

Poor physical fitness is independently associated with mild cognitive impairment in elderly Koreans

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ABSTRACT: The purpose of this study was to investigate the association between physical fitness and mild cognitive impairment (MCI) in elderly Koreans. This was a cross-sectional study that involved 134 men and 299 women aged 65 to 88 years. Six senior fitness tests were used as independent variables: 30 s chair stand for lower body strength, arm curl for upper body strength, chair-sit-and-reach for lower body flexibility, back scratch for upper body flexibility, 8-ft up-and-go for agility/dynamic balance, and 2-min walk for aerobic endurance. Global cognitive function was assessed using the Korean version of the Mini-Mental State Examination (MMSE). Potential covariates such as age, education levels, blood lipids, and insulin resistance (IR) markers were also assessed. Compared to individuals without MMSE-based MCI, individuals with MMSE-based MCI had poor physical fitness based on the senior fitness test (SFT). There were significant positive trends observed for education level ($p=0.001$) and MMSE score ($p<0.001$) across incremental levels of physical fitness in this study population. Individuals with moderate ($OR=0.341$, $p=0.006$) and high ($OR=0.271$, $p=0.007$) physical fitness based on a composite score of the SFT measures were less likely to have MMSE-based MCI than individuals with low physical fitness (referent, $OR=1$). The strength of the association between moderate ($OR=0.377$, $p=0.038$) or high ($OR=0.282$, $p=0.050$) physical fitness and MMSE-based MCI was somewhat attenuated but remained statistically significant even after adjustment for the measured compounding factors. We found that poor physical fitness was independently associated with MMSE-based MCI in elderly Koreans.

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INTRODUCTION

Mild cognitive impairment (MCI) is characterized as the transitional state between normal aging and dementia and is exemplified by abnormal memory loss for the age and educational level of the individual who otherwise exhibits no cognitive impairment [1]. Reports for the past decade on populations aged over 65 indicate that MCI affects between 1.7 and 22.5% of community-dwelling elders in Western countries [1] and between 14.9 and 24.1% of counterparts in Asian countries [2]. In Korea, a recent nationwide survey showed that the estimated prevalence of dementia and MCI was 8.1% and 24.1%, respectively. The same survey predicted that this prevalence would double every 20 years until 2050 in conjunction with the extended lifespan and rapidly growing elderly population in Korea [2].

Although anticholinesterase therapies such as donepezil, galantamine and rivastigmine can treat the symptoms of MCI and dementia [3], they do not significantly slow disease progression [4] and may have severe side effects [5]. These side effects, coupled with the projected dramatic increase in the number of patients with MCI and dementia in the coming decades, has created an urgent need for effective and inexpensive interventions. Physical activity and/or

fitness are emerging as promising lifestyle approaches that are evidence-based and relatively free of side effects, and can be used as an alternative or adjunct to those anticholinesterase therapies.

Physical activity and fitness are well-established lifestyle factors linked to maintained cognition in aging, and have been used as a basis for interventions to prevent cognitive decline and MCI and/or to delay dementia. In healthy older people, a high level of physical activity is associated with a high level of cognitive performance, including speed of information processing, attention [6], and executive functions (EF) [7]. A high level of physical activity may also reduce the risk for dementia in later life [8]. Since participating in physical activity improves various physical fitness domains including muscle strength, gait speed, functional mobility and balance [9], it is not surprising to find a positive relationship between physical fitness and cognitive function in healthy older people. [10]. In fact, longitudinal studies have shown that a decline in physical fitness preceded the onset of cognitive decline with normal aging [11-13]. In older populations, those who had better mobility [14], balance [15], strength [16] and aerobic fitness [17] had better cognitive

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functions. Consequently, a high level of physical fitness in domains such as balance [15] and strength [16] may also decrease the risk for dementia in later life [11]. Together, the previous findings suggest that physical activity and/or fitness may have an important role as a non-pharmacologic means to combat MCI and perhaps dementia in older people.

A growing body of evidence shows that insulin resistance (IR) increases the risk for cognitive decline and neurodegenerative diseases such as Alzheimer's disease (AD). IR is known to cause cognitive dysfunction and increase the risk of developing dementia due to reduced basal and insulin-induced activation of cerebral IRs, higher cerebral neuritic plaque loads, lower hippocampal volume and cognitive performance, inhibited brain glucose metabolism, and reduced memory recall. Along with MCI, on the other hand, IR is also inversely associated with physical activity and fitness. For example, the Insulin Resistance Atherosclerosis study showed that physical activity alters insulin sensitivity independently of changes in weight and body composition in adults [18]. Moderate to high levels of physical fitness may play a protective role in diabetes since individuals with low fitness are more likely to be insulin resistant [19]. Therefore, it seems possible that IR would modulate the association between physical fitness and AD in elderly adults. However, previous studies reporting the inverse association between physical fitness and MCI did not consider IR as a potential compounding factor [12-16]. Thus, it remains of interest to study whether the association between physical fitness and MCI is independent of IR in elderly adults. Further, gaining insight into this relationship would contribute to the development of new or improved options for the prevention and/or treatment of clinical conditions associated with cognitive declines and MCI. The goal of the current study was to use a cross-sectional research design to examine whether the association between physical fitness (strength, balance, mobility, and aerobic fitness) and MCI is independent of IR in elderly Koreans.

MATERIALS AND METHODS

Subjects. In a cross-sectional study, we initially recruited 500 study participants (165 men and 335 women aged ≥ 65 years and fluent in Korean) who participated in the Community-based Dementia Pre-screening Project conducted at 5 community healthcare centres located in the north-western Gyeonggi Province of South Korea between March 2013 and July 2014. All the participants consisted of community-dwelling elderly persons who represented the typical elderly population residing in a metropolitan city in South Korea.

Data were collected during three separate visits. At the first visit, demographic characteristics were gathered from 151 men (3 missing) and 335 women (11 missing), and general health status was assessed based on standardized self-administered questionnaires and interviews conducted by nurses specializing in geriatrics. After the first visit, a detailed medical history, including these variables, was obtained from the participants or their informants. Cardiovascular disease was defined as present if the participant had a history

of coronary artery disease, myocardial infarction, atrial fibrillation and other arrhythmias, heart valve disease, or congestive heart failure. Cerebrovascular disease was defined as present if the participant had a history of haemorrhagic or ischaemic stroke or transient ischaemic attacks. Consequently, 16 men and 10 women were excluded due to a known history of alcoholism ($n=8$) or neurological diseases ($n=2$) or head trauma or stroke ($n=3$) or any other physical illness affecting cognitive function ($n=13$). One week after the first visit, participants attended a second session at which neuropsychiatric specialists conducted a comprehensive neuropsychological test to assess global cognitive function. Within 2 hours of completing the cognitive function assessment, participants attended a third session at which exercise specialists conducted a senior fitness test to assess six domains of functional fitness [20]. Additionally, 12 men and 15 women did not show up or refused to complete either the Mini-Mental State Examination ($n=11$) or senior fitness test ($n=16$). Consequently, 433 (134 men and 299 women) out of 500 initial participants completed all the tests and were included in the final data analyses. The third visit involved an overnight fast, after which laboratory tests were performed to evaluate the general physical and metabolic health of the remaining 433 participants, including resting blood pressures, blood lipids, fasting glucose and insulin, and homeostasis model assessment of insulin resistance (HOMA-IR). Common geriatric disorders were also identified. The Sungkyunkwan University Institutional Review Board, in accordance with the Declaration of Helsinki of the World Medical Association, approved the study protocol. All participants provided written informed consent to participate in the study.

Cognitive function

Global cognitive function was assessed by trained nurses using the Korean version of the Mini-Mental State Examination (MMSE). The MMSE measures the cognitive level of elders in terms of orientation (10 points), short-term memory and recall (6 points), attention (5 points), phonic fluency (2 points), following verbal commands (4 points), judgment (2 points) and copying a double pentagon (1 point) [21]. Scores of MMSE ranged between 0 and 30, where higher scores indicate better cognition level. The most widely accepted and frequently used cut-off score for the MMSE is 23, with scores of 23 or lower indicating the presence of cognitive impairment. The Korean version of MMSE is the same as the MMSE described above, except instead of phonic fluency (2 points) they are rated on naming (2 points). The MMSE was validated in Korean elderly [22]. Those who had an age- and education-adjusted MMSE score of 23 or lower were classified as CASE, and those who had an age- and education-adjusted MMSE score of 24 or higher were classified as CON [22].

Senior fitness test

The various components of physical fitness can be assessed accurately in the laboratory and, in many cases, in the field by using a composite of performance tests. The Senior Fitness Test (SFT) as-

sesses the physiological capacity for carrying out normal daily activities independently and safely without the appearance of fatigue. Participants performed 10 minutes of warm-up as instructed by a trained fitness instructor. The test was then completed in the designed order: (1) Chair stand up for 30 seconds was to assess lower body strength, (2) Arm curl was to assess upper body strength, (3) Back scratch was to assess upper body (shoulder) flexibility, (4) Chair-sit-and-reach was to assess the flexibility of the lower extremities, (5) Eight-foot-up-and-go was to assess agility/dynamic balance as an index of basic mobility skills, and (6) The 6-minute walk test was to assess aerobic capacity. Detailed descriptions of procedures are available elsewhere [23] and test validity was published [20].

In order to study the role of physical fitness as a non-pharmacologic means for preventing MCI, a Z score was computed for each domain of the SFT as the number of SD units from the sample mean after normalization of the variables. A composite score was computed as a sum of Z-scores for the 6 SFT domains, including upper and lower body muscle strength, lower and upper body flexibility, agility/dynamic balance, and aerobic capacity, by sex. The participants were classified in the low- (lowest 25%), moderate- (middle 50%) or high-fitness (highest 25%) group based on the composite physical fitness score.

Covariates

Covariates such as age and level of education were assessed and included in the analyses. Education was defined as a categorical variable (high school education or less, vocational school or some college education, or college degree or higher). Measured body fatness, blood lipids, and IR markers such as glucose and insulin levels, and HOMA-IR were included as additional covariates.

Statistics

Characteristics of participants with and without MMSE-based MCI were compared using χ^2 tests for categorical variables and an independent t-test for continuous variable. Characteristics of participants according to incremental physical fitness levels were compared using a Kruskal–Wallis one-way analysis of variance for both categorical and continuous variables. Odds of MMSE-based MCI in relation to a composite score of physical fitness measures were estimated using logistic regression after adjustment for age and sex and level of education. Further analyses were conducted to adjust for additional potential confounders, such as body fatness parameters, blood lipids, and IR markers such as glucose and insulin levels and HOMA-IR. All analyses were performed at $p=0.05$ using SPSS statistical software, version 19 (SPSS, Inc.).

RESULTS

Table 1 presents demographic and physical characteristics of those who had age- and education-adjusted MMSE scores of 23 or lower (CASE) and those who had age- and education-adjusted MMSE scores of 24 or higher (CON). There were no significant differences

in sex, age, education level, BMI, and percent body fat between the CASE and CON groups. There were significant differences in several domains of physical fitness including upper body flexibility, agility/dynamic balance, and upper and lower body muscle strength between the CASE and CON groups. There were no significant dif-

TABLE 1. Characteristics of participants with and without mild cognitive impairment (MCI) in this study population.

	CON	CASE	p-value
Sex (M/F)	107/249	23/64	0.730
Age (yrs)	71.9±5.3	71.4±5.2	0.598
Education (yrs)	8.2±3.8	7.9±3.9	0.875
BMI (kg · m ⁻²)	24.3±2.9	24.6±2.6	0.219
Body fat (%)	30.5±6.8	30.6±7.0	0.772
Arm curl (no. of reps)	20.6±5.6	19.5±3.9	0.077
Chair stand (no. of stands)	17.3±4.9	16.1±4.2	0.084
2-min walk (m)	90.1±29.2	86.5±30.1	0.530
Back scratch (cm)	-8.7±12.9	-14.6±15.4	0.033
Chair-sit-and-stretch (cm)	8.4±13.7	5.2±12.8	0.072
8-ft up and go (s)	5.3±1.6	5.7±1.6	0.029
MMSE score	26.9±2.1	22.0±2.9	<0.001

Note: CASE: those who had age- and education-adjusted MMSE scores of 23 or lower. CON: those who had age- and education-adjusted MMSE scores of 24 or higher [20].

TABLE 2. Demographics, body fatness, global cognitive function, and metabolic profiles according to physical fitness levels.

	Low fit (n=108)	Moderate fit (n=217)	High fit (n=108)	P value for linear trend
Sex (M/F)	31/77	65/152	38/70	
Age (yrs)	74.8±6.4	71.2±5.6	69.7±4.8	<0.001
Education (yrs)	7.0±4.2	8.0±3.5	9.5±3.7	0.001
BMI (kg · m ⁻²)	24.4±3.3	24.6±2.7	23.7±2.7	0.148
Body fat (%)	31.4±7.2	30.9±6.9	29.0±5.9	0.109
MMSE score	24.1±3.6	26.3±2.6	28.4±2.2	<0.001
SBP (mmHg)	126.9±15.5	125.5±14.0	124.2±11.6	0.548
DBP (mmHg)	70.6±10.0	71.3±10.8	72.8±8.0	0.456
TG (mg · dl ⁻¹)	119.3±73.6	111.7±75.0	116.8±111.7	0.488
TC (mg · dl ⁻¹)	141.6±34.5	142.7±37.1	141.0±39.2	0.949
LDLC (mg · dl ⁻¹)	78.2±26.6	78.8±28.9	72.8±27.7	0.362
HDLC (mg · dl ⁻¹)	39.4±11.3	41.6±10.6	43.5±18.6	0.230
FBG (mg · dl ⁻¹)	118.7±27.9	115.2±18.4	114.4±23.7	0.506
Insulin (μU · ml ⁻¹)	7.8±8.5	7.9±5.6	6.6±4.0	0.210
HOMA-IR	2.37±2.79	2.33±1.90	1.90±1.28	0.305

Note: BMI: body mass index; MMSE: mini-mental state examination; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides; TC: total cholesterol; LDLC: low-density lipoprotein cholesterol; HDLC: high-density lipoprotein cholesterol; FBG: fasting blood glucose; HOMA-IR: homeostasis model assessment-estimated insulin resistance. Log₁₀ transformed TG, insulin and HOMA-IR were used for statistical analyses.

TABLE 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for mild cognitive impairment according to physical fitness levels.

	Low fit (N=108)	Moderate fit (N=217)	P values	High fit (N=108)	P values
Unadjusted	1.0 (referent)	0.425 (0.207~0.872)	0.020	0.337 (0.135~0.842)	0.020
Adjusted ^a	1.0 (referent)	0.343 (0.159~0.738)	0.006	0.253 (0.094~0.684)	0.007
Adjusted ^b	1.0 (referent)	0.341 (0.158~0.736)	0.006	0.247 (0.090~0.677)	0.007
Adjusted ^c	1.0 (referent)	0.377 (0.150~0.946)	0.038	0.282 (0.077~0.133)	0.050

Note:

Adjusted^a for age, sex and education.

Adjusted^b for age, sex, education, body mass index and percent body fat.

Adjusted^c for age, sex, education, body mass index, percent body fat, resting blood pressures, blood lipids, glucose, insulin and HOMA-IR

ferences in resting blood pressures, blood lipids and glucose, insulin, and HOMA-IR between the CASE and CON groups.

Table 2 represents characteristics of study participants according to physical fitness levels. A significant inverse trend ($p < 0.001$) was observed for age and a significant positive trend ($p < 0.001$) was observed for education across incremental physical fitness levels (lowest tertile to highest tertile), with no such linear trends for body mass index and percent body fat. As expected, significant positive trends were observed for 6 domains of physical fitness (i.e., upper and lower body muscle strength, upper and lower body flexibility, agility/dynamic balance, and aerobic capacity) across incremental physical fitness levels. In addition, a significant positive trend was observed for average MMSE score ($p < 0.001$) across incremental physical fitness levels. On the other hand, we found no significant linear trend for any of the measured metabolic risk factors across incremental physical fitness levels.

Table 3 represents odds ratios and 95% confidence intervals for mild cognitive impairment (MCI) according to physical fitness levels. Using age, sex, and education levels as covariates, individuals with moderate and high levels of physical fitness were less likely to have MMSE-based MCI than those who with low levels of physical fitness defined as low-fitness (referent, OR=1). The strength of the associations between incremental physical fitness levels and MMSE-based MCI was somewhat attenuated but remained statistically significant even when additionally adjusted for body fatness, resting blood pressures, blood lipids, and IR markers such as fasting glucose and insulin and HOMA-IR (OR=0.377 ($p=0.038$) and OR=0.282 ($p=0.050$) for moderate- and high-fitness, respectively).

DISCUSSION

One common outcome of aging is cognitive decline, including a negative impact on memory, attention, and perception. These declines have been identified as major risks for age-associated disease such as dementia [24]. IR, which is characterized by reduced insulin sensitivity and efficacy, is positively associated with normal aging and contributes to the development of MCI and dementia. On the other hand, physical activity and/or fitness are correlated with greater maintenance of cognitive ability, particularly executive control functions, with age [25]. In this study, we investigated whether the

association of physical fitness and MMSE-based cognitive impairment is independent of body fatness and IR markers in elderly Koreans.

After adjusting for age, sex and education level, the prevalence of MMSE-based MCI (as defined by an MMSE score of 23 or lower) was 21% in this study population, which is comparable to those previously reported [2]. Those who had MMSE-based MCI had significantly lower levels of physical fitness, especially upper body flexibility and agility/dynamic balance, compared to those without MMSE-based MCI. Further analyses showed that a composite score of physical fitness, calculated as a sum of 6 physical fitness measures, was inversely associated with age and positively with education level and MMSE scores. Finally, logistic regression analyses showed that the association between the composite score of physical fitness tests and MMSE-based MCI was somewhat attenuated but remained statistically significant even after being adjusted for compounding factors such as age, sex, education levels, body fatness, resting blood pressures, blood lipids and IR markers. This suggests that poor physical fitness is significantly associated with MMSE-based MCI independently of the measured compounding factors in this study population.

Our results are consistent with previous cross-sectional studies reporting a significant association between poor physical fitness and poor cognitive function in older adults [26-29]. Huh et al. [14] showed that executive function based on the lexical fluency test was associated with performance-oriented mobility assessment scores and isokinetic muscle strength in a population-based sample of 629 Korean adults aged 65 or older. In the EPIDOS cohort study consisting of 7421 community-dwelling older women (mean age 80.41 ± 0.04 years) living in five French cities, Annweiler et al. [16] found that compared to their counterparts, women with cognitive impairment had poor performance in dynamic balance and functional mobility, as assessed by the five-times-sit-to-stand test. Fitzpatrick et al. [27] found an association between cognitive function and physical fitness in 3035 healthy mobile participants of the Ginkgo Evaluation of Memory Study and reported that slow walking was significantly associated with cognitive impairment in healthy older adults. Similar to cross-sectional studies, prospective studies have also reported an association between poor physical fitness (including walking, balance, chair stand, and grip strength) [11] or neurologic gait

abnormalities [12] and the development of all-cause [11] or vascular dementia [12]. A gait that slowed over time was significantly associated with persistent cognitive impairment [13] as well as decline in several geriatric outcome measures including global health, falls and new difficulties with activities of daily living [30].

Although little is known about the links between physical fitness and cognitive function in older adults, both clinical and animal studies provided compelling evidence for the role of vascular adaptations including angiogenesis [31-32] as well as neurogenesis and synaptogenesis [31, 33]. In addition, growing evidence suggests that structural changes of the brain in older people are related to physical fitness, such as gait dysfunction [34-35], postural instability [36], and lack of cardiorespiratory fitness [37], suggesting that brain function is associated with physical fitness. For example, a previous multi-study analysis [38] demonstrated that older, fit adults had significantly greater activation in those cortical regions implicated in executive control (i.e., frontal, temporal, and parietal cortices) than a group of unfit adults. Other studies reported that lower brain volume in the prefrontal areas was associated with slower gait in high-functioning or cognitively normal older adults [39-40]. Neuroimaging studies have indicated that gait requires complex visuo-sensorimotor coordination, and is associated with activation of the medial frontoparietal region, including the primary sensory and motor areas, supplementary motor area, lateral premotor cortex, cingulate cortex, superior parietal lobule, precuneus, and the infratentorial region including the dorsal region [41-42]. Finally, Deary et al. [43] proposed the brain reserve hypothesis as another theoretical framework to explain the beneficial effect of physical fitness on cognitive function. This hypothesis is based on the ability to optimize or maximize performance through differential recruitment of brain networks, which

could reflect the use of alternative cognitive strategies. Mental and physical stimulation may increase such reserve during a person's whole life, resulting in improved cognitive function in old age and delayed clinical manifestations of MCI, dementia and AD. This hypothesis should be explored in future studies.

Considering the cross-sectional nature of the current study, however, additional research is necessary to determine the temporal relationship between poor physical performance and cognitive declines. In particular, physical training studies will be very important as they have the potential to identify and verify long-term beneficial effects of physical activity and fitness on the brain as well as overall general health in older adults.

CONCLUSIONS

In this study population, we found that poor physical fitness was significantly associated with MMSE-based MCI independently of compounding factors including demographics, body fatness parameters, and IR markers. This suggests that maintenance and/or promotion of physical fitness via regular physical activity should be an important component of a healthy lifestyle strategy to combat declines in cognitive functions as well as poor general health in elderly Koreans.

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REFERENCES

- Luck T, Luppia M, Briel S, Riedel-Heller SG. Incidence of mild cognitive impairment: a systematic review. *Dement Geriatr Cogn Disord*. 2010;29(2):164-75.
- Kim KW, Park JH, Kim MH, Kim MD, Kim BJ, Kim SK, Kim JL, Moon SW, Bae JN, Woo JI, Ryu SH, Yoon JC, Lee NJ, Lee DY, Lee DW, Lee SB, Lee JJ, Lee JY, Lee CU, Chang SM, Jhoo JH, Cho MJ. A nationwide survey on the prevalence of dementia and mild cognitive impairment in South Korea. *J Alzheimers Dis*. 2011;23(2):281-91.
- Birks J, Grimley Evans J, Iakovidou V, Tsolaki M. Rivastigmine for Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2009; (2):CD001191.
- Trinh NH, Hoblyn J, Mohanty S, Yaffe K. Efficacy of cholinesterase inhibitors in the treatment of neuropsychiatric symptoms and functional impairment in Alzheimer's disease: a meta-analysis. *JAMA*. 2003;289(2):210-6.
- Loy C, Schneider L. Galantamine for Alzheimer's disease and mild cognitive impairment. *Cochrane Database of Systematic Reviews*. 2006;1:CD001747.
- Angevaren M, Aufdemkampe G, Verhaar GHJ, Aleman A, Vanhees L. Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *Cochrane Database of Systematic Reviews*. 2008;3:Article ID CD005381.
- Kramer AF, Erickson KI. Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. *Trends Cogn Sci*. 2007;11(8):342-8.
- Lautenschlager NT, Cox K, Kurz AF. Physical activity and mild cognitive impairment and Alzheimer's disease. *Curr Neurol Neurosci Rep*. 2010;10(5):352-8.
- James BD, Boyle PA, Bennett DA, Buchman AS. Total daily activity measured with actigraphy and motor function in community-dwelling older persons with and without dementia. *Alzheimer Dis Assoc Disord*. 2011;26(3):238-45.
- Voelcker-Rehage C, Godde B, Staudinger UM. Physical and motor fitness are both related to cognition in old age. *Euro J Neurosci*. 2010;31(1):167-76.
- Wang L, Larson EB, Bowen JD, van Belle G. Performance-based physical function and future dementia in older people. *Arch Intern Med*. 2006;166(10):1115-20.
- Vergheze J, Lipton RB, Hall CB, Kuslansky G, Katz MJ, Buschke H. Abnormality of gait as a predictor of non-Alzheimer's dementia. *N Engl J Med*. 2002;347(22):1761-8.
- Marquis S, Moore MM, Howieson DB, Sexton G, Payami H, Kaye JA, Camicioli R. Independent predictors of cognitive decline in healthy elderly persons. *Arch Neurol*. 2002;59(4):601-6.
- Huh Y, Yang EJ, Lee SA, Lim J-Y, Kim KW, Paik N-J. Association between executive function and physical

- performance in older Korean adults: findings from the Korean Longitudinal Study on Health and Aging (KLoSHA). *Arch Gerontol Geriatr.* 2011;52(3):e156-61.
15. Sattler C, Erickson KI, Toro P, Schröder J. Physical fitness as a protective factor for cognitive impairment in a prospective population-based study in Germany. *J Alzheimer's Dis.* 2011;26(4):709-18.
 16. Anweiler C, Schott AM, Abellan van Kan G, Rolland Y, Blain H, Fantino B, Herrmann FR, Beauchet O. The five-times-sit-to-stand test, a marker of global cognitive functioning among community-dwelling older women. *J Nutr Health Aging.* 2011;15(4):271-6.
 17. Kramer AF, Erickson KI, Colcombe SJ. Exercise, cognition, and the aging brain. *J Appl Physiol.* 2006;101(4):1237-42.
 18. Travers SH, Labarta JI, Gargosky SE, Rosenfeld RG, Jeffers BW, Eckel RH. Insulin-like growth factor binding protein-I levels are strongly associated with insulin sensitivity and obesity in early pubertal children. *J Clin Endocrinol Metab.* 1998;83(6):1935-9.
 19. Sato Y, Iguchi A, Sakamoto N. Biochemical determination of training effects using insulin clamp technique. *Horm Metab Res.* 1984;16(9):483-486.
 20. Rikli RE, Jones CJ. Functional fitness normative scores for community-residing older adults, ages 60-94. *J Aging Phys Act.* 1999;7(2):162-81.
 21. 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):189-98.
 22. Lee JY, Dong Woo Lee, Cho SJ, Na DL, Hong Jin Jeon, Kim SK, You Ra Lee, Youn JH, Kwon M, Lee JH, Maeng Je Cho. Brief screening for mild cognitive impairment in elderly outpatient clinic: validation of the Korean version of the Montreal Cognitive Assessment. *J Geriatr Psychiatry Neurol.* 2008;21(2):104-10.
 23. Rikli RE, Jones CJ. *Senior Fitness Test Manual.* 2001 Champaign, IL: Human Kinetics.
 24. Wilson RS, Bennett DA, Bienias JL, Aggarwal NT, Mendes De Leon CF, Morris MC, Schneider JA, Evans DA. Cognitive activity and incident AD in a population-based sample of older persons. *Neurology.* 2002;59(12):1910-4.
 25. Kramer AF, Colcombe SJ, McAuley E, Eriksen KI, Scalf P, Jerome GJ, Marquez DX, Elavsky S, Webb AG. Enhancing brain and cognitive function of older adults through fitness training. *J Mol Neurosci.* 2003;20(3):213-21.
 26. Auyeung TW, Kwok T, Lee J, Leung PC, Leung J, Woo J. Functional decline in cognitive impairment—the relationship between physical and cognitive function. *Neuroepidemiology.* 2008;31(3):167-73.
 27. Fitzpatrick AL, Buchanan CK, Nahin RL, Dekosky ST, Atkinson HH, Carlson MC, Williamson JD; Ginkgo Evaluation of Memory (GEM) Study Investigators. Associations of gait speed and other measures of physical function with cognition in a healthy cohort of elderly persons. *J Gerontol A Biol Sci Med Sci.* 2007;62(11):1244-51.
 28. Shah KR, Carr D, Roe CM, Miller JP, Coats M, Morris JC. Impaired physical performance and the assessment of dementia of the Alzheimer type. *Alzheimer Dis Assoc Disord.* 2004;18(3):112-9.
 29. Soumare´ A, Tavernier B, Alpe´rovitch A, Tzourio C, Elbaz A. A cross-sectional and longitudinal study of the relationship between walking speed and cognitive function in community-dwelling elderly people. *J Gerontol A Biol Sci Med Sci.* 2009;64(10):1058-65.
 30. Viccaro LJ, Perera S, Studenski SA. Is Timed Up and Go better than gait speed in predicting health, function, and falls in older adults? *J Am Geriatr Soc.* 2011;59(5):887-92.
 31. Pereira AC1, Huddleston DE, Brickman AM, Sosunov AA, Hen R, McKhann GM, Sloan R, Gage FH, Brown TR, Small SA. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. *Proc Natl Acad Sci. USA.* 2007;104(13):5638-43.
 32. Churchill JD, Galvez R, Colcombe S, Swain RA, Kramer AF, Greenough WT. Exercise, experience and the aging brain. *Neurobiol Aging.* 2002;23(2):941-55.
 33. Swain RA, Harris AB, Wiener EC, Dutka MV, Morris HD, Theien BE, Konda S, Engberg K, Lauterbur PC, Greenough WT. Prolonged exercise induces angiogenesis and increases cerebral blood volume in primary motor cortex of the rat. *Neuroscience.* 2003;117(4):1037-46.
 34. Baezner H, Blahak C, Poggesi A, Pantoni L, Inzitari D, Chabriat H, Erkinjuntti T, Fazekas F, Ferro JM, Langhorne P, O'Brien J, Scheltens P, Visser MC, Wahlund LO, Waldemar G, Wallin A, Hennerici MG; LADIS Study Group. Association of gait and balance disorders with age-related white matter changes: the LADIS study. *Neurology.* 2008;70(12):935-42.
 35. Whitman GT, Tang Y, Lin A, Baloh RW: A prospective study of cerebral white matter abnormalities in older people with gait dysfunction. *Neurology.* 2001;57(6):990-4.
 36. Kido T, Tabara Y, Igase M, Ochi N, Uetani E, Nagai T, Yamamoto M, Taguchi K, Miki T, Kohara K. Postural instability is associated with brain atrophy and cognitive impairment in the elderly: the J-SHIP study. *Dement Geriatr Cogn Disord.* 2010;29(5):379-87.
 37. Burns JM, Cronk BB, Anderson HS, Donnelly JE, Thomas GP, Harsha A, Brooks WM, Swerdlow RH. Cardiorespiratory fitness and brain atrophy in early Alzheimer disease. *Neurology.* 2008;71(3):210-6.
 38. Colcombe SJ, Kramer AF, McAuley E, Erickson KI, Scalf P. Neurocognitive aging and cardiovascular fitness: Recent findings and future directions. *J Mol Neurosci.* 2004;24(1):9-14.
 39. Rosano C, Studenski SA, Aizenstein HJ, Boudreau RM, Longstreth WT Jr, Newman AB. Slower gait, slower information processing and smaller prefrontal area in older adults. *Age Ageing.* 2012;41(1):58-64.
 40. Rosano C, Brach J, Studenski S, Longstreth WT Jr, Newman AB. Gait variability is associated with subclinical brain vascular abnormalities in high-functioning older adults. *Neuroepidemiology.* 2007;29(3-4):193-200.
 41. Fukuyama H, Ouchi Y, Matsuzaki S, Nagahama Y, Yamauchi H, Ogawa M, Kimura J, Shibasaki H. Brain functional activity during gait in normal subjects: a SPECT study. *Neurosci Lett.* 1997;228(3):183-6.
 42. Hanakawa T, Katsumi Y, Fukuyama H, Honda M, Hayashi T, Kimura J, Shibasaki H. Mechanisms underlying gait disturbance in Parkinson's disease: a single photon emission computed tomography study. *Brain.* 1999;122(Pt 7):1271-82.
 43. Deary IJ, Whalley LJ, Batty GD, Starr JM. Physical fitness and lifetime cognitive change. *Neurology.* 2006;67(7):1195-200.