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Detection of pre-dementia cognitive impairment risk in community-dwelling older people

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Doctoral Thesis

Detection of pre-dementia cognitive impairment risk in community-dwelling older people

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Summary

Background and purpose

Dementia has been recognized as a major formidable public health challenge in modern aging societies. To facilitate preventive strategies against dementia, there is an emerging need for establishing population-based methods which can be used to detect pre-dementia cognitive impairment risk. Physical fitness measures have recently been found to be life-style related factors predicting future incidence of dementia. However, it has been still unclear whether physical fitness measures can serve as markers for detecting concurrent pre-dementia cognitive impairment risk in community-dwelling older people. Therefore, this doctoral thesis aimed to examine abilities of physical fitness measures as potential markers of pre-dementia cognitive impairment risk in community-dwelling older people.

Study 1: Determination of pre-dementia cognitive impairment risk in community-dwelling older people

The Montreal Cognitive Assessment (MoCA) is a neuropsychological instrument developed for screening mild cognitive impairment (MCI), a clinical phenotype of pre-dementia cognitive impairment risk. The MoCA has been validated as a promising MCI screening tool in previous institutional validation studies. In contrast, its scoring

characteristics in community-dwelling older people have been not yet fully understood. This study first investigated the scoring characteristics of the MoCA in Japanese community-dwelling older people free from dementia (n=1,848), for determining pre-dementia cognitive impairment risk. The mean MoCA score observed (22.3 points) was lower than that for normal controls (27.4 points) and was indeed close to that for MCI patients (22.1 points) in the original validation study. Furthermore, 81.3% of MoCA scores fell below the standard cut-off of 26 points for detecting MCI. These results suggest that it is not reasonable to use the standard cut-off of the MoCA for detecting MCI as pre-dementia cognitive impairment risk in the population. Accordingly, pre-dementia cognitive impairment risk was determined by poor cognitive function, an established late-life risk factor of incident dementia, defined as MoCA scores below mean minus 1.5 times standard deviation for age- and education-match groups.

Study 2: Associations of physical fitness measures with global cognition and pre-dementia cognitive impairment risk in community-dwelling older people free from dementia

This study was conducted to examine associations of five physical fitness measures with global cognition and pre-dementia cognitive impairment risk in Japanese community-dwelling older people free from dementia (n=1,552). Global cognition was

measured by the MoCA and pre-dementia cognitive impairment risk was determined by poor cognitive function as shown in the Study 1. 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 MoCA score after adjusting for age and sex. These associations were preserved after additional adjustment for years of formal education, body mass index, and other confounding factors. Furthermore, multiple logistic regression analyses demonstrated a significant association between each physical fitness measure and poor cognitive function after adjusting for all of the confounding factors.

Overall discussion and conclusion

The doctoral thesis determined pre-dementia cognitive impairment risk in community-dwelling older people (Study 1) and examined associations of five physical fitness measures with global cognition and pre-dementia cognitive impairment risk (Study2). The results showed that each of the five physical fitness measures was associated with global cognition and pre-dementia cognitive impairment risk in community-dwelling older people free from dementia. In conclusion, this doctoral thesis suggests that each of the physical fitness measures has a potential as a single marker of pre-dementia cognitive impairment risk in community-dwelling older people.

List of papers

This doctoral thesis consists of the following two original research papers:

Narazaki, K., Nofuji, Y., Honda, T., Matsuo, E., Yonemoto, K. and Kumagai, S. (2013) Normative data for the Montreal Cognitive Assessment in a Japanese community-dwelling older population. *Neuroepidemiology* 40, 23-29.

Narazaki, K., Matsuo, E., Honda, T., Nofuji, Y., Yonemoto, K. and Kumagai, S. (2014) Physical fitness measures as potential markers of low cognitive function in Japanese community-dwelling older adults without apparent cognitive problems. *Journal of Sports Science and Medicine* 13, 590-596.

Abbreviations

3MSE: Modified Mini-Mental State Examination

95% CI: 95% confidence interval

AD: Alzheimer's disease

ADL: activities of daily living

APOE: apolipoprotein E

AUC: area under the receiver operating characteristic curve

BMI: body mass index

GDP: gross domestic product

GS: gait speed

HS: handgrip strength

IADL: instrumental activities of daily living

K6: Kessler 6 psychological distress scale

LS: leg strength

MCI: mild cognitive impairment

MCR: Motoric Cognitive Risk

MMSE: Mini-Mental State Examination

MoCA: Montreal Cognitive Assessment

MRI: magnetic resonance imaging

OT: one-leg stand time

PAEE: physical activity energy expenditure

SD: standard deviation

SGS: Sasaguri Genkimon Study

SGS-1: baseline study of the Sasaguri Genkimon Study

SR: sit-to-stand rate

Acknowledgement

This accomplishment would be impossible without the contribution of many exceptional people. Therefore, I would like to express my gratitude as follow:

Baseline participants of the Sasaguri Genkimon Study: your willing participation in the baseline study while holding positive attitudes made me and other research members exceedingly appreciative. There is no doubt that your unstinting cooperation made the study valid and meaningful.

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Chapter 1

Background and purpose of the doctoral thesis

Chapter 1

Background and purpose of the doctoral thesis

1. Dementia as a major public health issue

Dementia is referred to as a persistent state of serious cognitive, functional and emotional decline from a previously higher level of functioning, which is mostly attributed to neurodegenerative disorders and is highly prevalent among older populations (Apostolova, 2014). A recent report by Japanese Ministry of Health, Labour and Welfare estimated that the number of Japanese people aged 65 or older suffering from dementia has reached 4.62 million in 2012, accounting for approximately 15 percent of the total older population in Japan (Asada, 2013). Dementia was the second largest cause of long-term care for Japanese older people in 2010 (Japanese Ministry of Health, Labour and Welfare, 2011) (Figure 1).

Although a specific estimation has not yet been reported in Japan, the global economic burden of dementia was estimated as $604 billion in 2010, which is equivalent to about 1% of world gross domestic product (GDP) or the GDP of a hypothetical country with the world's 18th largest economy (Wimo and Prince, 2011). In addition, a recent simulation study reported that the yearly monetary cost per patient which was attributable

to dementia ranged from $41,689 to $56,290 in the United States, depending on methods used to value informal care (Hurd et al., 2013). Based on the above reports, it is not unreasonable to perceive that dementia is becoming one of the most burdensome public health issues requiring urgent countermeasures not only in Japan but worldwide. In fact, reflecting the circumstances, the first-ever G8 (Group of Eight) Dementia Summit took place at the end of 2013, and the joint declaration for global cooperative actions against dementia was formally issued (G8 Health Ministers, 2013).

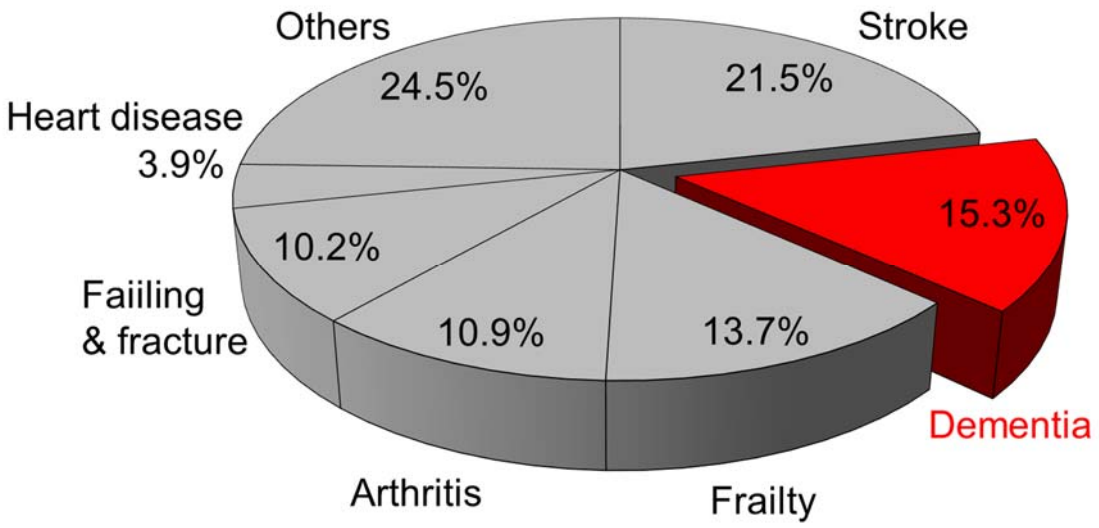

Figure 1. Primary causes of long-term care in Japan.

Note: This figure was drawn based on data in the Comprehensive Survey of Living Conditions 2010 (Japanese Ministry of Health, Labour and Welfare, 2011).

2. Preventive strategies against dementia

To overcome personal, social, and economic burdens brought by dementia, clinicians, researchers, and other field professionals have had a great interest in the establishment of preventive strategies against the disease. One hypothetical estimation by the Alzheimer's Association 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 (Alzheimer's Association, 2010; Sperling et al., 2011). Such estimation may clearly depict potential benefits of establishing the preventive strategies.

Likewise for other pathologies such as heart disease and diabetes mellitus, the preventive strategies of dementia can be classified into three levels: primary, secondary, and tertiary preventions (Gordon, 1983) (Figure 2). Because the latest evidence suggests that the pathophysiological process of dementia starts many years before the clinical diagnosis (Bäckman, 2008; Sperling et al., 2011), and the pathophysiological process is considered irreversible once being started while it can probably be slowed down, earlier detection of pre-dementia cognitive impairment risk in the secondary preventive care have been perceived as of the crucial steps to effectively prevent or slow the onset of dementia (Siemers, 2011; Sperling et al., 2011).

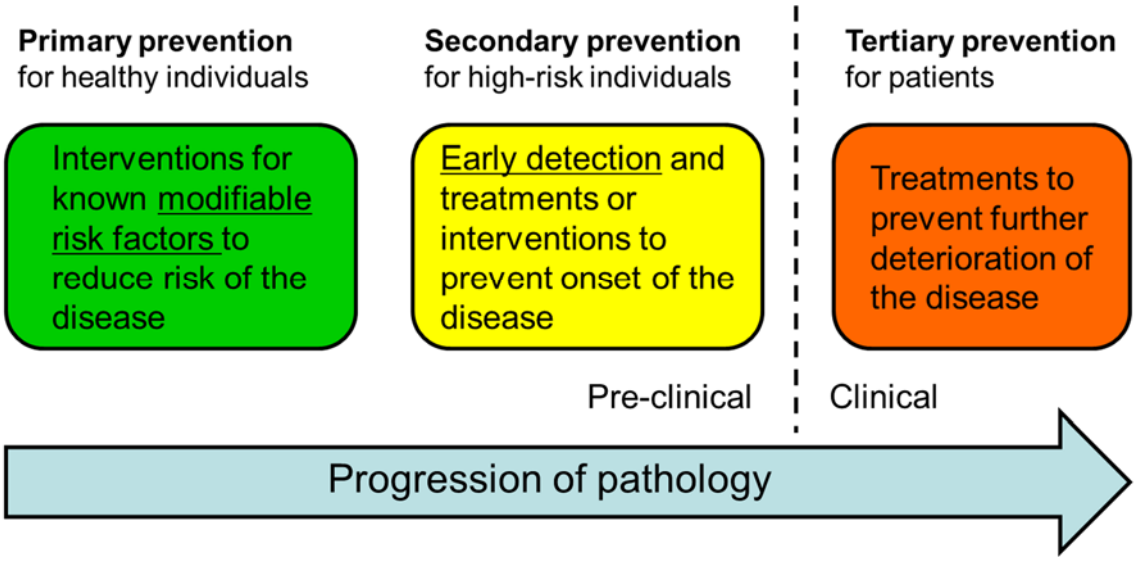

Figure 2. Three levels of preventive medicine.

Note: This figure depicts a general conceptual framework of preventive medicine consisting of three levels of prevention (Gordon, 1983), which can be applied for the preventive strategies against dementia.

3. Clinical-based detection of pre-dementia cognitive impairment risk

Given the apparent social need for establishing effective preventive strategies against dementia, various clinical-based attempts have been made to identify individuals at higher risk of dementia before the onset of the disease, and several clinical frameworks have been elaborated for the aim. Among those, mild cognitive impairment (MCI) and the pre-dementia phase of AD are considered two recently well-appreciated frameworks which are described in this section. These are not purely independent each other but the pre-dementia phase of AD partly include the framework of MCI. Other clinical-based concepts which might be relevant but not so commonly used in the present clinical research fields, such as AACD (aging-associated cognitive decline) and CIND (cognitive impairment, no dementia), are not addressed here but discussed elsewhere (Plassman et al., 2008; Stephan et al., 2007).

3-1. Mild cognitive impairment

MCI is defined as an intermediate state between normal cognitive aging and AD or other types of dementia (Petersen et al., 1999). Although it is not always the case, MCI has been reported to often develop into either AD or other forms of dementia, and therefore recognized as a high-risk state for dementia development (Petersen, 2011). The latest clinical criteria for diagnosing MCI consist of the following four items (Petersen et

al., 2009; Roberts and Knopman, 2013): (1) cognitive complaints or concerns, (2) objective decline in one or more cognitive domains including memory, executive function, attention, language, and visuospatial abilities, (3) essentially normal functional abilities or activities of daily living (ADL), and (4) absence of dementia. In addition, the latest criteria classify MCI into two phenotypes of amnestic MCI and non-amnestic MCI with two subtypes in each phenotype (Petersen, 2004) (Figure 3). Both the phenotype (amnestic and non-amnestic) and the number of cognitive domains impaired (single and multiple) are presumed to dictate future cognitive outcomes (Petersen, 2004). Specifically, amnestic MCI is presumed to have a high likelihood of progression to AD, while the multiple domain subtype may lead to higher rate of progression than the single domain subtype. In contrast, non-amnestic MCI is presumed to have a high likelihood of progression to non-AD dementias, where the single and multiple domain subtypes may likely progress to frontotemporal dementia and dementia with Lewy bodies, respectively. It is also presumed that both amnestic and non-amnestic MCI phenotypes could develop into the vascular dementia (Petersen, 2004). One study reported that incidence of dementia among MCI patients was approximately 20-40% (10-15% per year) in previous studies and that the incidence among MCI patients was higher than that among cognitively normal subjects in several studies (Roberts and Knopman, 2013).

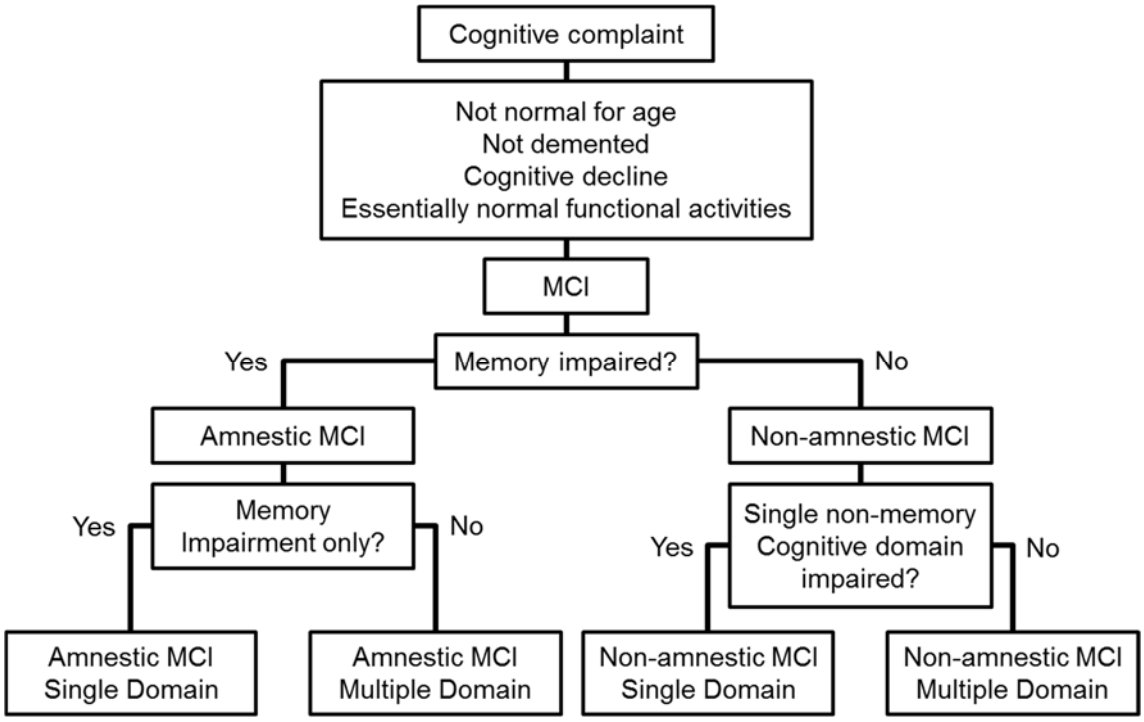

Figure 3. Current clinical criteria for diagnosing MCI and its subtypes.

Note: This figure was drawn based on Figure 5 of Petersen (2004) with minor modifications. MCI denotes mild cognitive impairment.

3-2. Pre-dementia phase of Alzheimer's disease

In 2010, the US National Institute of Aging and the Alzheimer's Association newly released the framework for the pre-dementia phase of AD (Albert et al., 2011; Jack et al., 2011; McKhann et al., 2011; Sperling et al., 2011). On this framework, the pre-dementia phase is classified into the following two stages: (1) MCI due to AD (as the symptomatic pre-dementia phase of AD) (Albert et al., 2011; Jack et al., 2011) and (2) preclinical AD (Jack et al., 2011; Sperling et al., 2011). These stages were defined based on accumulated research evidence regarding pathophysiological cascade leading to clinical cognitive impairment and subsequent AD. The MCI due to AD is defined mainly for clinical use, based on the aforementioned criteria for MCI with a combination of molecular and topographical biomarkers that are expected to determine the certainty with which a given MCI syndrome is due to AD (Albert et al., 2011). In contrast, the stage of preclinical AD is solely intended for research purposes and do not yield any clinical implications at this point of time (Sperling et al., 2011). This stage is divided into three substages depending on the degrees of asymptomatic (partly symptomatic) preclinical events observed by molecular and topographical biomarkers as well as neuropsychological instruments (Sperling et al., 2011) (Figure 4). Because of its novelty, prevalence, incidence, and clinical outcomes of the respective stages remain to be established at this point.

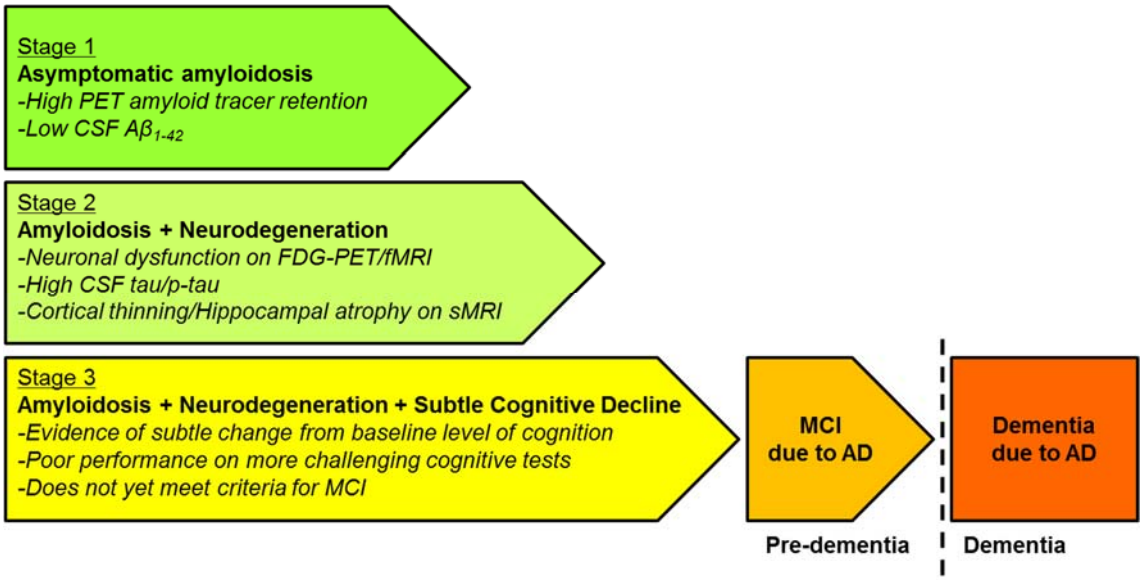

Figure 4. Graphic demonstration of the proposed framework for preclinical AD.

Note: This figure was drawn based on Figure 5 of Sperling et al., 2011 with minor modifications. In the original figure, it was noted that some individuals will not progress beyond Stage 1 or Stage 2 while individuals in Stage 3 are postulated to be more likely to progress to MCI and dementia due to AD. PET: position emission tomography; CSF: cerebrospinal fluid; Aβ: amyloid beta; FDG: fluorodeoxyglucose; fMRI: functional magnetic resonance imaging; sMRI: structural magnetic resonance imaging; MCI: mild cognitive impairment; AD: Alzheimer's disease.

3-3. Present status of clinical-based detection

Among the clinical-based frameworks developed for detecting pre-dementia cognitive impairment risk, MCI is probably the most prevailing one at this point, and a number of research findings support its ability to identify higher risk states of dementia (Petersen et al., 2014). However, there remain several issues which may prevent it from being an established diagnostic entity. Particularly, the present MCI definition covers a broad range of cognitive severity determined through the partly ambiguous criteria, which causes this pre-dementia syndrome highly heterogeneous (Stephan et al., 2012). The not negligible variability found in the aforementioned incidence of dementia among MCI patients and other outcomes may reflect the heterogeneity and may implicate the need for developing more objective and standardized criteria which yield consistent and comparable estimates (Roberts and Knopman, 2013). The use of cutting-edge technologies including biomarkers and imaging markers (as used for the MCI due to AD) is expected to improve the objectivity and standardizability of the criteria in the near future.

The framework for the pre-dementia phase of AD, especially the preclinical AD is attractive because of its potential to lead to earlier detection of individuals at higher risk of dementia before the onset of the disease. This framework also make a positive impact to relevant research domains by offering a “common language” to advance scientific

knowledge regarding the pre-dementia stages of the disease (Sperling et al., 2011). However, mainly due to its novelty, the concept of the pre-dementia phase of AD is yet to be established as a founded clinical framework.

4. Population-based detection of pre-dementia cognitive impairment risk

As discussed in the last section, clinical-based detection of pre-dementia cognitive impairment risk is advancing and expected to be established in the not-so-distant future. However, even if this will be the case, such clinical approach may not be able to be readily applied to the entire older population due to expense involved and limited accessibility for clinical resources required in the approach. Therefore, in parallel to the need for establishing clinical-based frameworks accurately detecting pre-dementia cognitive impairment risk in clinical settings, there exists another need for developing population-based wide-reaching measures applicable for screening individuals at higher risk of dementia in the entire older population (Stephan et al., 2010).

Given the above need, various population-based attempts have been started with the aim of classifying community-dwelling older individuals into proper risk categories for appropriate decision making in preventive cares against dementia. Many of these attempts have focused on examining cognitive profiles mainly using neuropsychological

instruments, while a few attempts have employed more integrative approaches by incorporating health-related factors into cognitive assessment. Moreover, some recent studies have addressed abilities of lifestyle-related factors as late-life indicators or markers of pre-dementia cognitive impairment risk in community-dwelling older people. In this section, these kinds of population-based attempts are addressed.

4-1. Cognitive assessment with neuropsychological instruments

The United States Preventive Services Task Force recently reported a thorough systematic review of population-based studies including those investigating the accuracy of brief cognitive screening instruments for detecting current dementia and MCI in community-dwelling primary care-relevant populations (Lin et al., 2013a; Lin et al., 2013b). Among 1,190 papers reviewed, they identified 27 fair- to good-quality studies that evaluated the diagnostic accuracy of 22 cognitive screening instruments for detecting MCI in primary care-relevant populations. According to the report, only six of these instruments, the Mini-Mental State Examination (MMSE) (Folstein et al., 1975), Informant Questionnaire on Cognitive Decline in the Elderly (Jorm and Jacomb, 1989), Clock Drawing Test (Agrell and Dehljn, 1998), Mini-Cog (Borson et al., 2000), Telephone Interview for Cognitive Status (Brandt, et al., 1988), and Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), were found to be examined in more than

one study (Ayalon et al., 2011; Borson et al., 2006; Callahan et al., 2002; Cook et al., 2009; Cruz-Orduña et al., 2012; Cullen et al., 2005; Donnelly et al., 2008; Ehreke et al., 2011; Ehreke et al., 2009; Holsinger et al., 2012; Jeong et al., 2004; Jorm et al., 1996; Kaufer et al., 2008; Lam et al., 2008; Lee et al., 2008a; Lee et al., 2008b; Li et al., 2006; Manly et al., 2011; Markwick et al., 2012; McDowell et al., 1997; Rideaux et al., 2012; Saxton et al., 2009; Scharre et al., 2010; Tariq et al., 2006; Tokuhara et al., 2006; Vercambre et al., 2010). Furthermore, on average, the diagnostic accuracy (e.g., sensitivity, specificity, and/or area under the receiver operating characteristic curve or AUC) for detecting MCI with these cognitive instruments was found to be lower than that for detecting dementia using these and other instruments (Lin et al., 2013a; Lin et al., 2013b).

Another systematic review also discussed the predictive accuracy of population-based cognitive screening models for future incidence of dementia (Stephan et al., 2010). As a part of the review, they identified seven screening models comprising single or multiple neuropsychological instruments which showed relatively good predictive accuracies for incident dementia in various follow-up periods (Jorm et al., 2005; Jungwirth et al., 2009b; Masur et al., 1994; Nakata et al., 2009; Nielsen et al., 1999; Rapp et al., 2005; Tierney et al., 2005). These models appear to be promising, but the authors noted that few studies

have performed rigorous statistical testing for validation, calibration, or sensitivity analysis, and none of the models have not been validated externally (Stephan et al., 2010).

Given the above results and the fact that most of the above studies were published during the past 10 years (Lin et al., 2013a), it is presumed that the population-based use of cognitive instruments and models for detecting pre-dementia cognitive impairment risk (e.g., current MCI and risk of incident dementia) is moving forward but still in the early development stage. Accordingly, standard procedures for the detection are yet to be established.

4-2. Integrative approach with cognitive and health-related assessment

The aforementioned review also identified two recent studies which proposed integrative models for detecting future dementia risk by incorporating health-related factors into cognitive assessment (Stephan et al., 2010). One research from the Cardiovascular Health Cognition Study devised a composite index named the Late-Life Dementia Risk Index (Barnes et al., 2009). This index was calculated from scores for multiple factors including age, cognitive performance measured by the Modified Mini-Mental State Examination (3MSE) and the Digit Symbol Substitution Test, body mass index (BMI), apolipoprotein E (APOE) ε4 allele status, cerebral magnetic resonance imaging (MRI) findings of white matter disease or ventricular enlargement, ultrasound

findings of internal carotid artery thickening, history of bypass surgery, fine motor performance (time to put on and button shirt), and alcohol consumption (range of index score: 0-15 points). Their validation analysis found high predictive accuracy of the Late-Life Dementia Risk Index for incident dementia within 6 years in community-dwelling older people with a mean age of 75 years at baseline (c statistic of 0.81). In addition, 56% of subjects with high scores of the index (8 points or higher) developed dementia over 6 years, while 23% of those with moderate scores (4-7 points) and only 4% of those with low scores (3 points or lower) (Barnes et al., 2009).

Another research from the Vienna Transdanube Aging Study also examined the predictive accuracy of multiple regression models with various sociodemographic and health-related factors for future incidence of probable dementia (Jungwirth et al., 2009a). The best multiple regression model combined measures of cognitive performance, verbal memory measured by the Word List-Delayed Recall Test and visual motor speed by the Trail Making Test A, with subjective memory complaints and the APOE ε4 allele status. The best model demonstrated high predictive accuracy for incidence of probable AD within 5 years in older people aged 75 years at baseline (sensitivity: 82.8%, specificity: 98.7%, AUC: 0.91).

Despite the limited number of studies with no external validation at this point, these

findings demonstrated relatively good predictive value of the integrative models for future incidence of AD and dementia. However, some of the health-related factors used in the integrative models are laboratory-based (e.g., the APOE ε4 allele, cerebral MRI, and ultrasound), and thus may not be the best fit for the aim of detecting individuals at higher risk of dementia in the entire older population. Although incorporation of non-cognitive risk factors and markers of cognitive impairment into detection models is expected to increase prediction accuracy by adding unique variance (Bäckman, 2008), feasibility and cost-effectiveness of gathering data for the factors/markers in population-based settings should also be taken into account to achieve the original aim (Stephan et al., 2010). From this standpoint, it can be worth examining potential abilities of lifestyle-related factors as late-life indicators or markers of pre-dementia cognitive impairment risk because these factors can be feasibly assessed in population-based settings.

4-3. Potential use of lifestyle-related indicators and markers

In addition to age (Jorm and Jolley, 1998), race (Tang et al., 2001), heredity (Corder et al., 1993) and other sociodemographic factors, types of lifestyle-related factors have been found to be associated with future incidence of dementia over the past decades (Barnes and Yaffe, 2009; Solfrizzi et al., 2008). Reported lifestyle-related factors include formal education (Stern et al., 1994), physical (Lindsay et al., 2002), cognitive (Wilson et al.,

2002), and social activities (Fratiglioni et al., 2000), depressive status (Jorm, 2001), diet (Luchsinger et al., 2007), smoking (Anstey et al., 2007), and alcohol consumption (Mukamal et al., 2003). Some of these factors, such as age and formal education, are established as determinants of cognitive function in community-dwelling older people and often used as late-life indicators of pre-dementia cognitive impairment risk (Crum et al., 1993). In contrast, most of the other lifestyle-related factors have not been well founded yet, and thus, no clear consensus has been reached on their abilities as late-life markers of pre-dementia cognitive impairment risk. This might be partly due to some inconsistencies across studies examining respective factors, including those regarding the timing of exposure and methods for measurements. Also, most previous studies have relied on questionnaire-based subjective data with some exceptions, which may limit comparison and integration of findings across studies and may cause the lack of consensus.

Besides previous reports regarding the above lifestyle-related factors, there have been increasing reports showing associations of objective physical fitness measures with cognitive decline and dementia risk (Buchman and Bennett, 2011; Clouston et al., 2013). In eight of these reports, physical fitness measured in late life, including handgrip strength, gait (timed walk), balance (one-leg stand), chair stand, composite muscle strength, and composite physical fitness, have been found to be associated with future incidence of

clinical events including MCI, AD, and dementia in community-dwelling older people (Aggarwal et al., 2006; Boyle et al., 2009; Buchman et al, 2011; Buchman et al., 2007; Sattler et al., 2011; Wang et al., 2006; Wilkins et al., 2013; Yamada et al., 2009). Furthermore, one recent study proposed a novel type of pre-dementia cognitive impairment risk so-called Motoric Cognitive Risk (MCR) by replacing objective cognitive decline in the clinical MCI criteria (see 3-1. Mild cognitive impairment) to slow gait relative to age- and sex-matched peers (Verghese et al., 2013). The authors found that community-dwelling older people having MCR at baseline were at higher risk of developing dementia and vascular dementia than cognitively intact counterparts. This study also suggested that MCR predicts future incidence of vascular dementia better than MCI. Despite the lack of validation of the observed associations in various populations and no clear evaluation of predictive accuracy at this time, the findings from these prospective studies may offer promise for physical fitness measures as potential late-life markers of pre-dementia cognitive impairment risk. In contrast, it has not been well documented whether physical fitness measures can serve as concurrent markers of pre-dementia cognitive impairment risk in community-dwelling older people. To our knowledge, there exists only two studies suggesting a role of gait speed as a marker of pre-dementia cognitive impairment risk by demonstrating its association with global

cognition in cognitively intact older people (Fitzpatrick et al., 2007; Mielke et al., 2013).

4-4. Present status of population-based detection

Population-based detection of pre-dementia cognitive impairment risk has emerged as an important public health challenge. Reflecting the demand for establishing practical methods to detect individuals at higher risk of dementia in the entire older population (Stephan et al., 2010), a fair number of attempts using neuropsychological instruments and cognitive models have been started mostly in Western countries over the last decade or two. Along with these attempts, recent studies have also addressed abilities of lifestyle-related factors as late-life indicators or markers of pre-dementia cognitive impairment risk in community-dwelling older people. Of these factors, increasing reports have found baseline physical fitness measures to be associated with incident dementia and cognitive impairment. Because they can be simply and objectively examined in population-based settings without requiring any clinical resources, physical fitness measures may have potentials as feasible late-life markers of pre-dementia cognitive impairment risk. However, it has been still unclear whether physical fitness measures can serve as markers of concurrent pre-dementia cognitive impairment risk in community-dwelling older people.

5. Purpose of the doctoral thesis

As discussed in the last section, it has been unclear whether physical fitness measures can serve as markers for detecting concurrent pre-dementia cognitive impairment risk in community-dwelling older people. Therefore, the purpose of this doctoral thesis was to examine abilities of physical fitness measures as potential markers of pre-dementia cognitive impairment risk in community-dwelling older people.

To address the purpose of the doctoral thesis, two original studies were conducted. The first study aimed to determine pre-dementia cognitive impairment risk in community-dwelling older people (Chapter 2). The second study then aimed to examine associations of physical fitness measures with global cognition and pre-dementia cognitive impairment risk in community-dwelling older people free from dementia (Chapter 3). Accordingly, overall discussion and conclusion were made in Chapter 4.

Chapter 2

Determination of pre-dementia cognitive impairment risk in community-dwelling older people (Study 1)

Chapter 2

Determination of pre-dementia cognitive impairment risk in community-dwelling older people (Study 1)

1. Introduction

MCI represents an intermediate clinical state between normal cognitive aging and AD or other types of dementia (Petersen et al., 1999). Although it is not always the case, MCI has been reported to often develop into AD or other forms of dementia, and therefore recognized as a high-risk state for dementia development (Petersen, 2011) or a clinical phenotype of pre-dementia cognitive impairment risk. In recent discussions, community-based screening of MCI is considered as one of the crucial steps to enable wide-reaching interventions for preventing or slowing the onset of dementia (Stephan et al., 2010).

The MoCA is a brief neuropsychological tool designed for screening MCI (Nasreddine et al., 2005) and is acknowledged as a promising instrument worldwide (Fujiwara et al., 2010; Lee et al., 2008a; Rahman and El Gaafary, 2009). Given the need for ethnic specific versions of neuropsychological tests (Escobar et al., 1986; Mungas et al., 1996), 63 versions of the MoCA are currently developed in 38 languages (www.mocatest.org). The MoCA has also been reported to have higher sensitivity to a subtle cognitive decline than

conventional tools such as the MMSE (Dong et al., 2010; Nasreddine et al., 2005; Pendlebury et al., 2010).

To date, two cohort studies reported scoring characteristics of the MoCA in population-based samples including a multiethnic United States population (Rossetti et al., 2011) and a Portuguese population (Freitas et al., 2011). Both studies, however, were conducted with subjects in a wide age range, and thus the sample sizes were scarce for the older age ranges. Accordingly, the ability of the MoCA as a MCI screening tool in community-dwelling older people has not yet been clearly validated. Such validation may be urgent especially for Japanese society undergoing the world's fastest aging with the highest life expectancy. Therefore, the purpose of the present study was to investigate scoring characteristics of the MoCA in Japanese community-dwelling older people free from dementia for examining whether the MoCA can be used for detecting MCI (as pre-dementia cognitive impairment risk) in the population.

2. Methods

2-1. Participants

The present study involved analysis of data from the baseline phase of the Sasaguri Genkimon Study (SGS) conducted from May to August 2011. The SGS is an ongoing

community-based prospective cohort study in a Japanese local town, Sasaguri Town, aiming to explore modifiable lifestyle factors causing older people to require long-term care. Subjects of the baseline study of the SGS (SGS-1) were all residents of the town who were aged 65 years or older and not certified as individuals requiring long-term care by the town in January 2011 (n=4,979). Sixty-six subjects were excluded due to being dead or moving out by the onset of the study. A set of study information sheets and a questionnaire was mailed to all remaining subjects (n=4,913) and 2,629 individuals, hereafter referred to as the participants of the SGS-1, responded to the mail by visiting a community center to submit the questionnaire and undergo multiple physical and cognitive tests in one of 31 group-testing sessions of the SGS-1, contacting study coordinators to set an appointment for an individual home-testing session, or visiting the city office to submit the questionnaire (recruitment rate: 53.5%). Of these, 2,129 individuals took part in MoCA tests. After the testing, we excluded 32 individuals unable to complete the MoCA properly and 12 individuals with missing information about their years of formal education. Furthermore, of the remaining individuals with complete data required for evaluating MoCA scores (n=2,085), we excluded 108 individuals with self-reported medical histories of stroke, depression, Parkinson's disease, and dementia, and 129 individuals with signs of apparent cognitive problems determined by a MMSE score

of <24. Accordingly, data from 1,848 participants (70.3% of the total participants of the SGS-1) were involved in the present study.

All the participants provided written informed consent to participate in the present study. The study protocol and the informed consent form were approved by the Institutional Review Board of Institute of Health Science, Kyushu University.

2-2. Measurements

We used the Japanese version of the MoCA for all measurements. The details of the Japanese version are described elsewhere (Fujiwara et al., 2010). Briefly, it was developed and validated by investigators including the inventor of the original MoCA (Dr. Nasreddine). As the original one (Nasreddine et al., 2005), the Japanese version of the MoCA was designed as a 30-point screening instrument administered in about 10 minutes and consists of the following 12 cognitive tasks: a five-item delayed recall task (5 points), a clock-drawing task (3 points), a cube-copying task (1 point), a trail-making task (1 point), a phonemic fluency task (1 point), a two-item verbal abstraction task (2 point), a target-tapping task (1 point), a serial subtraction task (3 points), a two-item digits-reading task (2 points), a three-item naming task (3 points), a two-item sentence-repeating task (2 points), and a six-item temporal and locational orientation task (6 points). In the standard procedure of the original as well as the Japanese versions, 1 point is added to the total

score of the cognitive tasks if an individual has 12 years or fewer of formal education and the final total score falling below 26 points is judged to have probable MCI. In addition to the MoCA, we used the Japanese version of the 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).

2-3. Procedures

All MoCA and MMSE tests were administered to the participants by trained personnel as part of the group-testing and home-testing sessions of the SGS-1. After the testing, MoCA scores were independently evaluated by two evaluators and double-checked between the two before finally determined. The inter-evaluator reliability shown as a percentage of agreement in MoCA scores was 93.3% in the initial evaluation. To demonstrate scoring characteristics in participants with the wide range of years of formal education, the preferred 1-point correction for education was not adopted.

2-4. Statistical analyses

All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC). To confirm influence of exclusion due to non-response, refusal of participation, refusal of MoCA tests, or incompletion on data required for evaluating MoCA scores, the

Wilcoxon rank-sum test and the chi-square test were conducted for continuous and categorical variables, respectively. Descriptive statistics were calculated for total MoCA scores and for scores of respective cognitive tasks. A multiple regression analysis was performed with the MoCA score as a dependent variable and age, sex, and years of formal education as independent variables. Additionally, to visualize changes in MoCA scores, simple regression analyses were conducted between the MoCA score and age in three education levels (≤9, 10-12, and ≥13 years of formal education). Furthermore, normative data for MoCA scores in the community-dwelling older people were developed with respect to four age levels (65-69, 70-74, 75-79, and ≥80 years old) and the three education levels aforementioned. Significance level was set at two-sided α=0.05.

3. Results

Individuals excluded due to non-response, refusal of participation, refusal of MoCA tests, or incompletion on data required for evaluating MoCA scores were not different from the remaining individuals with complete data in terms of age (median: 72 vs 73 years, interquartile range: 68-78 years for both groups, p=.611), sex (percentage for men: 44.7% vs. 42.1%, p=.071), and years of formal education (median: 12 years for both groups, interquartile range: 9-12 years for both groups, p=.221). The mean age and years

of formal education of the present participants were 73.2 years (standard deviation or SD: 5.9, median: 72, range, 65-93) and 11.2 years (SD: 2.5, median: 12, range, 2-23), respectively, with 41.3% of those being men (n=764). The mean MoCA score was 22.3 points (SD: 3.4, median: 23, range, 10-30), with 81.3% of scores falling below the preferred cut-off of 26 points for probable MCI. Histograms for scores of respective cognitive tasks were summarized in Figure 5.

In the multiple regression analysis, significant associations with the MoCA score were found for age (regression coefficient, -0.17; 95% confidence interval or 95% CI, -0.19 to -0.14; $p<.001$) and education (regression coefficient, 0.35; 95% CI, 0.29 to 0.41; $p<.001$) but not for sex (regression coefficient, 0.13; 95% CI, -0.16 to 0.43; $p=.367$). Figure 6 demonstrates the results of the simple regression analyses showing significant associations between the MoCA score and age in all the three education levels ($p<.001$). Specifically, higher age was associated with lower MoCA scores in all the education levels. Finally, normative data for the MoCA specific to the community-dwelling older people were determined with respect to the four age categories and three education levels (Table 1).

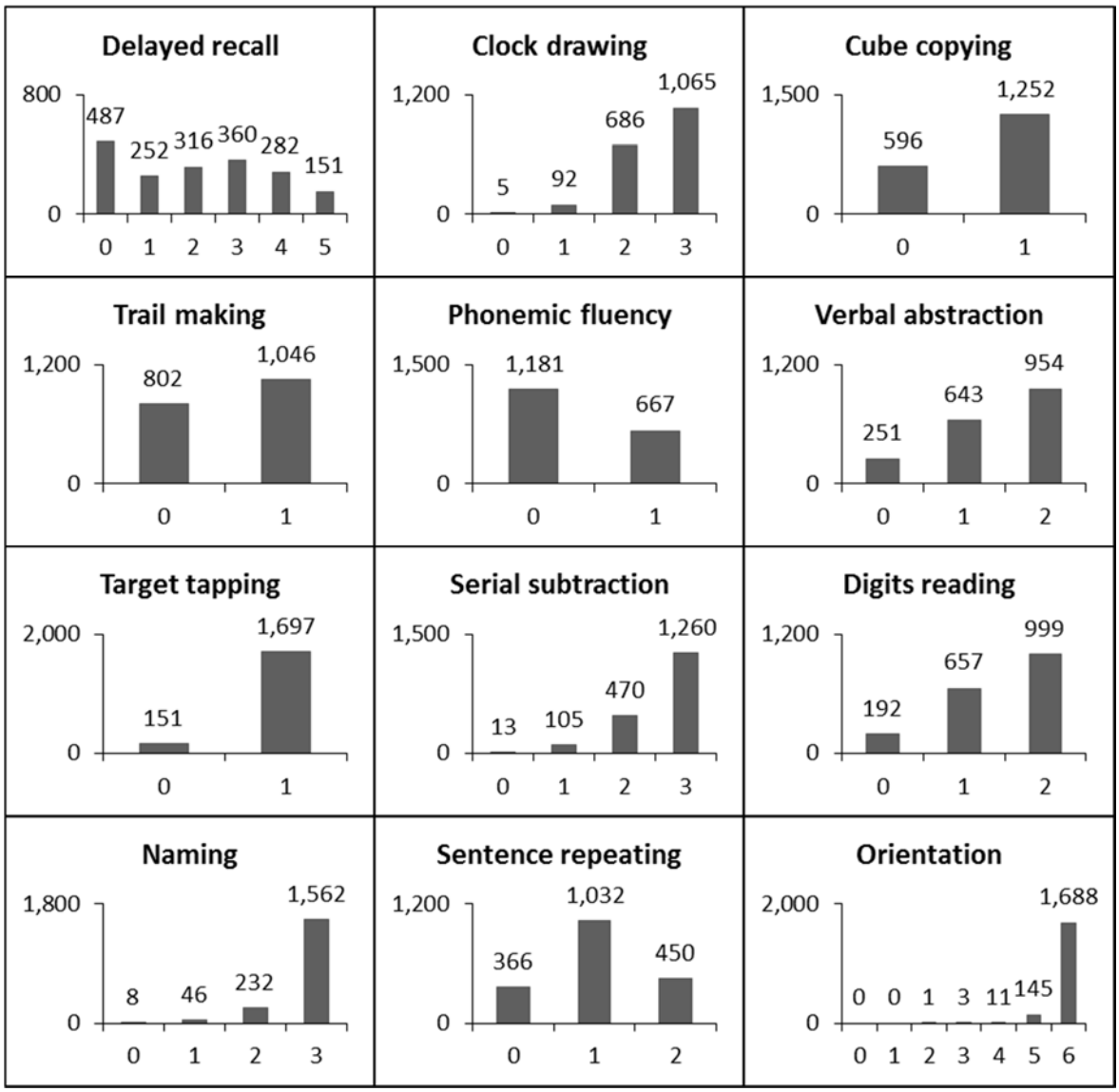

Figure 5. Histograms of scores for respective cognitive tasks in MoCA.

Note: Each panel shows a histogram for one of the 12 cognitive tasks in the MoCA. Horizontal and longitudinal axes of each panel indicate points scored and frequency count for each point, respectively. MoCA denotes Montreal Cognitive Assessment.

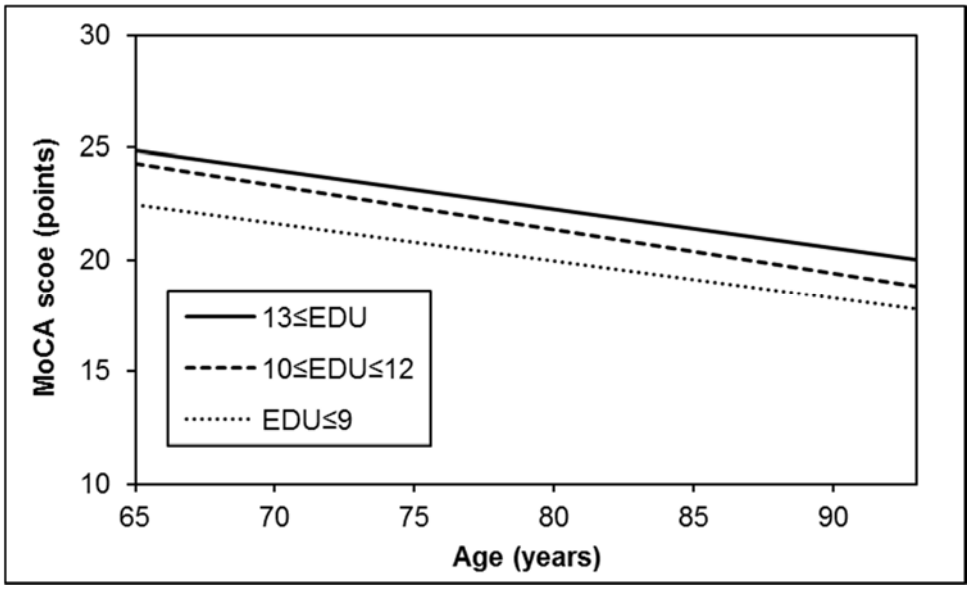

Figure 6. Regression lines between age and MoCA score in three education levels.

Note: Intercepts (at 65 years) and slopes for respective regression lines are as follows: 24.90 and -0.17 in 13≤EDU; 24.27 and -0.20 in 10≤EDU≤12; 22.54 and -0.17 in EDU≤9. MoCA and EDU denote Montreal Cognitive Assessment and years of formal education, respectively.

Table 1. Normative data for MoCA scores.

Age (years)	Education level (years)			
	≤ 9	10-12	≥13	Total by age
65-69	139	346	133	618
	22.1 (3.4)	23.9 (2.8)	24.6 (2.8)	23.7 (3.1)
	23 (10-28)	24 (14-30)	25 (14-30)	24 (10-30)
70-74	167	263	94	524
	21.6 (3.3)	22.7 (3.0)	23.8 (2.8)	22.6 (3.1)
	22 (14-29)	23 (15-30)	24 (17-29)	23 (14-30)
75-79	176	168	54	398
	20.2 (3.5)	21.8 (3.4)	22.5 (3.0)	21.2 (3.5)
	20 (12-28)	22 (14-29)	22 (16-28)	21 (12-29)
≥ 80	121	153	34	308
	19.7 (3.0)	21.0 (3.2)	22.3 (3.9)	20.6 (3.3)
	20 (14-28)	21 (13-29)	23 (12-29)	20 (12-29)
Total by education	603	930	315	1,848
	20.9 (3.5)	22.7 (3.2)	23.7 (3.1)	22.3 (3.4)
	21 (10-29)	23 (13-30)	24 (12-30)	23 (10-30)

Note: Data are expressed as number, mean (SD), and median (range). MoCA and SD denote Montreal Cognitive Assessment and standard deviation, respectively.

4. Discussion

Population-based screening for MCI is recognized as a key step to establish sound wide-reaching intervention programs for preventing or delaying older people from developing dementia (Stephan et al., 2010). Despite its promise, the ability of the MoCA as a MCI screening tool in community-dwelling older people has not yet been clearly validated. The purpose of the present study was to investigate scoring characteristics of the MoCA in Japanese community-dwelling older people free from dementia for examining whether the MoCA can be used for detecting MCI (as pre-dementia cognitive impairment risk) in the population.

The mean MoCA score of 22.3 points observed in the present study was lower than that for the normal controls (n=90, 27.4 points, SD 2.2) and was indeed close to that for the patients with MCI (n=94, 22.1 points, SD 3.1) in the original normative study performed by the development group of the MoCA (Nasreddine et al., 2005). These trends were unchanged even after the preferred 1-point correction of MoCA scores for formal education (mean 23.1 points; SD 3.4). Furthermore, approximately three-fourths or more of the scores (81.3% without the correction or 73.4% with the correction) fell below the preferred cut-off of 26 points for detecting MCI while the reported prevalence of MCI for older populations ranges from 15 to below 30% (Busse et al., 2006; Di Carlo et al., 2007;

Lopez et al., 2003; Manly et al., 2005; Manly et al., 2008). The present percentage is still high even considering potential inclusion of patients with undiagnosed dementia.

Because multiple population-based studies have also observed MoCA scores comparable to the present one (Freitas et al., 2011; Luis et al., 2009; Rossetti et al., 2011), this discrepancy may not be attributed to some administrative issues in the present study but to low external validity of the cut-off score due to the limited number of samples and/or possible selection bias for the non-population-based samples in the original study (Nasreddine et al., 2005). Other possible causes of the discrepancy are some cultural and linguistic artifacts occurring in the translation process of the original MoCA into the Japanese one (Bravo and Hebert, 1997; Escobar et al., 1986). Although the cross-cultural and cross-linguistic adaptations appear to be taken into account during the development process of the Japanese version (Fujiwara et al., 2010), the validity of the adaptations was examined with limited number of clinical-based subjects, and therefore, possibility of cultural and linguistic artifacts in population-based use cannot be ruled out.

As observed in previous population-based studies with subjects in a wide age range (Freitas et al., 2011; Rossetti et al., 2011), the present results have shown significant associations of age and education with the MoCA score in older samples. Specifically, MoCA scores were lower in participants with higher age and/or fewer years of formal

education. In contrast, no association was found between sex and the MoCA score. The effects of age and education have been well documented for neuropsychological tests in population-based studies and been taken into account with age- and education-specific norms when obtained scores are evaluated (Bravo and Hebert, 1997; Crum et al., 1993). Because both age and education are now recognized as risk factors of cognitive decline (Daviglus et al., 2011; Nithianantharajah and Hannan, 2009) rather than just biasing factors of the tests, it can be misleading and problematic to count the effects by correcting an obtained score for these variables and evaluate the corrected score using a single cut-off (Crum et al., 1993; Holsinger et al., 2007). In the light of this discussion, the current MoCA procedure comprising a 1-point correction for 12 or fewer years of formal education and subsequent evaluation with a single cut-off of 26 points may not be the best for screening MCI in population-based samples.

Taken together, it is considered reasonable to assume that the current MoCA procedure is somewhat premature for MCI screening in community-dwelling older people. However, because we did not employ a clinical diagnosis of MCI in the research design, the present study is unable to further propose any alternative cut-off and/or criteria for population-based MCI screening. Instead, we presented the age- and education-stratified normative data for MoCA scores in a Japanese community-dwelling older population free from

dementia, which may be able to allow clinicians and researchers to detect individuals with poor or abnormal cognitive function from the community-dwelling older samples while taking into account the influence of age and education. For example, if a 77-year-old patient with 9 years of formal education scored 14 points on the MoCA test, his or her personal physician can appreciate that the score was lower than the mean minus 1.5xSD (i.e., 20.2-1.5x3.5=15.0) for the age- and education-matched group free from dementia and can suspect that the patient may undergo pre-dementia cognitive impairment risk. Similarly, the normative data may be useful for the professionals when monitoring subtle cognitive change within a patient in longitudinal observations. Because late-life poor cognitive function is recognized as an established risk factor of incident dementia (Saxton et al., 2004; Tierney et al., 2005), this approach can be considered plausible.

Consistent with the present purpose, we excluded individuals self-reporting medical history of diseases contributing to or reflecting the development of clinical cognitive decline (Bhalla et al., 2009; Dalrymple-Alford et al., 2010; Dong et al., 2010; Petersen, 2011), as well as individuals with MMSE scores of <24 (Holsinger et al., 2007). There exists an argument that normative values should be representative and thus be developed from samples including both cognitively normal and abnormal individuals (Crum et al., 1993). However, the present exclusion may be conducive to enhancing the sensitivity of

detecting pre-dementia cognitive impairment risk with the present normative data by comparing a patient's score to that of a reference group free from dementia (Bravo and Hebert, 1997). Furthermore, the relatively wide range of the MoCA score observed (i.e., 10-30 points) with its significant associations with age and education may indicate the utility of the MoCA as a reasonable scale of cognitive function in community-dwelling older people free from dementia.

Our report has some limitations which are worth noting here. First, the sample of the present study may be affected to some extent by exclusion due to non-response, refusal of participation, refusal of MoCA tests, or incompletion on data required for evaluating MoCA scores. However, the influence is considered not sizable based on no significant differences in age, sex, and education observed between the excluded individuals and the remaining individuals with complete data. Second, because the present study was performed in the single Japanese town, generalizability of the results is somewhat limited. Yet, the present normative data can be considered applicable to other places in Japan because ethnicity and educational system have been almost homogeneous across Japan. Finally, in the normative data, some strata were formed with relatively small numbers of samples, and thus, probably less reliable in terms of age-education relationships.

Associations of MoCA scores with other sociodemographic factors, such as ethnicity,

culture, language, financial security, and family configuration, remain to be explored by future investigations in order to generalize the findings of this research. Obtaining these types of research findings might be essential before establishing the cut-off for population-based MCI screening. In parallel with exploring the future use of the MoCA as a population-based MCI screening tool, we are going to follow the present participants in prospective observations of the SGS to determine the ability of the test to predict future onset of dementia in the community-dwelling older population.

5. Conclusion

To our knowledge, the present study was the first to demonstrate scoring characteristics of the MoCA specific to community-dwelling older people not only in Japanese society but worldwide. This study suggests that the current MoCA procedure is somewhat premature for community-based MCI screening, while proposing alternative use of the present normative data for detecting pre-dementia cognitive impairment risk in community-dwelling older people. According to the findings, we determined pre-dementia cognitive impairment risk by defining poor cognitive function as MoCA scores below mean minus 1.5xSD for age- and education-match groups.

Chapter 3

Associations of physical fitness measures with global cognition and pre-dementia cognitive impairment risk in community-dwelling older people free from dementia (Study 2)

Chapter 3

Associations of physical fitness measures with global cognition and pre-dementia cognitive impairment risk in community-dwelling older people free from dementia (Study 2)

1. 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 for detecting

concurrent pre-dementia cognitive impairment risk in community-dwelling older people. Two recent population-based studies suggested a role of gait speed as a marker of pre-dementia cognitive impairment risk 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 pre-dementia cognitive impairment risk. Therefore, the purpose of the present study was to examine if each of physical fitness measures determined by five common tests would be associated with global cognition and pre-dementia cognitive impairment risk in Japanese community-dwelling older people free from dementia.

2. Methods

2-1. Participants

The present study was performed as part of the SGS-1 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 long-term care. Subjects of the baseline research were 2,629 town residents who were aged 65 years or older and not certified as individuals requiring long-term 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 disease, 526 individuals who refused or did not complete cognitive tests, 146 individuals with signs of apparent cognitive problems determined by a MMSE score of <24, 177 individuals who refused physical fitness tests, and 211 individuals with incomplete data on other measurements (Figure 7). 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.

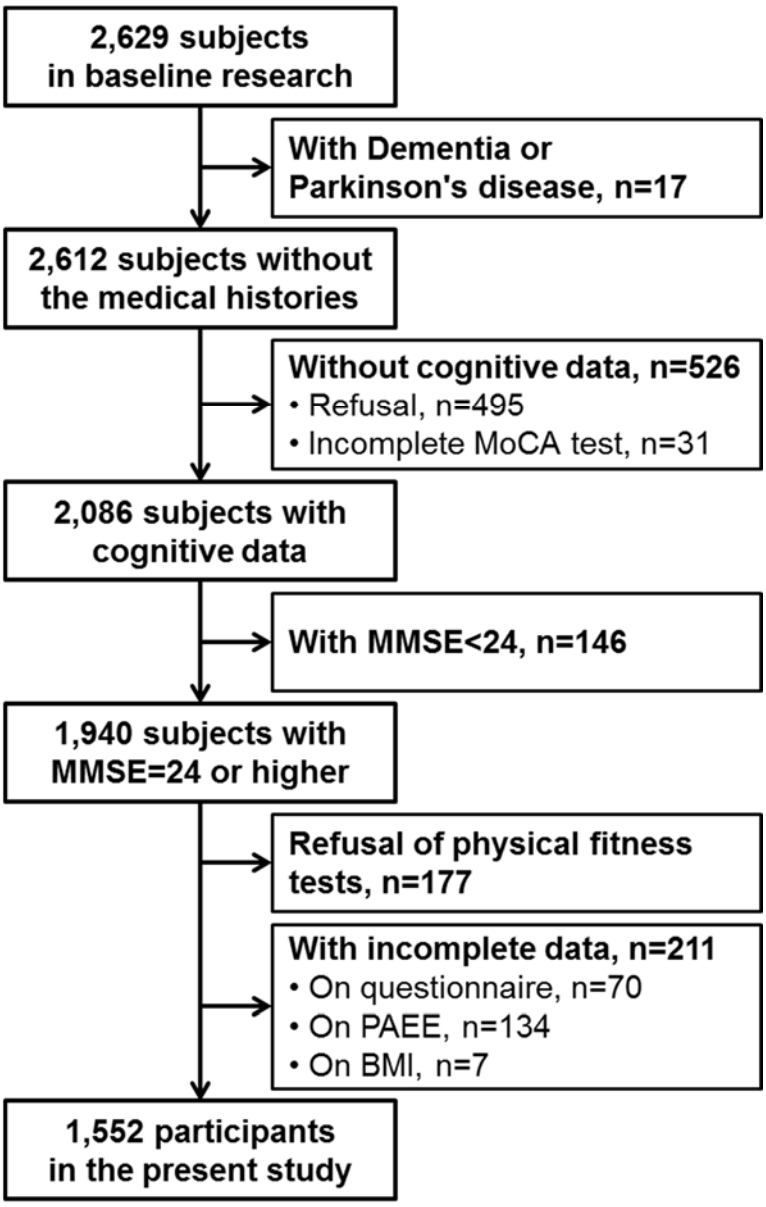

Figure 7. Flow chart of participation.

Note: 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.

2-2. Cognitive function measures

Cognitive function was measured with the Japanese version of the 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 evaluators (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 as an index of global cognition. Also, poor cognitive function was determined as an indicator of pre-dementia cognitive impairment risk using the MoCA normative data demonstrated in the last chapter (Table 1). Specifically, participants with MoCA scores 1.5 SD below the mean for age- and education-matched individuals were defined as those having poor cognitive function. 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).

2-3. 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.

2-4. 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 ± 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 ADL (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., 2007). 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).

2-5. Statistical analyses

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. To examine an association between each physical fitness measure and the poor cognitive function, a multiple logistic regression analysis was performed with adjustments for age, sex, years of formal education, BMI, 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 α=.05. All statistical analyses were performed using the SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. 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 2 shows characteristics of the present participants on these and other variables.

Results of the multiple linear regression analyses were summarized in Table 3. Each of the five physical fitness scores was significantly associated with the MoCA score after adjusting for age and sex (Model 1: $p<.001$). After additional adjustment for years of formal education and body mass index, each physical fitness score remained associated with the MoCA score (Model 2: $p<.001$). 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: $p<.001$).

Results of the multiple logistic regression analyses were presented in Table 4. Each of the five physical fitness measures was significantly associated with the poor cognitive function after adjusting for the confounding factors ($p<.05$). Adjusted odds ratios (95% CI) for having the poor cognitive function by 1-unit increase in each physical fitness measure range from 0.230 (0.070-0.756) for SR to 0.992 (0.987-0.997) for OT (Table 4).

Table 2. 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	0.65 (0.19)	0.55 (0.17)	0.63 (0.18)	0.52 (0.16)
GS, m/sec	1.93 (0.44)	1.68 (0.41)	1.76 (0.37)	1.44 (0.36)
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. SD denotes standard deviation.

Table 3. 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	0.10 (0.07-0.14)	<.001	0.09 (0.06-0.13)	<.001	0.08 (0.05-0.12)	<.001
LS, kg	1,473	0.07 (0.05-0.09)	<.001	0.06 (0.04-0.08)	<.001	0.06 (0.04-0.08)	<.001
SR, reps/sec	1,488	2.34 (1.42-3.26)	<.001	1.95 (1.05-2.85)	<.001	1.55 (0.64-2.45)	<.001
GS, m/sec	1,540	1.38 (0.96-1.80)	<.001	1.17 (0.76-1.57)	<.001	1.01 (0.59-1.43)	<.001
OT, sec	1,525	0.02 (0.01-0.02)	<.001	0.01 (0.01-0.02)	<.001	0.01 (0.01-0.02)	<.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).

Table 4. Adjusted odds ratios for having poor cognitive function by 1-unit increase in each physical fitness measure.

Independent variables	n	Case (%)	Odds ratio	95% CI	*p*
HS, kg	1,529	123 (8.0)	0.948	0.909-0.989	.0139
LS, kg	1,473	117 (7.9)	0.958	0.932-0.985	.0022
SR, rep/sec	1,488	118 (7.9)	0.230	0.070-0.756	.0155
GS, m/sec	1,540	125 (8.1)	0.458	0.277-0.756	.0023
OT, sec	1,525	123 (8.1)	0.992	0.987-0.997	.0011

Note: Poor cognitive function was defined by MoCA score 1.5 standard deviation below the mean for age and education matched group in the normative MoCA data shown as Table 1. Multiple logistic regression analysis was conducted for each physical fitness measure with adjustments for age, sex, years of education, BMI, economic status, PAEE, IADL, K6, hypertension, heart disease, diabetes, and stroke as covariates. HS: handgrip strength; LS: leg strength; SR: sit-to-stand rate; GS: gait speed; OT: one-leg stand time; MoCA: Montreal Cognitive Assessment; 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 odds ratio.

4. Discussion

The present study examined associations between five physical fitness measures and cognitive function in Japanese community-dwelling older people free from dementia. 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 and was also associated with the poor cognitive function defined by the MoCA score. These associations were independent of age, sex, years of formal education, BMI, and other confounding factors.

Examining lifestyle-related markers of cognitive functioning before the onset of dementia 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 pre-dementia cognitive impairment risk, research evidence is still limited. To our knowledge, only two studies have examined the potential role of physical fitness as a marker of pre-dementia cognitive impairment risk 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 from the Ginkgo Evaluation of Memory study group, the investigators used the 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 poor 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 cognition 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 pre-dementia cognitive impairment risk 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 similar associations of gait speed with global cognition as well as pre-dementia cognitive impairment risk in a Japanese older population free from dementia. Moreover, the present study further demonstrated novel associations of each of the other four physical fitness measures with global cognition and pre-dementia cognitive impairment risk in the Japanese population (Tables 3 and 4). A notable aspect of the present study is the use of the MoCA as a reasonable neuropsychological instrument to measure global cognition among the participants free from dementia. 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 cognition in population-based studies (Donoghue et al., 2012; King et al., 2013).

One possible mechanism underlying the observed associations is the concurrent deterioration of the brain regions responsible for cognitive and physical performance in the aging stage before the onset of dementia. 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.

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 dementia, 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 7). 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, $p<.01$; percentage of men: 50.8 vs. 41.8%, $p<.001$). 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%, $p<.005$; mean MoCA score: 21.8 vs. 22.4 years, $p<.001$). 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, especially to those outside of Japan, is limited. Therefore, further community-based studies in other populations should be performed to overcome this limitation.

5. Conclusion

In summary, the present study first demonstrated the associations of the five physical fitness measures with global cognition and pre-dementia cognitive impairment risk in Japanese community-dwelling older people free from dementia, independent of age, sex, years of formal education, body mass index, and other confounding factors.

Chapter 4

Overall discussion and conclusion

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The purpose of this doctoral thesis was to examine abilities of physical fitness measures as potential markers of pre-dementia cognitive impairment risk in community-dwelling older people. To address this purpose, two original studies were conducted. The first study investigated MoCA scores in Japanese community-dwelling older people free from dementia and determined pre-dementia cognitive impairment risk by defining poor cognitive function based on the MoCA normative data with respect to age and education. The second study examined associations between five physical fitness measures and cognitive function in Japanese community-dwelling older people free from dementia. This study found that each of the five physical fitness measures was linearly and positively associated with global cognition determined by the MoCA score, and was also associated with pre-dementia cognitive impairment risk determined in the first study, after adjusting for age, sex, years of education, BMI, and other confounding factors.

Based on the observed findings, this doctoral thesis offers a practical value of the physical fitness measures as objective means to assist identifying and monitoring early cognitive decline or pre-dementia cognitive impairment risk 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 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).

This doctoral thesis has some limitations which are worth noting here. First, although poor cognitive function defined as an indicator of pre-dementia cognitive impairment risk in the thesis is recognized as an established risk factor of dementia (Saxton et al., 2004; Tierney et al., 2005), we were unable to confirm its association with incident dementia

(or other phenotypes of clinical cognitive impairment) in the population. We are going to follow the community-dwelling older people in future prospective observations to examine the association to validate the practical significance of this index. Second, the doctoral thesis did not provide any normative data for the physical fitness measures, which may be required for practical assessment of pre-dementia cognitive impairment risk by these measures. Thus, we will try to develop these normative data in future studies. Finally, the present studies were conducted in the single Japanese town, generalizability of the present findings to other populations is considered limited. However, the findings may be able to be applicable to other places in Japan because ethnicity and social environment have been relatively homogeneous across Japan. In contrast, to confirm generalizability of the results to other regions outside of Japan, additional community-based studies should be performed in various populations across the world.

In conclusion, this doctoral thesis suggests that each of the five physical fitness measures has a potential ability as a single lifestyle-related marker of pre-dementia cognitive impairment risk in community-dwelling older people, and thereby can be used to help earlier detection of pre-dementia cognitive impairment risk in community-based preventive care. Further studies remain to be done to develop a specific method for detecting pre-dementia cognitive impairment risk with the physical fitness measures.

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