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Research article

Physical Fitness Measures As Potential Markers of Low Cognitive Function in Japanese Community-Dwelling Older Adults without Apparent Cognitive Problems

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Abstract

Detecting signs of cognitive impairment as early as possible is one of the most urgent challenges in preventive care of dementia. It has still been unclear whether physical fitness measures can serve as markers of low cognitive function, a sign of cognitive impairment, in older people free from dementia. The aim of the present study was to examine an association between each of five physical fitness measures and global cognition in Japanese community-dwelling older adults without apparent cognitive problems. The baseline research of the Sasaguri Genkimon Study was conducted from May to August 2011 in Sasaguri town, Fukuoka, Japan. Of the 2,629 baseline subjects who were aged 65 years or older and not certified as individuals requiring nursing care by the town, 1,552 participants without apparent cognitive problems (Mini-Mental State Examination score ≥24) were involved in the present study (59.0% of the baseline subjects, median age: 72 years, men: 40.1%). Global cognitive function was measured by the Japanese version of the Montreal Cognitive Assessment. Handgrip strength, leg strength, sit-to-stand rate, gait speed, and one-leg stand time were examined as physical fitness measures. In multiple linear regression analyses, each of the five physical fitness measures was positively associated with the Montreal Cognitive Assessment score after adjusting for age and sex ($p < 0.001$). These associations were preserved after additional adjustment for years of formal education, body mass index, and other confounding factors ($p < 0.001$). The present study first demonstrated the associations between multiple aspects of physical fitness and global cognitive function in Japanese community-dwelling older people without apparent cognitive problems. These results suggest that each of the physical fitness measures has a potential as a single marker of low cognitive function in older populations free from dementia and thereby can be useful in community-based preventive care of dementia.

Key words: Cognitive screening, community-based study, cross-sectional study, mild cognitive impairment, physical function, primary prevention.

Introduction

Dementia has been perceived as a burdensome public health issue in aging societies (Wimo et al., 2013; Wimo and Prince, 2011). One of the most urgent challenges in the primary care field is to detect signs of cognitive impairment as early as possible before clinical diagnosis. Earlier detection has been suggested to allow for effective medical treatments preventing or slowing the onset of dementia (Siemers, 2011; Sperling et al., 2011). Hence, there is a great need for identifying biomarkers and other lifestyle-related markers which help the detection of subtle cognitive impairment occurring in the preclinical or earlier phase of the disease.

Physical fitness has been reported to be a lifestyle-related factor predicting future incidence of dementia and cognitive impairment (Alfaro-Acha et al., 2007; Buchman et al., 2007; Sattler et al., 2011; Wang et al., 2006). In contrast, it has not been fully understood whether physical fitness measures can serve as markers of low cognitive function, a sign of cognitive impairment, in older people free from dementia. Two recent population-based studies suggested a role of gait speed as a marker of low cognitive function in the pre-dementia stage by demonstrating its association with global cognition in cognitively intact older people (Fitzpatrick et al., 2007; Mielke et al., 2013). However, the knowledge for other physical fitness measures has still been limited. The other measures not yet investigated include those often administered in community-based health checkups to evaluate different aspects of physical fitness. Because the primary detection essentially needs to cover community-dwelling older individuals having diverse physical functional status, it is worth understanding abilities of the other physical fitness measures as single markers of low cognitive function in the pre-dementia stage. Therefore, the aim of the present study was to examine if each of the physical fitness measures determined by five common tests would be associated with global cognitive function in Japanese community-dwelling older people without apparent cognitive problems.

Methods

Participants

The present study was performed as part of the baseline research of the Sasaguri Genkimon Study (SGS) conducted from May to August 2011. The design of the SGS has been described in detail elsewhere (Narazaki et al., 2013). Briefly, it is an ongoing community-based prospective cohort study in Sasaguri Town, a regional town on Kyushu Island located in the southwest part of Japan, aiming to explore modifiable lifestyle-related factors causing older people to require nursing care. Subjects of the baseline research were 2,629 town residents who were aged 65 years or older and not certified as individuals requiring nursing care by the town at the end of January 2011. Of the baseline subjects, we excluded 17 individuals with a medical history of dementia or Parkinson's

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disease, 526 individuals who refused or did not complete cognitive tests, 146 individuals with signs of apparent cognitive problems determined by a Mini-Mental State Examination (MMSE) score of <24, 177 individuals who refused physical fitness tests, and 211 individuals with incomplete data on other measurements (Figure 1). Accordingly, 1,552 participants were involved in the present study (59.0% of the baseline participants). Written informed consent was obtained from all the baseline subjects prior to their participation. This study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Institute of Health Science, Kyushu University.

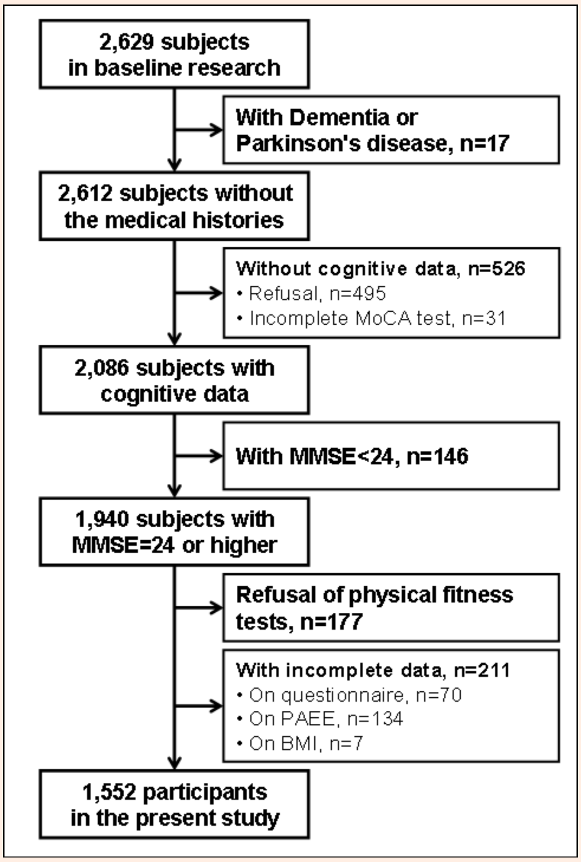

Figure 1. Flow chart of participation. This figure shows the flow of participation in the present study. MoCA, MMSE, PAEE, and BMI denote Montreal Cognitive Assessment, Mini-Mental State Examination, physical activity energy expenditure, and body mass index, respectively.

Cognitive function measures

Cognitive function was measured with the Japanese version of the Montreal Cognitive Assessment (MoCA). The details of this instrument are explained elsewhere (Fujiwara et al., 2010). Like the original one (Nasreddine et al., 2005), it is a 30-point tool for measuring global cognition in the nine domains of attention, calculations, concentration, conceptual thinking, executive functions, language, memory, orientation, and visuoconstructional ability. A higher MoCA score indicates better cognitive function. All MoCA tests were administered to the participants by trained examiners in accordance with the official instruction (Suzuki, 2010). After the measurement, MoCA scores were independently evaluated by two trained authors (K.N and T.H: 93.2% of agreement). Inconsistent evaluations between the two were judged together before final scores were determined. For the present study, MoCA scores without the 1-point correction for years of education were used. In addition to the MoCA, we performed the Japanese version of MMSE to screen apparent cognitive problems with the cut-off score of <24, as explained in the above section. This MMSE cut-off score has been widely used to detect abnormal cognitive status and to screen dementia in previous studies (Holsinger et al., 2007).

Physical fitness measures

Multiple aspects of physical fitness were objectively measured through five tests in a random manner: the handgrip test for measuring upper-extremity strength, the isometric knee extension test for lower-extremity strength, the five-times sit-to-stand test for lower-extremity agility, the 5-meter gait test for locomotive coordination, and the open-eyed one-leg stand test for postural balance. These five tests were selected because they are commonly administered in community-based regular checkups for older people in Japan. The handgrip test was performed twice for each hand using a digital grip dynamometer (TKK5401; Takei Scientific Instruments, Niigata, Japan) in a standing position. In this test, the participants were asked to grip the dynamometer as strongly as possible. The handgrip strength (HS: kg) was determined as an average of the highest scores of the left and right hands. The isometric knee extension test was also performed twice for each leg using a digital tension meter (TKK5710e; Takei Scientific Instruments, Niigata, Japan) in a seated position with the knee flexed at 90 degrees. During the test, the participants were asked to exert knee extensor force as strongly as possible against an anklet extended from the tension meter while crossing their arms on their chest. The leg strength (LS: kg) was defined in the same way as for the HS. In the five-times sit-to-stand test, the participants were requested to perform five consecutive chair stands as quickly as possible while crossing their arms on their chest, and the time (sec) spent to complete the task was recorded using a digital stopwatch. Only one trial was made for this test due to its strenuous nature. The sit-to-stand rate (SR: reps/sec) was determined by dividing 5 (reps) by the task time. The 5-meter gait test was conducted over a straight 11m lane with taped marks at the 3m and 8m points. The participants were asked to walk on the entire lane as fast as possible (but without running) in two trials, and the time (sec) for walking between the two marks was measured in each trial using a digital stopwatch. The gait speed (GS: m/sec) was calculated by dividing 5 (m) by the shortest task time in the two trials. In the open-eyed one-leg stand test, the participants tried to stand as long as possible up to 120 sec with a preferred leg while watching a taped mark on the wall 1m away from a toe line. This test was performed twice, and the time (sec) to failure of the task was measured in each trial using a digital stopwatch. The longer task time in the two trials was selected as the one-leg stand time (OT: sec). All of the five tests were administered by trained examiners with standardized procedures including standard instruction and practice. Additionally, the participants were encouraged to ask questions, if needed, throughout the procedures for better understanding and compliance. Higher values indicate better physical fitness in all of the five measures.

Other measurements

Age, sex, years of formal education, and economic status (comfortable, relatively comfortable, relatively uncomfortable, and uncomfortable) were obtained from a questionnaire. The physical activity energy expenditure (PAEE: kcal/day) was defined as average daily energy expenditure due to physical activity and objectively measured by a tri-axial accelerometer device (Active Style Pro HJA-350IT; Omron Healthcare, Kyoto, Japan) (Ohkawara et al., 2011). For this measurement, the participants were asked to wear the device all day (except for sleeping and water activities) for 7 days. The PAEE was determined only for those wearing the device for at least 10 hours a day on two or more days (mean ± standard deviation or SD of wearing period in the present participants: 6.8 ± 1.8 days). Body weight (kg) and height (m) were measured using conventional scales, and body mass index (BMI) was calculated by dividing the body weight by height squared (kg/m^2). Instrumental activities of daily living (IADL) were measured as part of the questionnaire using the five-item scale for instrumental self-maintenance of the Tokyo Metropolitan Institute of Gerontology Index of Competence (Koyano et al., 1991). The five items asked about the abilities of using public transportation, shopping for commodities, preparing meals, paying bills, and handling bank accounts in binary forms (able or unable). The participants answering “able” for all of the five items were regarded as independent in IADL and others as dependent in IADL. In the present study, the number of items answered with “able” was used as the index of IADL in regression analyses while the dependency in IADL was reported in demographic description. The psychological distress was measured by the Japanese version of the Kessler 6 psychological distress scale (K6) in the questionnaire (Sakurai et al., 2011). This is a 6-item and 24-point scale, and participants who scored 5 points or more on the scale were classified as having depressive status. In the present study, the K6 scores were used in regression analyses while the depressive status was reported in demographic description. Comorbidities of hypertension, heart disease, and diabetes and history of stroke were asked on the questionnaire in binary forms (presence or absence).

Statistical analysis

Mean ± SD or median (25th-75th percentiles) was calculated for continuous variables, appropriately, and frequency (%) for categorical variables. To confirm similarities between the present participants and the baseline subjects, the Wilcoxon rank-sum test and the chi-square test were conducted for continuous and categorical variables, respectively. To examine associations between physical fitness and cognitive function, multiple linear regression analyses were conducted for each of the five physical fitness measures in the following three models: Model 1: entered each physical fitness measure as an independent variable, MoCA as a dependent variable, and age and sex as covariates, Model 2: Model 1 plus years of formal education and BMI as covariates, Model 3: Model 2 plus economic status, PAEE, IADL, K6, comorbidities of hypertension, heart disease, and diabetes, and history of stroke as covariates. A significance level was set at two-sided $\alpha = 0.05$. All statistical analyses were performed using the SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

The median age (25th-75th percentiles) for the present participants was 72 (68-77) years and 40.1% of the participants were men (n = 623). The mean ± SD or median (25th-75th percentiles) of the MoCA and the physical fitness measures in the present participants were as follows: MoCA (n = 1,552): 22.4 ± 3.4 point, HS (n = 1,529): 27.2 ± 8.0 kg, LS (n = 1,473): 27.0 ± 10.3 kg, SR (n = 1,488): 0.60 ± 0.19 reps/sec, GS (n = 1,540): 1.72 ± 0.43 m/sec, OT (n = 1,525): 45.7 (15.1-120) sec. Table 1 shows characteristics of the present participants on these and other variables.

Results of the regression analyses were summarized in Table 2. Each of the five physical fitness scores was significantly associated with the MoCA score after adjusting for age and sex (Model 1: $p < 0.001$). After additional adjustment for years of formal education and body mass index, each physical fitness score remained associated with the MoCA score (Model 2: $p < 0.001$). After further adjustment for the other confounding factors (economic status, PAEE, IADL, K6, hypertension, heart disease, diabetes, and stroke), the association between each physical fitness score and MoCA was almost unchanged (Model 3: $p < 0.001$).

Discussion

The present study examined associations between five physical fitness measures and global cognitive function evaluated by the MoCA in Japanese community-dwelling older adults without apparent cognitive problems. The primary finding of the present study is that each of the five physical fitness measures was linearly and positively associated with the MoCA score. These associations were independent of age, sex, years of formal education, BMI, and other confounding factors.

Examining lifestyle-related markers of pre-dementia cognitive functioning is expected to be of value to promote early detection of subtle cognitive impairment in community-based settings. Despite the promise of physical fitness measures as markers of low cognitive function in the pre-dementia stage, research evidence is still limited. To our knowledge, only two studies have examined the potential role of physical fitness as a marker of low cognitive function in the stage by showing association between gait speed and global cognition in non-demented older people living in the United States (Fitzpatrick et al., 2007; Mielke et al., 2013). In one study

Table 1. Characteristics of the present participants.

Indexes	Men		Women	
	65-74 years	75+ years	65-74 years	75+ years
n	402	221	570	359
Age, years	69 (67-71)	79 (77-82)	69 (67-71)	79 (77-82)
MoCA, point	23.3 (3.1)	21.4 (3.3)	23.1 (3.2)	20.8 (3.5)
HS, kg	36.4 (5.6)	31.4 (5.5)	23.3 (3.9)	20.2 (4.1)
LS, kg	36.6 (9.9)	29.3 (8.6)	24.1 (6.9)	18.8 (6.5)
SR, reps/sec	.65 (.19)	.55 (.17)	.63 (.18)	.52 (.16)
GS, m/sec	1.93 (.44)	1.68 (.41)	1.76 (0.37)	1.44 (.36)
OT, sec	109.3 (35.0-120)	22.9 (7.2-47.6)	80.6 (24.6-120)	16.7 (5.8-43.4)
Education, years	12 (10-14)	11 (9-13)	12 (9-12)	10 (9-11)
Economy*, %	32.1	47.5	38.2	48.2
PAEE, kcal/day	557.5 (162.8)	453.6 (144.7)	536.3 (134.5)	405.6 (115.8)
BMI, kg/m^2	23.5 (2.7)	23.0 (2.8)	23.3 (3.4)	22.9 (3.3)
IADL†, %	16.9	14.0	1.4	6.7
K6‡, %	24.9	27.1	30.4	32.6
Hypertension, %	38.1	37.1	33.0	46.5
Heart disease, %	12.9	25.8	5.8	18.7
Diabetes, %	19.7	17.6	9.6	9.7
Stroke history, %	4.5	5.0	1.6	3.1

Note: continuous variables are represented as mean (SD) or median (25th-75th percentiles). * Percentage of participants answering "comfortable" and "relatively comfortable" in economic status; † percentage of participants regarded as dependent in instrumental activities of daily living (IADL score of <5); ‡ percentage of participants classified as having depressive status (K6 score of ≥5). MoCA: Montreal Cognitive Assessment; HS: handgrip strength; LS: leg strength; SR: sit-to-stand rate; GS: gait speed; OT: one-leg stand time; PAEE: physical activity energy expenditure; BMI: body mass index; IADL: instrumental activities of daily living; K6: Kessler 6 psychological distress scale.

from the Ginkgo Evaluation of Memory study group, the investigators used the Modified MMSE (3MSE) as a global cognitive test and excluded individuals with the test score of <80 from the study participants (Fitzpatrick et al., 2007). They found that the risk of low cognition defined as the 3MSE score of 80 to 85 was almost twice for participants in the slowest quartile of maximal walking speed compared with that for participants in the fastest quartile after adjusting for demographic and comorbid factors. Another study from the Mayo Clinic group also showed an association between usual walking speed and global cognitive function measured as a standard score of a neuropsychological battery covering four cognitive domains in older adults without diagnosed mild cognitive impairment and dementia (Mielke et al., 2013). These associations reasonably support the ability of gait speed as a marker of low cognitive function in the United States older people free from dementia, but comparable observations had not been made in other ethnicities including Japanese. The present study first demonstrated a similar association between gait speed and global cognition in a Japanese older population without apparent cognitive problems. Moreover, the present study further demonstrated novel association between each of the other four physical fitness measures and global cognition in the Japanese population (Table 2). A notable aspect of the present study is the use of the MoCA as a reasonable neuropsychological instrument to measure global cognitive function among the participants who were free from apparent cognitive problems. MoCA is a relatively new instrument devised to detect early cognitive changes with multiple domains for screening mild cognitive impairment (Nasreddine et al., 2005). This instrument has been reported to have higher sensitivity to subtle cognitive alterations than MMSE and other conventional tools (Nasreddine et al., 2005; Pendlebury et al., 2010), and has been used as a scale of global cognitive status in population-based studies (Donoghue et al., 2012; King et al., 2013).

One possible mechanism underlying the observed

Table 2. Associations between each physical fitness measure and MoCA.

Independent variables	n	Model 1		Model 2		Model 3	
		Regression coefficient (95% CI)	p	Regression coefficient (95% CI)	p	Regression coefficient (95% CI)	p
HS, kg	1,529	.10 (.07-.14)	<.001	.09 (.06-.13)	<.001	.08 (.05-.12)	<.001
LS, kg	1,473	.07 (.05-.09)	<.001	.06 (.04-.08)	<.001	.06 (.04-.08)	<.001
SR, reps/sec	1,488	2.34 (1.42-3.26)	<.001	1.95 (1.05-2.85)	<.001	1.55 (.64-2.45)	<.001
GS, m/sec	1,540	1.38 (.96-1.80)	<.001	1.17 (.76-1.57)	<.001	1.01 (.59-1.43)	<.001
OT, sec	1,525	.02 (.01-.02)	<.001	.01 (.01-.02)	<.001	.01 (.01-.02)	<.001

Note: Model 1: association between each physical fitness measure as an independent variable and MoCA as a dependent variable, with age and sex as covariates; Model 2: Model 1 plus years of education and BMI as covariates; Model 3: Model 2 plus other confounding factors (economic status, PAEE, IADL, K6, hypertension, heart disease, diabetes, and stroke) as covariates. MoCA: Montreal Cognitive Assessment; HS: handgrip strength; LS: leg strength; SR: sit-to-stand rate; GS: gait speed; OT: one-leg stand time; BMI: body mass index; PAEE: physical activity energy expenditure; IADL: instrumental activities of daily living; K6: Kessler 6 psychological distress scale. 95% CI denotes 95% confidential interval of regression coefficient. Coefficients of determination (adjusted R-squared) in the regression analyses are as follows: Model 1: 0.145, 0.138, 0.132, 0.148, 0.157; Model 2: 0.197, 0.192, 0.183, 0.198, 0.205; Model 3: 0.210, 0.206, 0.196, 0.209, 0.217 (for HS, LS, SR, GS, and OT, in respective models).

associations is the concurrent deterioration of the brain regions responsible for cognitive and physical performance in the pre-dementia stage of aging. Small to relatively large deterioration of overall brain structures is observed by magnetic resonance imaging even in healthy older adults (Resnick et al., 2003). Such deterioration may lead to concurrent alterations in cognitive and physical performance in the pre-dementia stage. Because all the physical fitness tests used in the present study require refined brain control for initiation of the tasks, recruitment of muscles, and motor coordination in given constraints, it can be plausible that the deterioration of the brain affects not only cognitive function but also the quality of physical performance objectified by the physical fitness measures.

Based on the observed results, the present study offers a practical value of the physical fitness measures as objective means to assist identifying and monitoring early cognitive impairment in community-based regular checkups. Virtually, all the physical fitness tests used in the present study are simple and require no clinical resources or sophisticated devices. For example, the gait test, sit-to-stand test, and one-leg stand test need only a stopwatch and can be self-performed even at home. In addition, considering the significant association for each physical fitness measure, the five tests may not necessarily have to be performed all together. Rather, any one or a few tests can be selected in the regular checkups, depending on the physical functional status of individuals being tested. Incorporating the physical fitness measures into community-based regular checkups may add information to help earlier detection of cognitive impairment which can allow potential patients to receive effective medical treatments to prevent or slow the onset of dementia sooner. If this will be the case in the near future, it could bring a positive economic impact to society. Indeed, an estimation showed that if new treatment delaying the onset of Alzheimer's disease (AD) by 5 years will be available in 2015, it could result in the reduction of the projected Medicare costs of AD by 45.1% (from \$627 billion to \$344 billion) in 2050 in the United States (Sperling et al., 2011).

The strengths of the present study are the relatively large population-based samples, the choice of the cognitive instrument (i.e., MoCA) suitable for examining the differences in cognitive function in the participants free from apparent cognitive problems, the use of multiple objective measures of physical fitness, and the variety of confounding measures including the accelerometer-derived PAEE and other health-related scales such as the IADL and K6. In contrast, the present report has several limitations which are worth noting here. First, the sample of the present study might be biased to some extent by the exclusion of subjects (Figure 1). Specifically, subjects excluded due to the refusal or incompletion of the cognitive tests were younger and had a higher proportion of men than the remaining subjects (median age: 72 vs. 73 years, $p < 0.01$; percentage of men: 50.8 vs. 41.8%, $p < 0.001$). However, since the excluded subjects are considered to have relatively good status on both physical and cognitive functions, the influence of the exclusion on the observed associations may not be considerable. Also, subjects excluded due to the refusal of the physical fitness tests and the other incomplete measures had a higher proportion of men and lower MoCA scores than the present participants (percentage of men: 48.2 vs. 40.1%, $p < 0.005$; mean MoCA score: 21.8 vs. 22.4 years, $p < 0.001$). Nevertheless, the influence of this exclusion may also not be sizable because the excluded subjects presumably had relatively lower physical functioning than the present participants besides the lower cognitive function. Second, the relatively large samples of the present study did not allow us to perform neurological examination to determine older individuals with clinical cognitive impairment. Instead, we used the MMSE cut-off score of <24 which has been widely used to screen dementia in clinical and population-based studies (Holsinger et al., 2007). Finally, because the present study was performed in a single Japanese town, generalizability of the results to other regions is limited. Therefore, further community-based studies in other populations should be performed to overcome this limitation.

Conclusion

In summary, the present study first demonstrated the associations between five physical fitness measures and global cognitive function in Japanese community-dwelling older people without apparent cognitive problems, independent of age, sex, years of formal education, body mass index, and other confounding factors. The present results suggest that each of the five physical fitness measures has a potential ability as a single lifestyle-related marker of low cognitive function in older populations free from dementia and thereby can be used to help earlier detection of cognitive impairment in community-based preventive care of dementia. Future studies will be conducted to develop a specific screening method for early cognitive impairment in the pre-dementia stage with using these physical fitness measures.

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Key points

- There is a great need for identifying lifestyle-related markers which help detect subtle cognitive impairment in the preclinical or earlier phase of dementia.
- In the present study, each of the five physical fitness measures employed was linearly and positively associated with the Montreal Cognitive Assessment score in the present older adults without apparent cognitive problems, after adjusting for age, sex, education, body mass index, and other confounding factors.
- The results suggest the potential of each physical fitness measure as a single lifestyle-related marker of low cognitive function in the population, which can be useful in community-based preventive care of dementia.

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