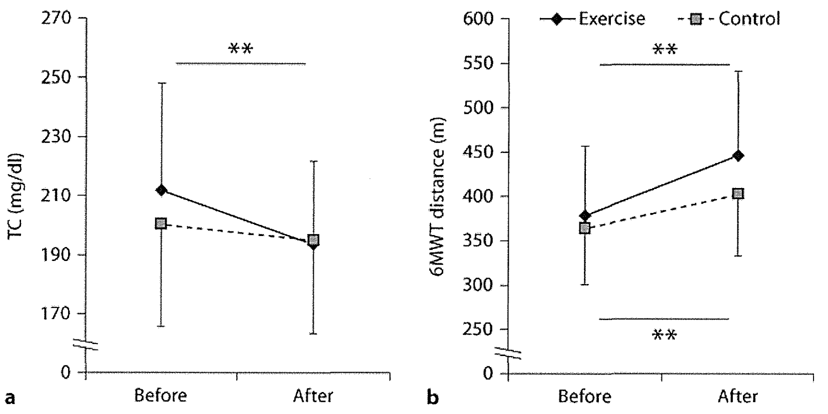

Fig. 2. The average values of TC (**a**) and 6MWT distance (**b**) in the exercise and control groups before and after the intervention. ** Significant difference between before and after the training within the group (Bonferroni post hoc test, $p < 0.005$).

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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References

1 Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B: Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985–1992.
2 Luck T, Luppa M, Briel S, Riedel-Heller SG: Incidence of mild cognitive impairment: a systematic review. Dement Geriatr Cogn Disord 2010;29:164–175.
3 Petersen RC: Mild cognitive impairment as a diagnostic entity. J Intern Med 2004;256:183–194.
4 Morris JC, Storandt M, Miller JP, McKeel DW, Price JL, Rubin EH, Berg L: Mild cognitive impairment represents early-stage Alzheimer disease. Arch Neurol 2001;58:397–405.
5 Angevaren M, Aufdemkampe G, Verhaar HJ, Aleman A, Vanhees L: Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. Cochrane Database Syst Rev 2008:CD005381.
6 van Uffelen JG, Chin APMJ, Hopman-Rock M, van Mechelen W: The effects of exercise on cognition in older adults with and without cognitive decline: a systematic review. Clin J Sport Med 2008;18:486–500.
7 Smith PJ, Blumenthal JA, Hoffman BM, Cooper H, Strauman TA, Welsh-Bohmer K, Browndyke JN, Sherwood A: Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. Psychosom Med 2010;72:239–252.
8 Voss MW, Prakash RS, Erickson KI, Basak C, Chaddock L, Kim JS, Alves H, Heo S, Szabo AN, White SM, Wojcicki TR, Mailey EL, Gothe N, Olson EA, McAuley E, Kramer AF: Plasticity of brain networks in a randomized intervention trial of exercise training in older adults. Front Aging Neurosci 2010;2:32.
9 Erickson KI, Voss MW, Prakash RS, Basak C, Szabo A, Chaddock L, Kim JS, Heo S, Alves H, White SM, Wojcicki TR, Mailey E, Vieira VJ, Martin SA, Pence BD, Woods JA, McAuley E, Kramer AF: Exercise training increases size of hippocampus and improves memory. Proc Natl Acad Sci USA 2011;108:3017–3022.
10 Broderick DF, Schweitzer KJ, Wszolek ZK: Vascular risk factors and dementia: how to move forward? Neurology 2009;73:1934–1935.
11 de la Torre JC: Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. Lancet Neurol 2004;3:184–190.
12 Li J, Zhang M, Xu ZQ, Gao CY, Fang CQ, Deng J, Yan JC, Wang YJ, Zhou HD: Vascular risk aggravates the progression of Alzheimer's disease in a Chinese cohort. J Alzheimers Dis 2010;20:491–500.
13 Solomon A, Kivipelto M, Wolozin B, Zhou J, Whitmer RA: Midlife serum cholesterol and increased risk of Alzheimer's and vascular dementia three decades later. Dement Geriatr Cogn Disord 2009;28:75–80.
14 Panza F, D'Introno A, Colacicco AM, Capurso C, Parigi AD, Capurso SA, Caselli RJ, Pilotto A, Scafato E, Capurso A, Solfrizzi V: Cognitive frailty: predementia syndrome and vascular risk factors. Neurobiol Aging 2006;27:933–940.
15 Solfrizzi V, Panza F, Colacicco AM, D'Introno A, Capurso C, Torres F, Grigoletto F, Maggi S, Del Parigi A, Reiman EM, Caselli RJ, Scafato E, Farchi G, Capurso A: Vascular risk factors, incidence of MCI, and rates of progression to dementia. Neurology 2004;63:1882–1891.
16 Li J, Wang YJ, Zhang M, Xu ZQ, Gao CY, Fang CQ, Yan JC, Zhou HD: Vascular risk factors promote conversion from mild cognitive impairment to Alzheimer disease. Neurology 2011;76:1485–1491.
17 Larson EB, Wang L, Bowen JD, McCormick WC, Teri L, Crane P, Kukull W: Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 2006;144:73–81.
18 Kemoun G, Thibaud M, Roumagne N, Carette P, Albinet C, Toussaint L, Paccalin M, Dugue B: Effects of a physical training programme on cognitive function and walking efficiency in elderly persons with dementia. Dement Geriatr Cogn Disord 2010;29:109–114.
19 De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger Cats V, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D: European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J 2003;24:1601–1610.

20 Tsuzuku S, Kajioka T, Endo H, Abbott RD, Curb JD, Yano K: Favorable effects of non-instrumental resistance training on fat distribution and metabolic profiles in healthy elderly people. Eur J Appl Physiol 2007;99:549–555.
21 Williams AD, Almond J, Ahuja KD, Beard DC, Robertson IK, Ball MJ: Cardiovascular and metabolic effects of community based resistance training in an older population. J Sci Med Sport 2011;14: 331–337.
22 Martins RA, Verissimo MT, Coelho e Silva MJ, Cumming SP, Teixeira AM: Effects of aerobic and strength-based training on metabolic health indicators in older adults. Lipids Health Dis 2010;9:76.
23 Carvalho J, Marques E, Ascensao A, Magalhaes J, Marques F, Mota J: Multicomponent exercise program improves blood lipid profile and antioxidant capacity in older women. Arch Gerontol Geriatr 2010;51:1–5.
24 Morris JC: The Clinical Dementia Rating (CDR): current version and scoring rules. Neurology 1993; 43:2412–2414.
25 Schulz KF, Altman DG, Moher D, CONSORT Group: CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c332.
26 Carroll S, Tsakirides C, Hobkirk J, Moxon JW, Dudfield M, Ingle L: Differential improvements in lipid profiles and framingham recurrent risk score in patients with and without diabetes mellitus undergoing long-term cardiac rehabilitation. Arch Phys Med Rehabil 2011;92:1382–1387.
27 Thompson G: Which lipid fraction is the target and how often should this be monitored? Heart 2010; 96:413–414.
28 Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM: Two-, six-, and 12-minute walking tests in respiratory disease. Br Med J (Clin Res Ed) 1982;284:1607–1608.
29 Nagai K, Yamada M, Tanaka B, Uemura K, Mori S, Aoyama T, Ichihashi N, Tsuboyama T: Effects of balance training on muscle coactivation during postural control in older adults: a randomized controlled trial. J Gerontol A Biol Sci Med Sci 2012;67:882–889.
30 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106: 3143–3421.
31 Kelley GA, Kelley KS, Tran ZV: Exercise, lipids, and lipoproteins in older adults: a meta-analysis. Prev Cardiol 2005;8:206–214.
32 Swardfager W, Herrmann N, Cornish S, Mazereeuw G, Marzolini S, Sham L, Lanctot KL: Exercise intervention and inflammatory markers in coronary artery disease: a meta-analysis. Am Heart J 2012;163:666–676.e1–e3.
33 Kelley GA, Kelley KS: Effects of aerobic exercise on lipids and lipoproteins in adults with type 2 diabetes: a meta-analysis of randomized-controlled trials. Public Health 2007;121:643–655.
34 Kelley GA, Kelley KS: Aerobic exercise and lipids and lipoproteins in men: a meta-analysis of randomized controlled trials. J Mens Health Gend 2006;3:61–70.
35 Pescatello LS, Murphy D, Costanzo D: Low-intensity physical activity benefits blood lipids and lipoproteins in older adults living at home. Age Ageing 2000;29:433–439.
36 Durstine JL, Grandjean PW, Davis PG, Ferguson MA, Alderson NL, DuBose KD: Blood lipid and lipoprotein adaptations to exercise: a quantitative analysis. Sports Med 2001;31:1033–1062.
37 Yaffe K, Barrett-Connor E, Lin F, Grady D: Serum lipoprotein levels, statin use, and cognitive function in older women. Arch Neurol 2002;59:378–384.
38 Reitz C, Tang MX, Luchsinger J, Mayeux R: Relation of plasma lipids to Alzheimer disease and vascular dementia. Arch Neurol 2004;61:705–714.
39 Frisardi V, Solfrizzi V, Seripa D, Capurso C, Santamato A, Sancarlo D, Vendemiale G, Pilotto A, Panza F: Metabolic-cognitive syndrome: a cross-talk between metabolic syndrome and Alzheimer's disease. Ageing Res Rev 2010;9:399–417.
40 Refolo LM, Malester B, LaFrancois J, Bryant-Thomas T, Wang R, Tint GS, Sambamurti K, Duff K, Pappolla MA: Hypercholesterolemia accelerates the Alzheimer's amyloid pathology in a transgenic mouse model. Neurobiol Dis 2000;7:321–331.

Dement Geriatr Cogn Disord Extra 2012;2:445–455
DOI: 10.1159/000343486
Published online: October 25, 2012

41 Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J, American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics – 2011 update: a report from the American Heart Association. Circulation 2011;123:e18–e209.
42 Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R: Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Lancet 2007;370:1829–1839.
43 Consensus conference. Lowering blood cholesterol to prevent heart disease. JAMA 1985;253:2080–2086.
44 Nigam PK: Serum lipid profile: fasting or non-fasting? Indian J Clin Biochem 2011;26:96–97.
45 Yu-Poth S, Zhao G, Etherton T, Naglak M, Jonnalagadda S, Kris-Etherton PM: Effects of the National Cholesterol Education Program's Step I and Step II dietary intervention programs on cardiovascular disease risk factors: a meta-analysis. Am J Clin Nutr 1999;69:632–646.