FRAILTY AND ITS ASSOCIATION WITH COGNITIVE FUNCTION AMONG NON-DEMENTED JAPANESE COMMUNITY-DWELLING OLDER ADULTS

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Doctoral Dissertation

FRAILTY AND ITS ASSOCIATION WITH COGNITIVE FUNCTION AMONG NON-DEMENTED JAPANESE COMMUNITY-DWELLING OLDER ADULTS

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Abstract

Frailty is a very important clinical syndrome and common in older adults. Development and/or improvement in available tools for frailty screening enables early and accurate detection of frailty in the primary care settings. The frailty phenotype proposed and validated by Fried and colleagues is the most commonly used definition in community settings worldwide, which defines the presence of frailty and pre-frailty using five core components of the frailty cycle: unintentional weight loss, low grip strength, exhaustion, low gait speed, and low physical activity. The low physical activity component of the frailty phenotype has been assessed with various self-reported questionnaires, which are prone to possible recall bias and a lack of diagnostic accuracy. In additions, in spite of widespread diffusion, the frailty phenotype was argued to place too much emphasis on physical losses of the older people. Recently, there is increasing research focus on the relationship between frailty and cognition, both of which are common but yet least understood in older adults. Although the available evidence from previous epidemiological studies have consistently shown that frailty can be presented in dementia patients at various stages including pre-dementia states, the evidence of the role of frailty on cognitive function amongst non-demented or cognitively healthy subjects remains limited. With the recent exploration of the association between frailty and cognition, more fundamental unclear questions were come up with. Further studies are necessary to explore the relationship between subtle preventable cognitive decline and frailty and the specific domains involved amongst non-demented older adults, which would help to develop approach to preventing or slowing down the progression of both of the two

conditions.

The general purpose of this research, using epidemiological observational data from a large cohort of community-dwelling elderly persons, was to provide empiric evidence of frailty and its association with cognitive function. The specific aims were to 1) better facilitate the screening of frailty by defining the low physical activity using a tri-axial accelerometer and examine the correlates of frailty; 2) explore the association between frailty and global cognitive performance and specific cognitive domains among non-demented community-dwelling older adults, which may indicate possible common pathways that can be targeted in interventions for both of these two conditions.

Data were drawn from the baseline survey of the Sasaguri Genkimon Study, a cohort study carried out in a west Japanese suburban community. Frailty phenotypes were defined by the following five components: unintentional weight loss, low grip strength, exhaustion, slow gait speed, and low physical activity. Of these criteria, physical activity was objectively measured with a tri-axial accelerometer. Global cognitive performance was evaluated using the Montreal Cognitive Assessment and the Mini-Mental State Examination. Firstly, a cross-sectional analysis including 1,527 community-dwelling older men and women aged 65 and over was conducted to screen for frailty. To confirm the measure's internal validity, a latent class analysis was performed to assess whether the five components could aggregate statistically into a syndrome. Then correlates of frailty was examined using multiple stepwise logistic regression models. Secondly, another cross-sectional analysis was performed among a sample consisted of 1,565 older adults with complete data and no evidence of dementia. Multinomial logistic regression

analyses were performed to examine relationship between total and domain-specific Montreal Cognitive Assessment and the Mini-Mental State Examination scores, and odds of pre-frailty and frailty.

In the study of screening for frailty with objectively-measured physical activity, the estimated prevalence of frailty was 9.3% (95% confidence intervals, CI, 8.4 - 11.2); 43.9% were pre-frail (95% CI, 41.5 - 46.4). The percentage of low physical activity was 19.5%. Objectively-assessed physical activity and other components aggregated statistically into a syndrome. Overall, increased age, poorer self-perceived health, depressive and anxiety symptoms, not consuming alcohol, no engagement in social activities, and cognitive impairment were associated with increased odds of frailty status, independent of co-morbidities.

In the study of examining the association between frailty and global cognitive function, total Montreal Cognitive Assessment and the Mini-Mental State Examination scores and their domain-specific scores decreased across the non-frail, pre-frail and frail groups. Poorer total Montreal Cognitive Assessment and the Mini-Mental State Examination scores, as well as their domain-specific scores, were associated with the greater likelihood of being frail, but not with pre-frailty after full adjustment. The strength of the association with frailty was greater for total Montreal Cognitive Assessment score than for the total Mini-Mental State Examination score. Domain-specific scores for visuospatial abilities and attention domains in both of the Montreal Cognitive Assessment and the Mini-Mental State Examination were consistently associated with the likelihood of pre-frailty and frailty, even after mutually adjusted for all domains.

To conclude, this research has contributed to the understanding of frailty and its association with cognition in several ways. The findings of the present research confirmed the internal construct validity of the frailty phenotype that defined the low physical activity domain with the objective measurement of physical activity. Accelerometry may potentially standardize the measurement of low physical activity and improve the diagnostic accuracy of the frailty phenotype criteria in primary care setting. The potential role of factors associated with frailty merits further studies to explore their clinical application. In addition, there are significant differences in global cognitive performance among the non-frail, pre-frail and frail subpopulations. The significant association of frailty and cognitive performance in non-demented population indicated that there could seemly be other intrinsic pathological/etiological pathways behind this link. Further studies are needed to disentangle possible common pathways that can be targeted in prevention and management for both of these two conditions.

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Abbreviations

95% CI = 95% Confidence Interval

AD = Alzheimer's Disease

AIC = Akaike Information Criterion

AIDS = Acquired Immunodeficiency Syndrome

BIC = Bayesian Information Criterion

BMI = Body Mass Index

CDR = Clinical Dementia Rating Scale

CHS = Cardiovascular Health Study

CSHA = Canadian Study of Health and Aging

CVD = Cardiovascular Disease

IADL = Instrumental Activities of Daily Living

K6 = Kessler Psychological Distress Scale

LCA = Latent Class Analysis

LSNS = Lubben Social Network Scale

MCI = Mild Cognitive Impairment

MMSE = Mini-Mental State Examination

MMSE-J = Japanese version of Mini-Mental State Examination

MoCA = Montreal Cognitive Assessment

OR = Odds Ratio

PAEE = Physical Activity Energy Expenditure

RR = Relative Risk

SD = Standard Deviation

SGS = Sasaguri Genkimon Study

VIF = Variance Inflation Factor

WHAS =Women’s Health and Aging Study

β = Unstandardized Regression Coefficient (beta)

Chapter 1. Introduction

The accelerated aging of the population is a worldwide phenomenon. The proportion of people aged 60 years and older worldwide is estimated at 12 percent in 2013, set to increase more rapidly in the next four decades to reach 21 percent in 2050 (United Nations. Department of Economic and Social Affairs Population Division 2013). In more developed regions, this proportion is expected to reach 32 percent in 2050. Not everyone can age successfully. Aging are notable for heterogeneity and vary widely from individuals to individuals (Shatenstein 2011). However, a substantial proportion of older adults will undergo chronic conditions or diseases, disability, declined cognitive and physical capacity, and less engage with life due to complex mechanisms of aging derived from underlying genetic and environmental factors (Rubinstein & de Medeiros 2014; Kirkwood 2005; Shatenstein 2011). The care burden for those populations who did not achieve successful aging have been consequently increased demands for medical and care resources and thus pose a great challenge to global public healthcare system (World Health Organization 2014; United Nations. Department of Economic and Social Affairs Population Division 2013). Earlier in 1990s, an American Medical Association white paper concluded the significance of preparing for the problems in caring for the elderly and emphasized the growing population of *frail*, *vulnerable* older adults, “the group of patients that presents the most complex and challenging problems to the physician and all health care professionals.” (Council on Scientific Affairs 1990)

1-1 Frailty, A Common and Important Clinical Syndrome

Medical practitioners have often used the term “frailty” to characterize the weak and vulnerable subgroups of older adults (Rockwood et al. 1999; Fried et al. 2004). The concept of “frailty” is a novel attempt to explain the heterogeneity of aging in older adults and is an important concept for clinical practitioners and policy-makers (Collard et al. 2012). Distinct from co-morbidity which refers to the concurrent occurrence of two or more distinguishably different disease processes, and disability which is the difficulty or inability to carry out activities of daily living (ADLs) or instrumental activities of daily living (IADLs), frailty is an important clinical entity with its own unique content and challenges in clinical management, although these concepts are interrelated and overlapping with each other (Fried et al. 2004). In the past two decades, investigators from many disciplines have contributed to better understanding of clinical and physiological characteristics of frailty and to highlight the vulnerability of frail older adults to poor health outcomes (Walston et al. 2006; Xue 2012; Clegg et al. 2013; Sourial et al. 2013; Panza et al. 2014). A consensus group consisting of delegates from 6 major international, European, and US societies, in a conference based on the International Association of Gerontology and Geriatrics and World Health Organization white paper in 2012, created a major consensus point of frailty that frailty is an important medical syndrome. In addition, they also reached a consensus on that simple screening tests are available to be used to recognize persons with frailty or at risk of frailty, and that all persons older than 70 years should be screened for frailty because frailty is a manageable condition (Walston et al. 2006). This group placed importance on defining frailty, as frail persons are high users of community resources, hospitalization, and nursing homes and early intervention with frail persons will assumedly improve quality of life and reduce costs of care (Walston et al. 2006).

Frailty is theoretically defined as a clinically recognizable state of increased vulnerability to stressors, characterized by decreased reserve capacity to maintain homeostasis resulting from age-related cumulative decline across multiple physiologic systems during a lifetime (Fried et al. 2001; Rockwood et al. 2004; Shamliyan et al. 2013; Clegg et al. 2013; Song et al. 2010). Figure 1-1 illustrates the status of vulnerability as comparing the changes in functional ability after a minor stress event in the fit elderly with changes in frail elderly (Clegg et al. 2013). Frailty confers higher risk of adverse outcomes, such as falls, delirium, disability, admission to long-term care, hospitalization, and decreased survival (Fried et al. 2001; Rockwood et al. 2004; Shamliyan et al. 2013; Clegg et al. 2013; Song et al. 2010). Frailty is common in patients with comorbidities. For example, according to a systematic review conducted for the call from the American Heart Association and the Society of Geriatric Cardiology, frailty is prevalent in patients with cardiovascular disease (CVD) and the combination of frailty and CVD is associated with a high risk for mortality (Afilalo et al. 2009), and relates to Acquired Immunodeficiency Syndrome (AIDS) (Althoff et al. 2014), respiratory impairment (Vaz Fragoso et al. 2012), chronic kidney disease (Roshanravan et al. 2012), dementia (Gray et al. 2013), and so on.

Frailty is a transitional state in a dynamic process that can improve or worsen over time (Lang et al. 2009). Previous studies have reported that transitions between overall frailty states (non-frail, pre-frail, frail) are fairly common, with individuals worsening or improving over time (Gill et al. 2006; Kressig et al. 2001; Espinoza et al. 2012). Pre-frail individuals have more than twice the risk of becoming frail compared with non-frail people (Fried et al. 2001). Results from a cohort study of 3,018 Chinese community-

living adults aged 65 years or older showed that the overall frailty status of approximately one fourth of the participants improved after 2 years of follow up (Lee et al. 2014). In other words, frailty can be prevented or even reversed before the onset of physical and/or mental disability, by exercise (Clegg et al. 2014), nutrition (Morley et al. 2013) and interdisciplinary intervention targeting identified characteristics of frailty and problems identified during geriatric assessment (Fairhall et al. 2015). Thus the intrinsic characteristic of frailty, such as its high prognostic value and its reversibility, renders significance to practice in primary care setting from the perspective of promoting successful aging and active life expectancy.

1-2 Main Operational Definitions and Proposed Models of Frailty

To our knowledge, frailty remains an evolving definition (Walston et al. 2006). While many efforts have been contributed to this emerging research field by researchers from diverse disciplines, there is no universal consensus regarding specific operational criteria in different practice settings. In an attempt to establish a standardized definition of frailty, Fried and colleagues proposed frailty phenotype in the Cardiovascular Health Study (CHS). They assumed that many of these factors are related and can be unified, theoretically, into a cycle of frailty associated with declining energetics and reserve. Given the increasing consensus that biomarkers of frailty include age-related declines in lean body mass, strength, endurance, balance, walking performance, and low activity, as shown in Figure 1-2, the frailty status is identified based on the presence of the following five components (Fried 2001): unintentional weight loss (indicative of chronic undernutrition), poor grip strength, exhaustion (suggestive of poor endurance and energy, as an indicator of VO_2 max), slow gait speed, and low physical activity. Individuals with

the presence of three or more affected components are considered as being frail; those with one or two affected components as pre-frail and those without absence of all components as not frail. This model has been the most widely used approach to the classification of frailty as a biological and functional limitation (Bouillon et al. 2013). Notably, having taken into consideration the fact that the frailty phenotype was developed in white population, we may point out that minor modification of frailty phenotype might be necessary in different populations since the lowest quintile approach of operationalized definition of frailty requires different cutoff points in different populations.

The cumulative deficit model is another widely accepted reliable frailty model, which was developed by Rockwood and colleagues in the Canadian Study of Health and Aging (CSHA) (Rockwood et al. 2005). In this model, the Frailty Index was proposed as a means of assessing individual aging, representing the aging process as the accumulation of deficits which, while age related, are not usually known as risks for diminished life expectancy (Mitnitski et al. 2001). The principle of the Frailty Index is to count cumulative deficits in health, including symptoms, signs, abnormal laboratory values, disease classifications, and disabilities (Searle et al. 2008). The more deficits a person cumulated, the more likely that person is to be frail (Rockwood & Mitnitski 2007).

As a matter of fact, the Fried's frailty phenotype and the Frailty Index have showed overlapping identification of a segment of population being frail and considerable convergence of predicting adverse health outcome (Rockwood, Melissa, et al. 2007). However, the frailty phenotype and the Frailty Index are different instruments for different purposes and are to be considered complementary in the evaluation of the older

person: the Frailty Index may summarize the results of a comprehensive geriatric assessment providing a marker of deficits accumulation, while the frailty phenotype categorically defines the presence/absence of a condition of risk for subsequent adverse events (Cesari et al. 2014).

Overall, although the complexity of frailty poses a challenge to traditional health care delivery, frailty as a diagnostic category with the accompanying risks and poor prognosis can be incorporated into many clinical decisions and discussions (Lacas & Rockwood 2012). More efforts need to be done to develop and/or improve available tools for frailty screening in the primary care setting, so as to facilitate its widespread application in the clinical practice in the primary care.

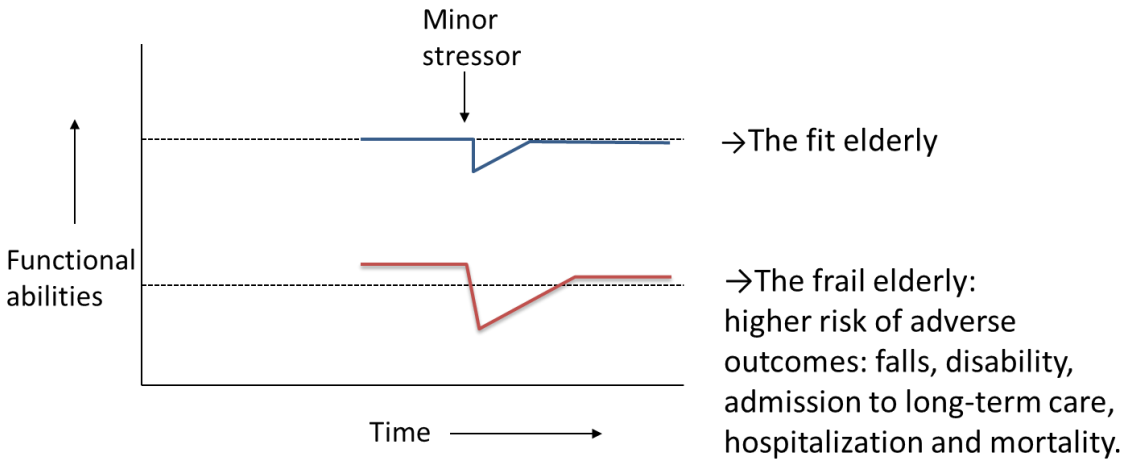

Figure 1-1 Vulnerability of frail elderly people to a sudden change in health status after a minor illness (From Clegg et al., 2013).

The blue line represents a fit elderly individual who, after a minor stressor event such as an infection, has a small deterioration in function and then returns to homoeostasis. The red line represents a frail elderly individual who, after a similar stressor event, undergoes a larger deterioration, which may manifest as functional dependency, and who does not return to baseline homoeostasis. The two horizontal dashed lines represent the homoeostasis level of functional abilities before the stressor event.

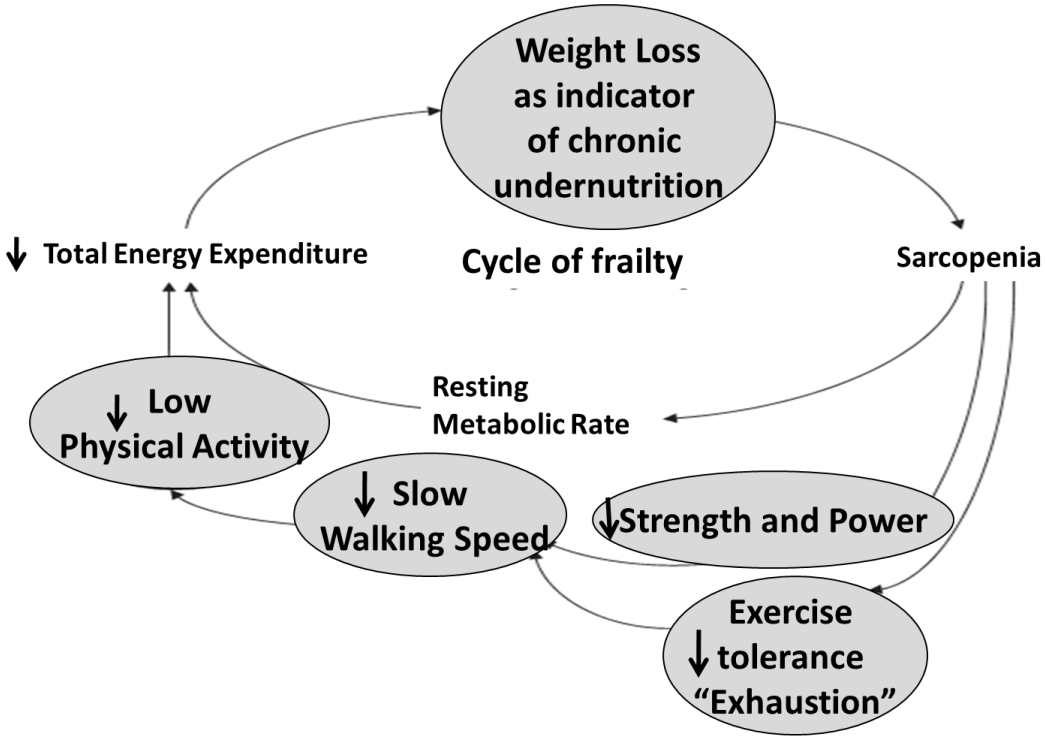

Figure 1-2 Cycle of frailty (From Fried 2001)

1-3 Prevalence and Correlates of Frailty

Early identification of subgroups of the population could be beneficial for planning for the capability of health and social systems to care for increasing numbers of frail older people over time (Syddall et al. 2010). Previous studies consistently demonstrated that frailty increased markedly with advancing age (Clegg et al. 2013). According to a recent systematic review, the prevalence of frailty in community-dwelling elderly adults differed enormously, ranging from 4.0% to 59.1%; as refining studies that used frailty phenotype, reported prevalence of frailty ranged from 4.0% to 17.0% and the weighted average prevalence was 9.9% with 95% confidence interval (CI) of 9.6-10.2 for frailty, and 44.2% (95% CI 44.2-44.7) for pre-frailty (Collard et al. 2012). The substantial discrepancies in data on prevalence of frailty could be to some extent assumedly explained by generally different operational definitions of frailty and inclusion or exclusion criteria.

Exploring factors that are associated with frailty is a basic research concern. Identification of correlates of frailty status facilitates the development of early preventive interventions of the occurrence of frailty. Studies exploring factors that are associated with frailty are essential to practically generate hypotheses for future study about causality to better predict risk of frailty or theoretically underpin the frailty model. Increased efforts are necessary to identify ways to better predict risk of frailty and to develop interventions to prevent the occurrence of frailty in the elderly, given the global trend of an aging population (Sourdet et al. 2012). Although research regarding potential risk factors of frailty and its possible causal relationship, which may be targeted in effective intervention and management, should have high priority, correlational studies of frailty are essential

to practically generate hypotheses for future study about causality and theoretically test/underpin the frailty model.

When restricted to studies that used frailty phenotype, data are largely from European and US Countries. In the CHS, the prevalence of frailty was 6.9% among 5,317 community-dwelling men and women aged 65 years and older, and individuals who were older age, male gender, being African American, having lower education and income, poorer health and higher rates of co-morbid chronic disease and disability were more likely to be frail (Fried et al. 2001). In the Women's Health Initiative Observational Study, a prevalence of 16.3% was estimated for frailty, and older age, co-morbidity, smoking, depressive symptoms, lower income, living alone and poorer self-reported health were associated with increased likelihood of frailty (Woods et al. 2005). A 7.5-year incidence of frailty was 9% among women who were non-frail at baseline in the Women's Health and Aging Study II (Xue et al. 2008). The prevalence of frailty in 10 European countries including Sweden, Denmark, the Netherlands, Germany, Austria, Switzerland, France, Italy, Spain, and Greece, was 4.1% for individuals aged 50 – 64 years and 17.0% for 65 years of age and older and demographic characteristics did not account for international differences in frailty rate except for education (Santos-Eggimann et al. 2009). Syddall et al. estimated a frailty prevalence of 8.5% among UK community-dwelling young-old (64–74 years) men (n = 320) and women (n = 318), and older age, younger age of leaving education, not owing/mortgaging one’s home and reduced car availability were associated with increased odds of frailty (Syddall et al. 2010). To date, there is a constellation of possible associated factors with increased frailty that have been reported, including less years of education, lower income, living alone, smoke, depressive symptoms, poorer self-

perceived health status, poorer social ties, disability, polypharmacy, cognitive function and co-morbidities (Kressig et al. 2001; Fried et al. 2001; Syddall et al. 2010; Chen et al. 2010; Jürschik et al. 2012; Castell et al. 2013; Garcia-Garcia et al. 2011; González-Vaca et al. 2014). However, findings on those health, social, environmental and psychological factors of frailty are inconsistent.

While non-modifiable risk factors of frailty status can be valuable in identifying individuals at risk of frailty and pre-frailty who can be targeted for appropriate interventions, better understanding potential modifiable risk factors and their specific contributions to development and transitions of frailty may be helpful to develop multidimensional approaches for prevention, evaluation and interventions of frailty. In addition, to some extent the intermediate status, pre-frailty, can provide an opportunity for potentially more effective intervention by reducing the likelihood of progression into the frail state, since frailty is not an irreversible process.

Japan is the most rapidly aging country and has the highest proportion of elderly people in this world (Japan Ministry of Health Labour and Welfare 2008). Investigation of potential correlates the frailty syndrome in the Japanese population could be potentially beneficial regarding of accelerating rapidly aging population worldwide. A prospective observational study in Japan revealed that timed walk, pulse pressure, cognition deficits and hearing deficit were associated with frailty and predicted a frailty incidence of approximately 16.0 % after 5-year follow-up based on the CSHA Clinical Frailty Scale, among 407 Japanese elderly people aged 70 and over, none of whom were frail at baseline (Doba et al. 2012). Shimada and colleagues estimated a prevalence of frailty of 11.3%

among 4,745 community-dwelling adults 65 years and older, average age 71 years, while correlates variables of frailty such as medical history and lifestyle were not available (Shimada et al. 2013). They defined frailty with Fried phenotype criteria but low physical activity was operationalized by two self-reported questions instead of calculation of energy expenditure and specific cutoff points was used for other components instead of lowest quintile approach. In a study of 444 older Japanese men and women aged 65–95 years, participants were classified into 4 subgroups: the non-frail, pre-frail, frail and independent using a health check-up questionnaire and Fried criteria together and reported a rate of 3% being frail (Nemoto et al. 2012). Taken together, Japanese studies on the prevalence and determinants of frailty remain inadequate and consequently limit the comparability of results between studies.

1-4 Overview of Available Evidence of Association between Frailty and Cognition

Another thing that represents major public healthcare priorities is dementia. Cognitive impairment, Alzheimer's disease (AD), and other subtypes of dementia remains one of the biggest global health challenges worldwide (Prince et al. 2014). In 2015, 46.8 million people worldwide are living with dementia and this number will almost double every 20 years (Prince et al. 2015). According to the National Livelihood Survey in 2013, dementia has been the second leading cause of placement in long-term nursing care in Japan, followed by frailty (Japan Ministry of Health Labour and Welfare 2014). Although disability trajectory is particularly heterogeneous and varies for different condition, the condition with the least variation was advanced dementia, which was characterized by high levels of disability throughout the last year of life (Gill et al. 2010). Cognitive decline in late life is associated with loss of functional independence in activities of daily living,

nursing home placement, and mortality (Yaffe et al. 2002; Yaffe et al. 2006; Gill et al. 2010). Recently there is increasing research focus how and at what point physical and cognitive decline influence one another, both of which are common but yet least understood in older adults (Tolea et al. 2015). Here this section will review the existing evidence on the association between frailty and cognition.

Evidence from Systematic/Narrative Reviews

Although a number of observational epidemiological studies have been conducted to explore the relationship between frailty and dementia/Alzheimer's disease risk, cognitive impairment, or cognitive decline, we could not find any meta-analyses performed in the existing few systematic or narrative reviews. The first critical review on the link between frailty and cognition was conducted in 2011 by Panza and colleagues (Panza et al. 2011). The authors summarized the findings of both cross-sectional and longitudinal studies that examined whether frailty related to different cognitive outcomes, including cognitive impairment or decline, predementia, and dementia. This review focused on the different models of frailty in predementia and dementia, highlighting the scarcity of information on the association and the significance of identifying possible links between frailty and cognitive impairment.

Two years later, Robertson and colleagues conducted a comprehensive review and retrieved relevant studies including those already contained within the previous review conducted by Panza et al., and several newly published papers (Robertson et al. 2013). They comprehensively reviewed the existing epidemiological and clinical studies which examined the associations between cognition and an operationalized definition of frailty

in the aging population except for specific patient population, although this review did not assess the quality of studies for study selection. The authors illustrated the significant association between frailty and cognitive impairment. Seven cross-sectional studies demonstrated higher rates of cognitive impairment in frail compared to pre-frail or robust older people. Twelve longitudinal studies have identified frailty as a predictor of dementia as well as more general cognitive impairment. The reciprocal relationship, that cognitive impairment indicates future frailty, has also been reported in three epidemiological studies based on samples of community dwelling older adults. The authors also summarized the results of studies that focused or relevant reported findings on mechanisms underlying this link. Mediators or possible pathways that have been proposed to explain the link between frailty and cognition contain AD pathology, hormones, nutrition, chronic inflammation, cardiovascular risks and mental health, but there is a lack of experimental evidence to support these suggestions. Studies which examined whether indicators of frailty are associated with cognitive impairment showed inconsistent results. In addition, only two epidemiological studies reported that frailty is associated with specific cognitive domains such as executive function, processing speed, attention. The authors suggested future studies are needed to understand the direction of the association, and the predictive value of frailty measures in identifying those at risk of preventable cognitive decline, such as subtle cognitive changes at early stage.

Finally, very recently two new critical reviews were published. Canevelli et al. retrieved 14 studies published from June 2013 to May 2014 (Canevelli et al. 2015). These 14 studies were mainly confirmatory of the previous studies. The authors highlighted the limited evidence on the interactions between frailty components and domain specific

cognitive function. Searle and Rockwood focused on frailty as a deficit accumulation, and reported a narrative synthesis of recent evidence of neuropathology data from community-based autopsy studies, which have shown that frail individuals have brains that show multiple deficits without necessarily demonstrating cognitive impairment (Searle & Rockwood 2015). The accumulation of neuropathological lesions in the aging brain linking frailty and cognitive impairment could be reflected more by physical frailty than by cognitive impairment. The authors proposed that frailty and cognitive impairment have shared mechanisms of accumulated deficits at molecular levels, cellular levels to tissue, and organ and system levels. The health deficits occur not just in late life, but throughout life course. In other words, when exploring approaches to preventing frailty and dementia, it is imperative to conduct studies in highly selected, younger, healthier individuals to provide 'proof of concept' information.

Evidence from New Studies

As discussed in the previous review, the frail older people scored lower on cognitive tests, and were more likely to be cognitively impaired, and had higher rates of dementia, compared to those who are pre-frail or non-frail in several cross-sectional studies that used frailty phenotype (Avila-Funes et al. 2009; Jürschik et al. 2012; Jacobs et al. 2011; Macuco et al. 2012; Yassuda et al. 2012; Ni Mhaoláin et al. 2011) and the Frailty Index (Rockwood, Melissa, et al. 2007; Armstrong et al. 2010), as well as other criteria (Bilotta et al. 2012). Furthermore, frailty has been reported to be a predictor of late-life cognitive impairment and decline (Auyeung et al. 2011; Lee et al. 2011), and incident dementia (Gray et al. 2013), vascular dementia (Avila-Funes et al. 2012; Solfrizzi et al. 2013) in a number of longitudinal studies that have used physical frailty phenotype. The Frailty

Index has also been reported to predict cognitive decline (Mitnitski, Fallah & Rockwood 2011; Mitnitski, Fallah, Rockwood, et al. 2011; Rockwood, Abeysundera, et al. 2007), mild cognitive impairment (MCI) (Boyle et al. 2010; Rockwood et al. 2005), and AD and other types of dementia (Song et al. 2011; Buchman et al. 2007; Buchman et al. 2008) in longitudinal studies. Additionally, the reciprocal relationship that Mini-Mental State Examination (MMSE) performance, and subjective cognitive changes predicted incident frailty has also been observed in large samples (Raji et al. 2010; Aranda et al. 2011; Doba et al. 2012). However, some large scale studies with longer follow-up periods reported that frailty was not significantly associated with cognitive decline (Samper-Ternent et al. 2008; Dramé et al. 2011) , and AD or other dementias except for vasular dementia (Avila-Funes et al. 2012; Gray et al. 2013; Solfrizzi et al. 2013). Cognitive performance assessed with the Minimum Data Set was not significantly predictive to the incidence of frailty either (Doba et al. 2012).

Several newly published population-based studies that were not included in previous reviews described above were identified. The main characteristics of these studies are described in Tables 1-1 and 1-2, without including those already contained within the previous review conducted by Robertson and colleagues (Robertson et al. 2013). Table 1-1 presents cross-sectional studies exploring the relationship between frailty and cognition. Shimada et al. observed that the combined prevalence of frailty and mild cognitive impairment was 2.7% in 5,104 Japanese elderly adults and frail elderly were more likely to have mild cognitive impairment (Shimada et al. 2013). Ferrer et al. also reported the overall prevalence of frailty combined with cognitive impairment, and dementia in older adults aged 86 years. Two studies explored the association of frailty with specific

cognitive domain of visuomotor speed and sustained attention (Rolfson et al. 2013; O'Halloran et al. 2014). Four studies mainly examined the relationship of frailty with the cognitive outcome defined as impairment in MMSE, performance in neurocognitive tests, and composite score of cognitive performance and cognitive domains among non-demented older adults (Kulmala et al. 2014; Robertson et al. 2014; Han et al. 2014; Wu et al. 2015). Two of the four studies were conducted in a large sample of 10,388 and 4,649 community-dwelling older people. In addition to cross-sectional studies, five new prospective studies were identified (Table 1-2). In the other four studies, the follow-up between baseline frailty status and cognitive outcomes ascertaining ranged from 1 to 10 years (Alencar et al. 2013; Song et al. 2014; Armstrong et al. 2015), as well as a new study testing the relationship between baseline cognition and transitions in frailty status (Lee et al. 2014). Alencar et al. found significant association between baseline frailty and subsequent cognitive decline in MMSE, while no association between frailty and cognitive decline measured by the Clinical Dementia Rating Scale (CDR) or between frailty and the incidence of cognitive impairment (Alencar et al. 2013). Song et al. found that the number of cumulated deficits as one increment increased in Frailty Index predicts incident dementia with 10-year follow-up in the CSHA, with age-adjusted odds ratios of 1.18 (95% CI 1.12 to 1.25) in men and 1.08 (95% CI 1.04 to 1.11) in women (Song et al. 2014). In the Honolulu-Asia Aging Study, two follow-up periods were separately considered to address the stochastic nature of transitions in cognition given a possible situation that people who improved in cognition at the beginning during a period time of follow-up, may experience greater subsequent decline later in cognition (Armstrong et al. 2015). Baseline frailty was found to be associated with an increased risk of cognitive decline at 3 years ($\beta = 0.18$, 95% CI 0.08 - 0.29) and at 6 years ($\beta = 0.40$, 95% CI 0.27 -

0.54). There was notable heterogeneity across previous studies that may be largely attributable to the inclusion criteria regarding age and cognitive status for sampling which may greatly confound results, length of follow-up period, and the assessment of frailty and cognitive outcomes. In view of the growing interest on this topic, the cognitive outcomes in recent studies exploring the relationship are shifting from cognitive impairment or dementia towards cognitive capacity/reserve amongst cognitively healthy/non-demented populations. Particularly, some domain specific cognitive functions frequently decline prior to other domains at the early stage of physiologic and mental degeneration. Increasing interests are arising in interactions between these cognitive domains and frailty. However, available evidence remains limited.

To summarize, frailty is a very important clinical syndrome and common in older adults. Development and/or improvement in available tools for frailty screening in the primary care setting enables early and accurate detection of frailty in the primary care. Although the available evidence from previous epidemiological studies have consistently shown that frailty can be presented in dementia patients at various stages including pre-dementia state, the evidence of the role of frailty on cognitive function amongst non-demented or cognitively healthy subjects remains limited. With the recent exploration of the association between frailty and cognition, more fundamental unclear questions were come up with. That is, for example, the direction of the association, how low cognitive performance influenced transitions from non-frail state to being pre-frail or frail and how being pre-frail or frail related to cognitive performance changes over time, and which specific cognitive function could be strongly associated with the risk of frailty, and vice versa. Further studies are necessary to explore the relationship between subtle cognitive

decline and frailty and the specific domains involved amongst non-demented older adults, which would help to develop approach to preventing or slowing down the progression of both of the two conditions.

1-5 Purpose

The general purpose of this research, using epidemiological observational data from a large cohort of community-dwelling elderly persons, was to provide empirical evidence of frailty and its association with cognitive function. The specific aims were to 1) better facilitate the screening of frailty and examine the correlates of frailty, and to 2) explore the association between frailty and global cognitive performance, and specific cognitive domains among non-demented community-dwelling older adults, which may indicate possible common pathways that can be targeted in interventions for both of these two conditions.

Table 1-1 Frailty and cognitive performance, cognitive impairment or dementia: new evidence from cross-sectional studies

Author and year	Study (design) & participants	Frailty measure	Cognition measure (s)	Confounders	Main relevant findings
Shimada et al. 2013	Obu Study of Health Promotion for the Elderly in Japan, aged 65+, N = 5,104	Frailty phenotype	Diagnosis of MCI	Age, sex, education	The overall prevalence of frailty, MCI, and frailty and MCI combined was 11.3%, 18.8%, and 2.7%. Frailty associated with MCI (OR = 2.0, 95% CI 1.5-2.5)
Ferrer et al. 2013	Octabaix study, community-dwelling older adults aged 86 years, N = 273	Frailty phenotype	Diagnosis of dementia	None	The overall prevalence of frailty and cognitive impairment (MMSE< 24) and frailty and dementia combined was 55.4%, and 26.8%, respectively
Rolfson et al. 2013	Oxford Project To Investigate Memory and Aging, aged 65+, N = 236	Frailty phenotype, EFS and frailty index,	MMSE and visuomotor speed	Age, sex, education	Visuospeed associated with frailty index and frailty phenotype, while a relationship was only observed in the frailty index after adjusting for MMSE
Kulmala et al. 2014	Good Care of the Elderly Study, in Finland, aged 76–100 years, N = 654	Frailty phenotype	MMSE and Clinical diagnosis of dementia	Age, gender, length of education, smoking status, chronic conditions and medications.	Frail persons have MMSE impairment (OR 7.8, 95% CI 4.0–15.0), dementia (OR 8.0, 95% CI 4.0–15.9), VaD (OR 5.6, 95% CI 1.2–25.8) and Alzheimer's disease (OR 4.5, 95% CI 2.1–9.6) than persons who were robust
Han et al. 2014	Living Profiles of Older People Survey in South Korea, community dwelling older adults, aged 65+, N = 10,388	Frailty phenotype	MMSE	Age, sex, marital status, education, income, employment, smoking, drinking, self-rated health, depression, BMI, ADL, IADL, the number of comorbidities	Cognitive impairment was associated with an increased risk of frailty in men (OR = 1.81, 95% CI 1.25–2.60)

Table 1-1 (Continued.)

Author and year	Study (design) & participants	Frailty measure	Cognition measure (s)	Confounders	Main relevant findings
O'Halloran et al. 2014	Irish Longitudinal Study on Ageing in Ireland, community dwelling adults aged 50+, N = 4,317	Frailty phenotype	Sustained attention to response task, cognitive processing speed and executive function	Age, gender, number of chronic conditions, and number of medications excluding supplements	Mean reaction time (OR = 1.72, 95% CI 1.03–2.86) was associated with frailty and fast frequency variability (OR = 1.43, 95% CI 1.07–1.91) with pre-frailty in the 65+ age group
Robertson et al. 2014	Irish Longitudinal Study on Ageing in Ireland, community-dwelling adults aged 50+, N = 4,649	Frailty phenotype	MMSE, MoCA, color trails test, Cambridge mental disorders of the elderly examination memory and executive function subtests, 10-word recall, sustained attention	Age, age-squared, sex, education, chronic conditions, and number of medications	Global cognitive function and all domains except self-rated memory and processing speed was significantly worse in pre-frail and frail group than robust group
Wu et al. 2015	I-Lan Longitudinal Aging Study in Taiwan, community-dwelling adults aged 50+ without dementia or cognitive complaints, N = 1,686	Frailty phenotype	MMSE, the delay free recall in verbal learning test, Boston naming test, verbal fluency test, Taylor complex figure test, digital backward, and clock drawing test	Age, gender, education, and the variables whose p value less than 0.1 for comparison between frailty groups	The pre-frail and frail persons had poorer MMSE performance and all neuropsychological scores, and showed a more dose-dependent risk for one or more cognitive domain impairments than the robust (OR = 1.28, 95% CI 1.03-1.60) in pre-frailty versus (OR = 1.79, 95% CI 1.05-3.04) in frailty

Notes. MMSE = mini-mental state examination; OR = Odds ratio; CI = confidence interval; MCI = mild cognitive impairment; ADL = activities of daily living; IADL = instrumental activities of daily living; VaD = vascular dementia; BMI = body mass index; MoCA = Montreal cognitive assessment; ID = intellectual disabilities; EFS = Edmonton Frailty Scales

Table 1-2 Frailty and cognitive decline, cognitive impairment or dementia: new evidence from longitudinal studies

Author and year	Study (design) & participants	Frailty measure	Cognition measure (s)	Confounders	Main findings
Alencar et al. 2013	Jenny de Andrade Faria Institute of Elderly and Women's Healthcare in Brazil, Baseline age: 65+ N = 207 Follow up: 1 years	Frailty phenotype	MMSE, CDR to determine cognitive impairment	Age, gender, schooling and marital status, nutritional status (BMI), hospitalization, falls and number of medications in regular use, depression, IADL, ADL, AADL	Frailty was associated with subsequent cognitive decline in MMSE (RR = 4.6; 95% CI 1.93–11.2). No association was found between frailty and cognitive decline measured by the CDR (RR = 2.1; 95% CI 0.68–6.7) or between frailty and the incidence of cognitive impairment (RR = 1.2; 95% CI 0.18–8.3).
Lee et al. 2014	Community-dwelling older adults in Hong Kong, Baseline age: 65+ N = 3,018 Follow up: 2 years	Frailty phenotype	MMSE	Age, gender, socioeconomic status, physical activity, mood symptoms, smoking, medical conditions, hospitalizations	Lower cognitive function was risk factors for worsening in the robust
Song et al. 2014	Canadian Study of Health and Aging, Baseline age: 65+ N = 7,239 Follow up: 10 years	Frailty index	3MS, clinical diagnosis of dementia	Age	The ORs per Frailty index increment were 1.18 (95% CI 1.12 to 1.25) in men and 1.08 (95% CI 1.04 to 1.11) in women in relation to dementia.
Armstrong et al. 2015	Honolulu-Asia Aging Study, Japanese-American men, Baseline age: 71-93 years N = 3,845 Follow up: 3 and 6 year	Frailty index	CASI	Age, education	Baseline frailty was associated with an increased risk of cognitive decline at 3 years (β = 0.18, 95% CI, 0.08 - 0.29) and 6 years (β = 0.40, 95% CI, 0.27 - 0.54).

Note. CDR = Clinical Dementia Rating Scale; IADL = instrumental activities of daily living; BADL = basic activities of daily living; AADL = advanced activities of daily living; MMSE = mini-mental state examination; OR = odds ratio; RR = relative ratio; CI = confidence interval; MCI = mild cognitive impairment; SPMSQ = Short Portable Mental Status Questionnaire; CASI = Cognitive Abilities Screening Instrument; 3MS = modified Mini-Mental State examination.

Chapter 2 - Study 1:

Screening for Frailty Phenotype with Objectively-Measured Physical Activity in Community-Dwelling Older Adults

The following article was originally published in the journal *BMC Geriatrics* and formatted for this dissertation.

S. Chen, T. Honda, T. Chen, K. Narazaki, Y. Haeuchi, A. Supartini and S. Kumagai. Screening for frailty phenotype with objectively-measured physical activity in a west Japanese suburban community: evidence from the Sasaguri Genkimon Study. BMC Geriatrics, 2015, 15:36.

2-1. Abstract

Background: The low physical activity domain of the frailty phenotype has been assessed with various self-reported questionnaires, which are prone to possible recall bias and a lack of diagnostic accuracy. The primary purpose of this study was to define the low physical activity domain of the frailty phenotype using accelerometer-based measurement and to evaluate the internal construct validity among older community-dwellers. Secondly, we examined potential correlates of frailty in this population.

Methods: We conducted a cross-sectional study of 1,527 community-dwelling older men and women aged 65 and over. Data were drawn from the baseline survey of the Sasaguri Genkimon Study, a cohort study carried out in a west Japanese suburban community. Frailty phenotypes were defined by the following five components: unintentional weight loss, low grip strength, exhaustion, slow gait speed, and low physical activity. Of these criteria, physical activity was objectively measured with a tri-axial accelerometer. To confirm our measure's internal validity, we performed a latent class analysis (LCA) to assess whether the five components could aggregate statistically into a syndrome. We examined the correlates of frailty using multiple stepwise logistic regression models.

Results: The estimated prevalence of frailty was 9.3% (95% confidence intervals, CI, 8.4-11.2); 43.9% were pre-frail (95% CI, 41.5-46.4). The percentage of low physical activity was 19.5%. Objectively-assessed physical activity and other components aggregated statistically into a syndrome. Overall, increased age, poorer self-perceived health, depressive and anxiety symptoms, not consuming alcohol, no engagement in

social activities, and cognitive impairment were associated with increased odds of frailty status, independent of co-morbidities.

Conclusions: This study confirmed the internal construct validity of the frailty phenotype that defined the low energy expenditure domain with the objective measurement of physical activity. Accelerometry may potentially standardize the measurement of low physical activity and improve the diagnostic accuracy of the frailty phenotype criteria in primary care setting. The potential role of factors associated with frailty merits further studies to explore their clinical application.

Keywords: frail older people; aging; prevalence; accelerometer; community health

2-2. Introduction

Frailty has been recognized as a biological syndrome (Clegg et al. 2013). It is theoretically defined as a clinically recognizable state of increased vulnerability to stressors, characterized by a decreased reserve capacity to maintain homeostasis resulting from an age-related cumulative decline across multiple physiologic systems (Clegg et al. 2013; Xue 2012). Frailty confers an increased risk of adverse health outcomes, including falls, delirium, disability, hospitalization, long-term care, and mortality (Fried et al. 2001; Song et al. 2010). The incidence and prevalence of frailty are expected to increase with population aging, which consequently poses a great challenge to public healthcare and social care systems as demands for medical and care resources increase (Collard et al. 2012). Therefore, early screening for frailty in routine clinical practice, especially in primary care settings, is of great significance considering its high prevalence, reversibility, and prognostic value (Castell et al. 2013; Iqbal et al. 2013).

The best evidence-based process to detect frailty and grade its severity is comprehensive geriatric assessment, but this is a resource-intensive process (Clegg et al. 2013; Iqbal et al. 2013). Although there is no universal consensus regarding specific operational criteria in different practice settings, two main operational definitions receiving broad acceptance are the frailty phenotype proposed and validated by Fried and colleagues in the Cardiovascular Health Study (CHS) and the Frailty Index proposed and validated by Rockwood and colleagues in the Canadian Study of Health and Aging (Fried et al. 2001;

Rockwood et al. 2005). The Fried frailty phenotype is the most commonly used definition in community settings worldwide (Bouillon et al. 2013). Compared to the Frailty Index, the frailty phenotype has been deemed more suitable for the immediate identification of non-disabled elders who are at increased risk for negative events, such as non-institutionalized community-dwellers (Rockwood, Melissa, et al. 2007; Cesari et al. 2014).

The CHS frailty phenotype defines the presence of frailty and pre-frailty using five core components of the frailty cycle: unintentional weight loss, low grip strength, exhaustion, low gait speed, and low physical activity. In this measure, the presence of three or more components indicates frailty, one to two components designates pre-frailty, and zero components specify that the individual is not frail. Of these five components, low physical activity has been assessed in previous studies using questionnaires, which seemingly are feasible for routine practice, but prone to possible recall bias and a lack of diagnostic accuracy and comparability between different questionnaires. Specifically, for the frailty phenotype, the physical activity energy expenditure was assessed with the Minnesota Leisure Time Activity questionnaire, which does not capture physical activities in contexts other than specific leisure physical activities included in the questionnaire (Fried et al. 2001). Furthermore, many studies have used various questionnaires containing different kinds of leisure physical activities from those of the CHS (Syddall et al. 2010; Avila-Funes et al. 2008; Garcia-Garcia et al. 2011; Shimada et al. 2013). The measurement of the low physical activity domain has not been standardized, which to some extent hinders the widespread application of the frailty phenotype in primary care practice. Thus, we addressed this issue in our study. We defined the low physical activity domain of the frailty phenotype using accelerometer-based measurement to detect frailty

and evaluated whether our measures could statistically aggregate into a syndrome on their own, among older community-dwellers in a suburban area in Japan. Secondly, we examined correlates of frailty across a constellation of social, psychological, environmental, and health-related factors.

2-3 Methods

Study population

Cross-sectional data were derived from the baseline survey of the Sasaguri Genkimon cohort study, an ongoing population-based prospective observational study (Narazaki et al. 2013). The cohort was recruited from the town of Sasaguri, a suburb of the Fukuoka metropolitan area on Japan's Kyushu Island. It is characterized as a region of low population mobility and a conventional Japanese lifestyle. The population of the town was 31,606 in January 2011 at the time of baseline survey. Based on data from the national census, the distributions of age, gender, education, and occupation in Sasaguri and for the whole of Japan are shown in Figure 2-1.

The inclusion criterion was all primary residents aged 65 years and older and the exclusion criterion was inhabitants placed in residential long-term care, as identified by the national long-term care insurance system. There were 4,979 potential participants, representing 15.7% of the residents in this district. We contacted all potential participants by sending brochures and questionnaires by mail, except for those who had died or moved out of the district (n = 66) since the time of baseline measurements. Of the 4,913 individuals we contacted, 2,629 completed questionnaires, for a response rate of 53.5%. Individuals who did not respond were older (74.1 ± 7.1 vs. 73.5 ± 6.2, p = 0.002) but there

was no gender difference for the respondents (p = 0.92). For the present study, we excluded those individuals who did not participate in any physical tests. In cases where frailty could potentially be a consequence of a single condition, we excluded subjects with a history of dementia, Parkinson's disease, stroke, or a Mini-mental State Examination (MMSE) score <18. This exclusion was based on the CHS exclusion criteria (Fried et al. 2001). Individuals with missing or invalid accelerometer data were also excluded. Among those who provided accelerometer data, 89.8% were adherent to the accelerometer protocol. The final sample consisted of 1,527 older men (n = 593) and women (n = 934) who had complete data for the other components of frailty (Figure 2-2). Comparisons of the characteristics between the excluded and included sample in this study were conducted (see Table 2-1).

Measures

Operational definition of the frailty phenotype

All five of the original components of the CHS frailty phenotype, as well as their methodology to produce population specific cut-off points were retained in our study. The operational definition of each component was as follows (see details in Table 2-2). Individuals with three, and one to two affected components of the frailty measures were respectively considered as frail and pre-frail (intermediate frailty status) and those without any affected components were considered not frail. Of note, we measured low energy expenditure of physical activity objectively with a tri-axial accelerometer (Active Style Pro, HJA350-IT, Omron Healthcare, Co. Ltd, Kyoto, Japan) for at least one week. The accelerometer data are known to be more accurate than estimates from self-reported

questionnaires and increasingly diffused in the general population (Murphy 2009). Low physical activity was defined as scoring in the lowest 20% of energy expenditure of physical activity per day, stratified by gender. The accelerometer computed energy expenditure using its built-in algorithm based on recorded intensity and duration of activities. Data were quantified as kilocalories per kilogram of body weight expended per day (kcal/kg/day). A valid day was defined by wearing the tri-axial accelerometer for more than 600 minutes. Participants with ≥ 3 valid days were eligible for all analyses.

Shrinking was defined as unintentional weight loss > 2–3 kg in the previous 6 months. This threshold is commonly accepted in Japan and was originally used as an indicator of nutrition for identifying vulnerable community-dwelling older adults in the long-term care insurance system by the Japan Ministry of Health, Labour and Welfare (Tsutsui & Muramatsu 2005; Fukutomi et al. 2013). This is similar to the original CHS definition of >10 lbs (4.5 kg) in the year prior (Fried et al. 2001). Weakness was defined as scoring in the lowest 20% of grip strength, measured by a handheld dynamometer (GRIP-D, T.K.K. 5401; Takei Scientific Instruments Co. Ltd, Niigata, Japan), and was stratified by gender and body mass index (kg/m^2). A measurement was taken for each hand, alternating between hands, and repeated again. We then averaged the greater values for both hands. Exhaustion was indicated by a positive answer to either of the following two self-reported questions. Participants were asked how they felt in the last one month: "Did you feel that everything you did was an effort?" and "Did you feel exhausted without any reason?" Slowness was identified as scoring in the slowest 20% of gait speed, based on the time for a 5-meter walking test at one's maximum walking speed, stratified by gender and standing height. Gait speed was measured by a standard test procedure using a stop watch,

as we have previously described elsewhere (Narazaki et al. 2014). Participants were instructed to walk eleven meters at their maximum speed, starting from a motionless standing position. The time was recorded between the third meter and the eighth meter.

Socio-demographic and socio-psychological variables

A questionnaire captured socio-demographic information about educational attainment (years of formal education), income status (very poor, poor/fair, or good), living alone (yes/no), employment status (yes/no), and housing tenure (owned/mortgaged, rented, or other). Participants' social networks were measured with the Japanese version of the Lubben Social Network Scale (LSNS-6), which is used worldwide as a screening tool for social isolation in community-dwelling elderly, and a cut-off score of 12 was adopted as recommended (Kurimoto et al. 2011). Self-perceived health was rated with a four-point scale asking how the respondent would rate one's general health. The possible answers were as follows: poor, fair, good, and very good. Respondents were categorized into two groups: poor/fair and good/very good. The Japanese version of the Kessler Psychological Distress Scale (K6) was used to measure depressive and anxiety symptoms. The K6 has been increasingly used in community settings with an optimal cut-off score of > 4 indicating depressive and anxiety symptoms in Japan (Sakurai et al. 2011).

Health behavioral variables and comorbidities

With respect to health behaviors the questionnaire also inquired whether participants currently smoked or drank and if they did habitual exercise, or had any hobbies (e.g., music, painting, gardening, writing, reading, photography, pottery), as well as about their frequency of going outdoors (once a week or less/more than once a week). The question

regarding engagement in any social activity (e.g., clubs for the elderly, volunteer work, religion-related activities, group activities, community activities, and business or professional activities) was answered with "yes/no." Self-reported medical history data on having been diagnosed with chronic diseases (high blood pressure, chronic heart disease, hyperlipidemia, diabetes mellitus, minor trauma fracture, depression, chronic pulmonary disease, digestive disease, chronic renal disease, osteoarthritis or rheumatism, and cancer) were recorded.

Cognitive, physical, and social function capacity variables

Measures of function capacity included cognitive function, instrumental activities of daily living (IADLs), intellectual activity, and social role limitations. Cognitive function was measured using the MMSE with a cut-off point of 23/24 points indicating cognitive impairment (Ideno et al. 2012). IADLs, intellectual activity, and social role limitation were measured with the 13-item Tokyo Metropolitan Institute of Gerontology Index of Competence, which focuses on the competence to perform tasks in studies of elderly community residents (Koyano et al. 1991). Negative responses indicating inability to perform a specific task or needing assistance with it were identified as a disability in that task.

Ethical Considerations

This cohort study protocol was approved by the Institutional Review Board of the Institute of Health Science Center, Kyushu University and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Statistical Analyses

To confirm our measure's internal construct validity, we performed latent class analysis (LCA) to assess whether the five components could aggregate statistically into a model. The goal of LCA is to identify clusters of similar type of observations, estimating the characteristics of these latent groups (Linzer & Lewis 2011; Linzer & Lewis 2013). The LCA hypothesis was that the population of older community-dwellers could be stratified into subpopulations characterized by sentinel patterns of aggregation of the frailty components with elimination of all confounding between the five frailty components (Bandeen-roche et al. 2006). We conducted the LCA in R version 3.1.2, using latent class analysis package version 1.4 (http://dlinzer.github.com/poLCA). We coded the five components as dichotomous variables to make a dataset for the LCA and computed the observed frequencies of 32 possible patterns of combinations of the frailty criteria. The LCA package in R used expectation-maximization and Newton-Raphson algorithms to find maximum likelihood estimates of model parameters. The appropriate number of latent classes was selected by comparing goodness-of-fit of models, including the most widely used parsimony measures of model fit: the Bayesian information criterion (BIC), Akaike information criterion (AIC), and Pearson's χ^2 (Linzer & Lewis 2011). Models that minimize values of the BIC and/or AIC were preferred.

Characteristics of participants were summarized by frailty status with means and standard deviation (SD) for continuous variables and frequencies with 95% confidence intervals (CIs) for categorical variables. Prevalence of frailty status was computed as percentages with 95% CIs. For associations of frailty with all independent variables, the p-value for the trend was assessed using the Cochran-Mantel-Haenszel test. Odds ratios and 95% CIs

for each factor were calculated using univariate logistic analyses and mutually adjusted multivariate logistic analyses with backward-elimination. Multicollinearity between independent variables was ruled out by a variance inflation factor (VIF) test, with a value less than 2 indicated as appropriate. To exclude the possible confounding influence of co-morbidities on the associations between independent variables and frailty, we adjusted for co-morbidities that were significantly associated with frailty by bivariate analyses: minor trauma fracture, high blood pressure, chronic heart disease, diabetes, chronic pulmonary disease, digestive disease, and osteoarthritis or rheumatism. Finally, to elucidate the potential influence of gender on correlates of frailty, we stratified the multivariate model by gender. The multivariate model was evaluated with the Hosmer-Lemeshow goodness-of-fit test and Nagelkerke's coefficient of determination. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, N.C., USA). The statistical significance was set at $p < 0.05$.

2-4 Results

Distribution of sample characteristics and prevalence of frailty

In this study, participants were 65 to 93 years of age, with a mean age (SD) of 73.3 (6.0) years and 38.8% were men. The mean (SD) of educational attainment was 11.1 (2.5) years. The percentages of frailty components were 19.5% for low physical activity, 14.8% for unintentional weight loss, 18.6% for low grip strength, 18.3% for exhaustion, and 17.1% for slow gait speed (Table 2-3). The mean (SD) length of accelerometer wearing time was 6.9 (1.6) days. In regards to the prevalence of frailty, 43.9% of the participants were

identified as pre-frail (intermediate frailty status). The rates of frailty stratified by gender were 9.3% for both men and women. Figure 2-3 shows the prevalence of frailty by gender and age group. The prevalence of frailty increased considerably with each successive 5-year age grouping. The two curves representing men and women were similar, whilst the percentage of frailty increased dramatically starting in the 75–79 age group for men and the 80–84 age group for women.

Internal construct validity of frailty criteria

We found that the one-class latent model did not produce adequate expected frequencies of the observed frailty patterns. Both two-class and three-class latent models demonstrated a good model fit (Pearson Chi square p = 0.43 and 0.53), indicating that our measures of the frailty phenotype, which defined the low physical activity domain with accelerometer-based measurement, could be aggregated statistically into a syndrome and demonstrated satisfactory internal validity (Table 2-4). Comparisons of the maximum log-likelihood, AIC, and BIC, did not reveal a better model fit for the three-class latent model than for the two-class latent model. In other words, our data did not suggest that the three-class phenotype was better than the two-class phenotype at stratifying people into subgroups characterized by sentinel patterns of aggregation of the frailty components. The increase of conditional probabilities of low physical activity from less-to-more frail classes within both the 2-class and 3-class models was similar to those of two other objectively-measured components: low grip strength and slow gait speed (data not shown).

Correlates of frailty

A trend test of all factors across frailty status revealed that those individuals who were identified as frail were older, less educated, more likely to be socially isolated, living alone, unemployed, currently not consuming alcohol, did not own or mortgage their own home, and had poorer self-perceived health and high levels of depressive and anxiety symptoms, than those who were not frail or pre-frail. They had significantly higher rates of functional limitations, including limitations in IADLs, intellectual activity, and social roles, as well as cognitive impairment. Those who did go outdoors less than once a week and did not engage in any hobbies, habitual exercise, or social activities were more likely to be frail and pre-frail (see Table 2-5).

The odds ratio with a one-year increment in age was 1.26 (95% CI, 1.22-1.31) for being frail and 1.09 (95% CI, 1.07-1.11) for being pre-frail, compared with the non-frail subgroups, meaning 26% higher odds of frailty and 9% higher odds of pre-frailty per unit increase of age (Table 2-6: Model 1). Participants who claimed to currently consume alcohol had lower odds of being frail. Living alone was associated with an increased odds ratio of pre-frailty, but it was not significant for frailty. Engagement in social activities showed a marked 53% reduction in the odds of frailty in the population. Those who reported poorer self-perceived health were almost four times more likely to be frail and two times more likely to be pre-frail. Higher depressive and anxiety symptoms were associated with significantly higher odds of frailty and pre-frailty. Cognitive impairment was associated with higher odds of being frail after adjusting for co-morbidities. An adjustment for comorbidities in the second model (Table 2-6: Model 2) did not alter the variables that showed independent statistically significant associations with frailty and pre-frailty. Finally, we analyzed correlates of frailty by stratifying the data by gender to

examine its potential effect. Frailty was associated with living alone, not currently consuming alcohol, no engagement in social activities, social isolation, and cognitive impairment in women, but not in men (see Table 2-7). Adjustment for co-morbidities of each gender did not alter significant variables (data not shown).

2-5 Discussion

In this report, we defined the low physical activity domain of the frailty phenotype with accelerometer-based measurement and confirmed the statistical aggregation of the five components of the frailty phenotype into a syndrome using LCA models. The accelerometer-based measurement of the low physical activity domain could potentially be beneficial in improving the diagnostic accuracy of the frailty phenotype and increasing its feasibility in primary care practice. We observed that frailty affected approximately one out of ten elderly adults aged 65 and over in this community-dwelling population, in which the care burden of frailty is the focus of exponentially rising demands for public healthcare resources. We also found significant associations between frailty status and age, living alone, self-perceived health, depressive and anxiety symptoms, current alcohol consumption, engagement in social activities, and cognitive impairment, independent of co-morbidities.

The CHS frailty phenotype has been shown to have satisfactory internal validity in the Canadian Study of Health and Aging (Rockwood, Melissa, et al. 2007). Prior LCAs of the frailty phenotype have been performed in the Women's Health and Aging Study (WHAS) and the Survey of Health, Ageing and Retirement in Europe and have demonstrated satisfactory internal validity (Bandeen-roche et al. 2006; Romero-Ortuno

& Soraghan 2014). Likewise, using LCA, we found that the five frailty criteria aggregated statistically into a syndrome. We further observed that the estimated probabilities of low physical activity exhibiting within latent frail classes were similar to those of two other objectively-measured components, regardless of whether subjects were stratified into two or three latent classes. These results suggest that our measures have satisfactory construct validity and could be used in this population. Additionally, our results did not conclude that classifying subjects into three subgroups (or classes) was better than two subgroups in characterizing the population. However, the CHS frailty definition of three phenotypes has been reported to have acceptable criterion validity as it identifies a profile of adverse health outcomes (Fried et al. 2001; Rockwood, Melissa, et al. 2007; Avila-Funes et al. 2008; Bandeen-roche et al. 2006).

Our study established a frailty prevalence of 9.3%, which is in line with previous studies that defined frailty using Fried's criteria (Collard et al. 2012). Of note is that a large scale population-based survey in Japan reported a frailty prevalence of 11.3% based on the Fried phenotype among community-dwelling adults aged 65 years and older, which was slightly higher than the prevalence in our study (Shimada et al. 2013). Perhaps the discrepancy could be explained by the fact that they measured physical activities based on self-reported binary questions or that they did not use the lowest quintile approach for cut-off points. In the present study, we defined low physical activity with objective measurement and the percentages of low physical activity were 19.1% for men and 19.8% for women, which were generally lower than what was reported in the previous study. Many previous studies have reported proportions of low physical activity that range widely from 20% to 30% (Syddall et al. 2010; Avila-Funes et al. 2008; Bandeen-roche et

al. 2006; Santos-Eggimann et al. 2009). The large discrepancies between previous studies can at least be partly explained by the various methods used to measure physical activity, ranging from validated questionnaires to two simple questions. Limiting comparisons to studies that calculated energy expenditure with validated questionnaires and that used the lowest quintile approach seems likely to ensure that at least the populations identified are similar. However, essentially different questionnaires capture different types of leisure physical activities, for example, only six of the 18 leisure activities considered in the CHS were evaluated in the WHAS (Bandeen-roche et al. 2006), suggesting that different populations may be characterized as having low physical activity, even if the proportion of low physical activity would be similar, with respect to people's preferences for these activities.

The agreement between accelerometer- and questionnaire-based measurement of physical activity is relatively poor (Sabia et al. 2014). The cut-off points of energy expenditure of physical activity in this study were 6.20 kcal/kg/day for men and 7.13 kcal/kg/day for women. Obviously, the estimates of energy expenditure were much higher than those in the CHS, since tri-axial accelerometers are capable of recording energy expenditure derived from a variety of daily physical activities rather than specific physical activities. Although accelerometer-based measurement may be less comparable to existing or historical cohorts, this objective measure of low physical activity may potentially standardize measurement in future cohorts and improve diagnostic accuracy of the frailty phenotype. In addition, the objective measurement of physical activity using an accelerometer can be administered by non-professionals, which could possibly raise the feasibility of the Fried frailty criteria in primary care settings. In terms of different types

of accelerometers, bi- and tri-axial accelerometers are more accurate for assessing energy expenditure of physical activity in free-living conditions than the uni-axial accelerometer. The uni-axial accelerometer is unlikely to assess the energy expenditure of complex body movement with body axis rotation, because it only detects vertical acceleration of body movement. Old adults are usually engaged in low- and moderate- intensity daily physical activities. Therefore, we used tri-axial accelerometers in this study, since the tri-axial accelerometer can more accurately assess low-intensity activities by its specific algorithm for low-intensity physical activitiesas compared to the uni- and bi-axial accelerometer (Midorikawa et al., 2007; Rothney et al., 2008). Commercial products of tri-axial accelerometer devices have been increasingly distributed and available in the general population after validation, even in the form of smartphone applications (Nolan et al. 2013).

In CHS, participants who were taking Sinemet, Aricept and antidepressants were excluded, while we didn't collect the data of medication. We noticed that the rate of "weight loss" in CHS was lower than the rate in this cohort, and the rate of 14.4% in the Three-City Study, 12.7% in Women's Health and Aging Study, while close to 5.6% in the Irish Longitudinal Study on Aging. The differences between the populations may be an alternative explanation to this large discrepancy. And depression could be another explanation of the discrepancy of the proportion of "weight loss". However, in the final sample of this study, only 11 of 1527 individuals reported a medical history of having been diagnosed with depression which may not be adequate to explain this difference in the proportion of 'weight loss'. We speculate that the approach of this measurement could be another explanation. Theoretically, it is not the ideal approach regarding that 4.5kg of

weight loss in one year could be due to exercise instead of physical declines. The accurate measurement of "weight loss" might be low muscle mass, which is more consistent to "declines in lean body mass" in the theoretical frailty cycle hypothesized by Fried and colleagues. Low muscle mass is included in the definition of sarcopenia assessed by the dual X-ray absorptiometry or the bio-impedance analysis, although so far the level of feasibility of this objective measure is quite low in the practice.

It is intriguing that we found that the prevalence of frailty was similar in both genders. This finding was consistent with some reports (Garcia-Garcia et al. 2011; Chang et al. 2012), while a systematic review showed a greater difference in the weighted prevalence of frailty between men and women (9.6% vs. 5.2%) (Collard et al. 2012). The lack of a gender difference could be partly explained by the differences between North American or European and Japanese populations. Alternatively, there was a higher prevalence of frailty among men in our study than in other international studies. The age distribution for Japanese elderly men is different than for men from other nations: Japanese elderly men aged 65 years or older live longer and the proportion of the oldest old aged 80 years or older among elderly men is higher than those of men in many other nations (https://www.cia.gov/library/publications/the-world-factbook/geos/ja.html). The age distribution for elderly men in our study was similar to the national age distribution, as shown in Figure 2-1. Moreover, Japanese elderly men have reported a similar prevalence of sarcopenia with that of women (Yamada et al. 2013), which plays a central role in the pathogenesis of frailty (Fried et al. 2001).

We found many similarities between the results in our studies and those reported in

previous research (Avila-Funes et al. 2012), we found that the rate of frailty increased dependent on age after adjusting for co-morbidities. Frail individuals reported poorer self-perceived health (Castell et al. 2013). A possible reason for is that as the level of frailty increases, so does the tendency to rate their health poorly (Chang et al. 2012; Ament et al. 2012). Although we used a psychological distress scale to measure depressive and anxiety symptoms in our study, our result, which indicated a significant association with frailty, is in agreement with findings reported in previous studies using other depression measures (Garcia-Garcia et al. 2011; Jürschik et al. 2012; Woods et al. 2005). Living alone, another factor that has been found to be related to frailty, is related to poorer nutrition, which is a cardinal component of frailty (Fried et al. 2001). The diversity of social ties might exert a beneficial effect on frailty (Jürschik et al. 2012; Gobbens et al. 2010), while living alone may indicate poorer social ties (Kurimoto et al. 2011).

In agreement with some previous studies (Castell et al. 2013), we observed that frailty was unrelated to socioeconomic status, such as education, income, employment status, or house tenure. This may be explained by the universal health coverage of social health insurance in Japan, especially for the oldest elders, and by the equity in social economic conditions adequate to health maintenance (Ikegami et al. 2011). The observed associations between cognitive impairment and frailty could be explained by several mechanisms, such as Alzheimer's disease pathology, hormone dysregulation, and impaired nutrition (Robertson et al. 2013). Concordant with previous studies (Syddall et al. 2010; Gobbens et al. 2010), we also observed that current alcohol consumption was associated with lower odds of frailty. The association may be explained by an avoidance of alcohol (Woo et al. 2010) or a decrease of alcohol-related socialization among those

who were frail, in line with Japanese culture that people commonly believe drinking alcohol facilitates socialization and mutual understanding between individuals (Taguchi et al. 2014). Older adults who engaged in social activities were less likely to become frail. Frequent engagement in social activities could help to maintain physical and mental fitness (Fushiki et al. 2012) and then compensate for age-related decline in reserve and function. Another explanation is that withdrawal from social activities could be a behavioral precursor of frailty. These findings favored the notion that an overt state of frailty may be preceded by behavioral adaptation, such as withdrawal from social activities, made in response to declining physiologic reserve and capacity (Xue 2012). Early detection of frailty and pre-frailty before decreased reserves become more pronounced helps to shift towards more appropriate goal-directed and individualized care provision. The potential role of the correlates of frailty and pre-frailty in prevention and intervention merits further studies to explore their clinical application, since frailty is a reversible process.

Strengths and limitations

To our knowledge, this is the first attempt, to date, using a tri-axial accelerometer to define energy expenditure of physical activity for the frailty phenotype. We examined a wide range of potential correlates of frailty covering social, psychological, environmental, and health-related factors. This study also has several important limitations. The sample was not nationally representative. The cross-sectional design prevents conclusions of directional relationships. There might have been selection bias due to the relatively low participation rate. However, given the similar prevalence findings in our study and previous studies, we may extrapolate that potential response or selection biases would not

tend to lead to underestimation or over-estimation in the prevalence of frailty in this study.

2-6 Conclusions

In summary, we defined the low physical activity domain of the frailty phenotype with accelerometer-based measurement for detecting frailty. We confirmed that five frailty components can statistically aggregate into a syndrome, providing evidence for the internal construct validity of our measures. Objective measurement may potentially standardize the low physical activity component and improve diagnostic accuracy of the frailty phenotype. Frailty is prevalent in this community-dwelling population. We also found significant associations between frailty status and age, living alone, self-perceived health, depressive and anxiety symptoms, current alcohol consumption, engagement in social activities, and cognitive impairment, independent of co-morbidities. The potential role of those factors associated with frailty in the prevention and intervention of frailty and pre-frailty merits further studies to explore their clinical application.

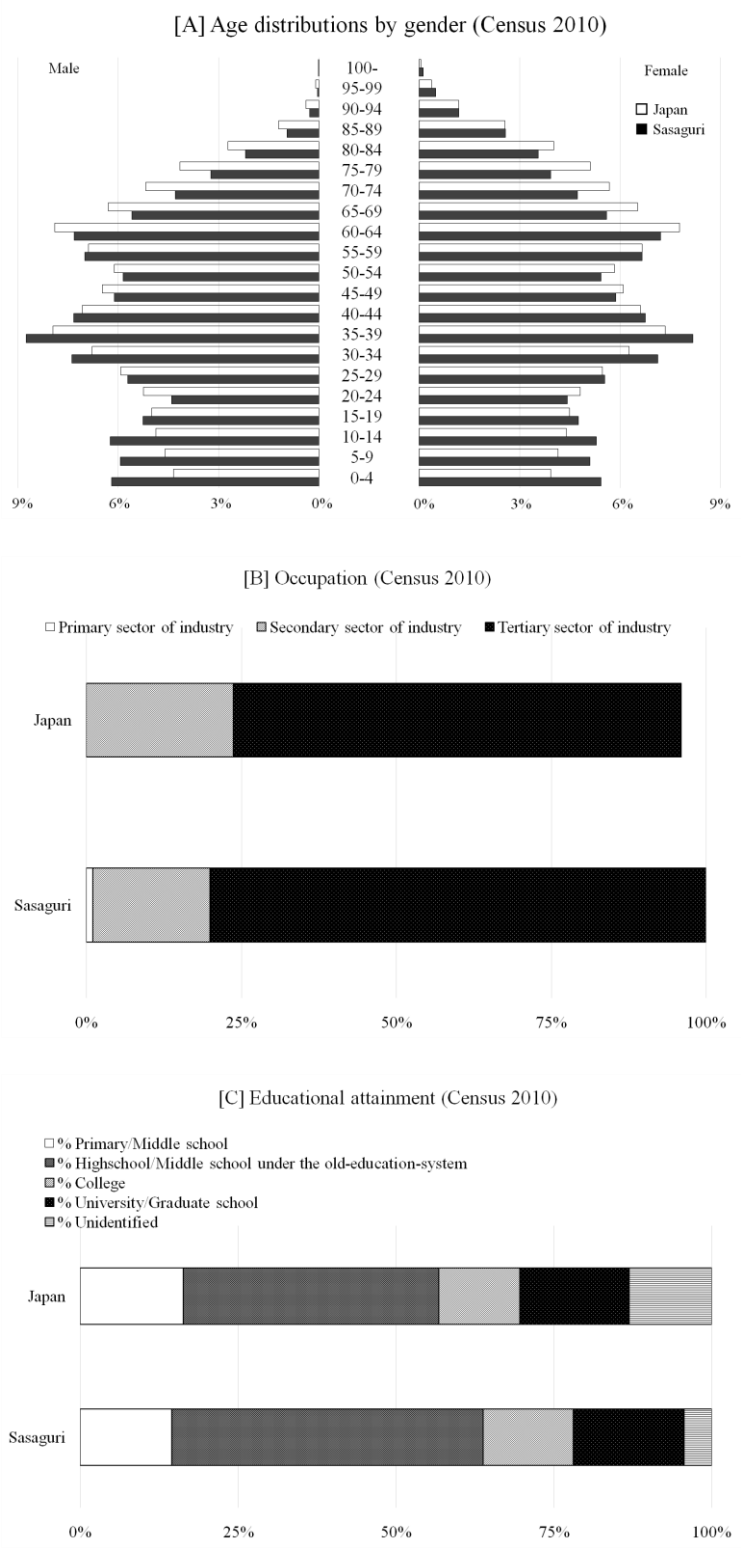

Figure 2-1 Comparisons of age (A), gender (B), education and occupational (C) distribution in the Sasaguri town and in the whole Japan in 2010 (National Census 2010)

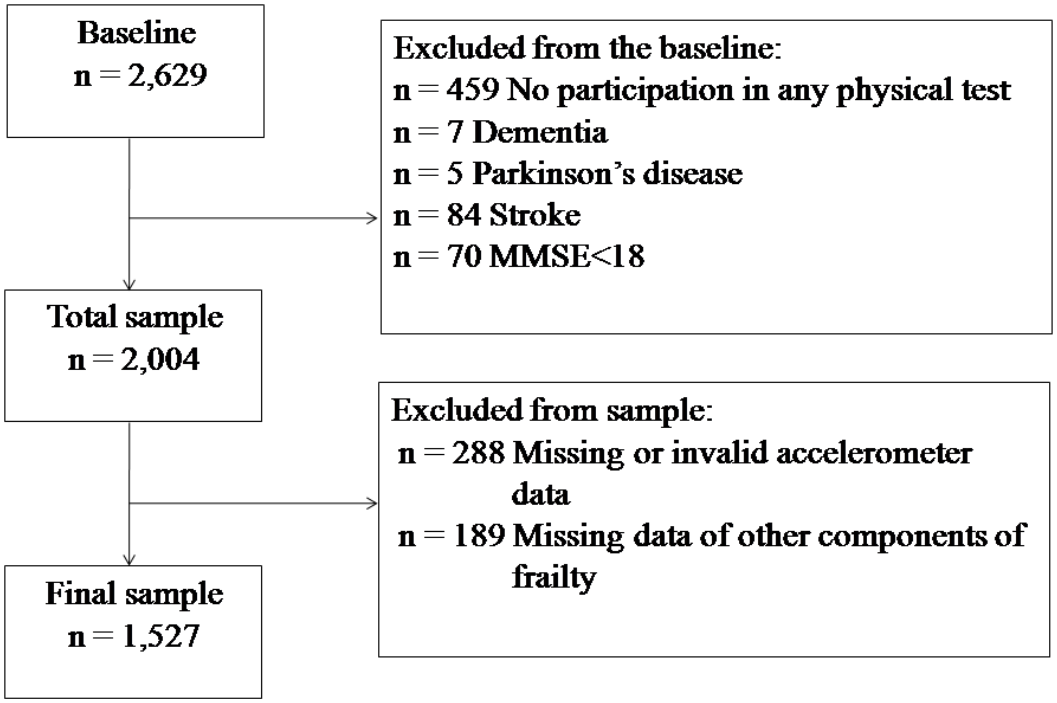

Figure 2-2 Assembly of the study sample

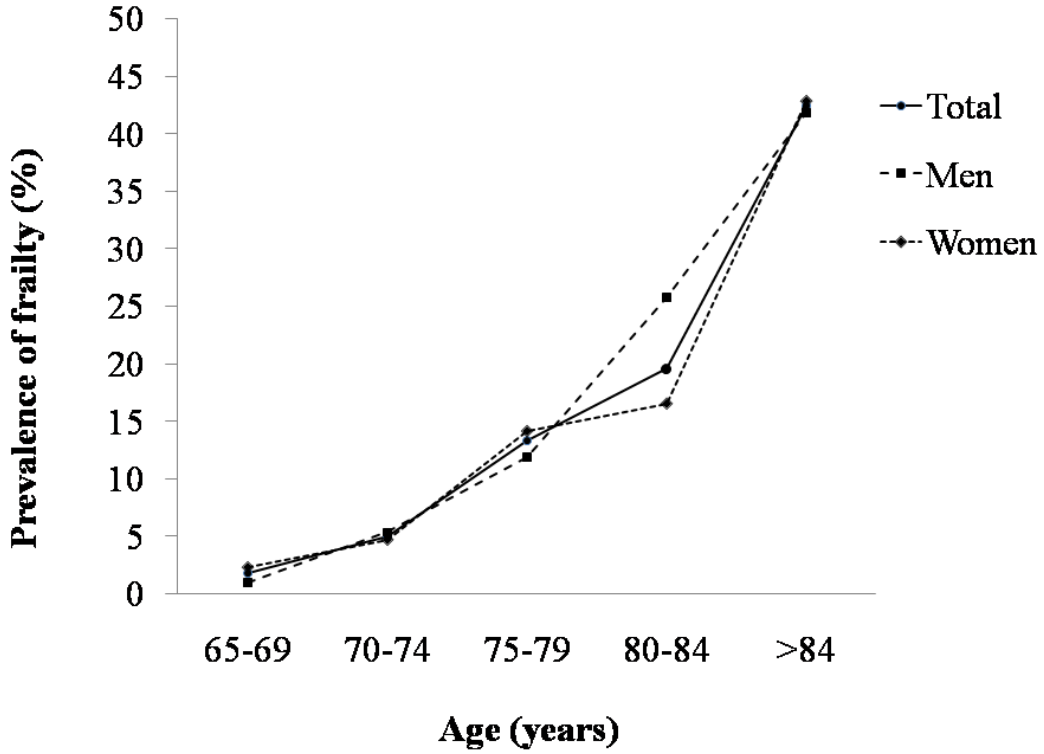

Figure 2-3 Estimated prevalence of frailty by gender and age in the Sasaguri Genkimon Study

Table 2-1 Comparisons between the excluded and included sample in this study.

	Excluded n=1,102	Included n=1,527	*p* value
Gender (% men)	50.3	38.8	<.001
Living alone, %	10.8	13.2	0.06
Income status (% very poor/poor)	65.0	60.2	0.02
Housing tenure (% owned/mortgaged)	13.8	9.9	0.002
Self-perceived health (% poor/fair)	24.1	20.1	0.02
Socially isolated (LSNS<12)	22.9	18.1	0.01
Currently employed, %	24.3	17.2	<.001
Current smoking, %	12.7	7.8	<.001
Current alcohol consumption , %	44.2	38.9	0.01
Going outdoors (% rarely)	9.7	4.3	<.001
Habitual exercise (% yes)	55.2	61.4	<.001
Engagement in social activities (% yes)	62.5	76.6	<.001
Having hobbies (% yes)	78.6	84.7	<.001
IADLs limitations (% difficulty ≥ 1 tasks)	15.0	8.3	<.001
Intellectual activity limitations (% difficulty ≥ 1 tasks)	35.2	27.0	<.001
Social role limitations (% difficulty ≥ 1 tasks)	50.4	39.4	<.001
Cognitive impairment (% MMSE score < 24)	15.0	4.7	<.001
	Mean (SD)	Mean (SD)	
Age, years	73.8 (6.5)	73.3 (6.0)	0.06
Education, years	11.0 (2.6)	11.1 (2.5)	0.31
K6 score, points	3.5 (3.8)	3.2 (3.4)	0.13

Note. LSNS = Lubben Social Network Scale; IADLs = Instrumental Activities of Daily Living; K6 = Kessler Psychological Distress Scale; MMSE = Mini-Mental State Examination

Table 2-2 Operational definition of frailty phenotype in Sasaguri Genkimon Study.

	Definition
Shrinking	Unintentional weight loss > 2–3 kg in the prior 6 months.
Weakness	Grip strength in the lowest 20%, stratified by gender and BMI (kg/m^2)
Male	≤ 25.00 kg for BMI < 18.5, ≤ 30.00 kg for 18.5 ≤ BMI < 25, ≤ 31.50 kg for 25 ≤ BMI < 30, ≤ 33.00 kg for BMI ≥ 30
Female	≤ 17.50 kg for BMI < 18.5, ≤ 19.50 kg for 18.5 ≤ BMI < 25, ≤ 20.50 kg for BMI 25 ≤ BMI < 30, ≤ 19.75 kg for BMI ≥ 30
Exhaustion	Positive answer to either of two self-reported questions. Participants were asked how they felt in last one month: "Did you feel that everything you did was an effort?", "Did you feel exhausted without any reason?"
Slowness	Time of 5-metre walk test at one's maximum waking speed in the highest 20%, stratified by gender and standing height (gender-specific cutoff: a medium height).
Male	Time ≥ 3.56 s for height < 162.0 cm or Time ≥ 3.21s for height ≥ 162.0 cm
Female	Time ≥ 4.25 s for height < 148.7 cm or Time ≥ 3.61s for height ≥ 148.7 cm
Low physical activity	Lowest 20% of energy expenditure of physical activity by a tri-axial accelerometer; quantified as kilocalories/kg (body weight), stratified by gender.
Male	≤ 6.20 kcal/kg/day
Female	≤ 7.13 kcal/kg/day
Overall frailty status	Non-frail: 0 affected component. Pre-frail: 1–2 affected components. Frail ≥ 3 affected components.

Table 2-3 Frailty phenotype components in percentages.

	Total n=1527	Men n=593	Women n=934
Frequency of individual criterion, %			
Shrinking	14.8	16.5	13.7
Weakness	18.6	17.9	19.1
Exhaustion	18.3	16.9	19.3
Slowness	17.1	16.9	17.2
Low physical activity	19.5	19.1	19.8
Number of frailty criteria present, %			
0	46.8	47.1	46.8
1	29.9	29.9	29.9
2	14.1	13.8	14.2
3	7.0	7.4	6.8
4	2.2	1.9	2.4
5	0.1	0.0	0.2
Prevalence of frailty status, %			
Pre-frail	43.9	43.7	44.1
Frail	9.3	9.3	9.3

Table 2-4 Latent class analysis model fit of frailty criteria (n=1,527).

	1-class model	2-class model	3-class model
Maximum log-likelihood	-3553.3	-3432.6	-3427.9
AIC	7116	6887	6889
BIC	7143	6945	6980
Pearson χ^2	262.5	21.5	13.0
	($p < 0.001$)	($p = 0.43$)	($p = 0.53$)

Notes: AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Table 2-5 Distribution of characteristics of the sample by frailty status.

Characteristics	Non-frail			Pre-frail			Frail			*p* for trend
	n	%	95% CI	n	%	95% CI	n	%	95% CI	
All	714	46.9	44.3-49.3	671	43.9	41.5-46.4	142	9.3	7.9-10.9	
Socio-demographic, socio-psychological factors										
Gender										0.88
Men	279	47.1	43.1-51.1	259	43.7	39.7-47.7	55	9.3	7.2-11.9	
Women	435	46.6	43.4-49.8	412	44.1	41.0-47.3	87	9.3	7.61-11.4	
Age (years)										<0.001
65-69	316	61.8	57.6-66.0	186	36.4	32.3-40.7	9	1.8	0.9-3.3	
70-74	220	52.0	47.3-56.7	182	43.0	38.1-47.8	21	5.0	3.3-7.5	
75-79	120	36.3	31.3-41.6	167	50.5	45.1-55.8	44	13.3	10.1-17.4	
80-84	47	24.8	19.3-31.5	105	55.6	48.4-62.5	37	19.6	14.6-25.8	
≥ 85	11	15.1	8.6-25.0	31	42.5	31.8-53.9	31	42.5	31.8-53.9	
Living alone										0.01
Yes	75	37.1	30.8-44.0	104	51.5	44.6-58.3	23	11.4	7.7-16.5	
No	639	48.2	45.5-50.9	567	42.8	40.2-45.5	134	8.9	7.6-10.6	
Education (years)										<0.001
< 11	432	54.6	51.1-58.1	318	40.2	36.8-43.7	41	5.2	3.8-7.0	
≥ 12	282	38.5	35.0-42.1	350	47.8	44.2-51.4	101	13.8	11.5-16.5	
Income status										0.60
Very poor/poor	415	46.0	42.8-49.3	404	44.8	41.6-48.1	56	9.2	7.5-11.3	
Fair/good	286	48.0	44.0-52.0	254	42.6	38.7-46.6	83	9.4	7.3-12.0	
Housing tenure										0.01
Owned/mortgaged	657	47.9	45.2-50.5	595	43.3	40.7-46.0	121	8.8	7.4-10.4	
Rented/other	56	37.3	30.0-45.3	75	50.0	42.1-57.9	19	12.7	8.3-18.9	
Self-perceived health										<0.001
Poor/fair	76	24.8	20.3-29.9	165	53.8	48.2-59.2	66	21.5	17.3-26.4	
Good/very good	638	52.4	49.6-55.2	504	41.4	38.7-44.2	75	6.2	4.9-7.7	
Psychological distress										<0.001
Yes (K6 > 4)	113	25.2	21.4-29.4	254	56.6	52.0-61.1	82	18.3	15.0-22.1	
No	601	55.8	52.8-58.7	417	38.7	35.8-41.6	60	5.6	4.4-7.1	
Socially isolated										<0.001
Yes (LSNS < 12)	85	30.9	25.7-36.6	142	51.6	45.8-57.5	48	17.5	13.4-22.4	
No	626	50.4	47.6-53.2	525	42.3	39.6-45.0	91	7.3	6.01-8.9	
Currently employed										<0.001
Yes	146	55.7	49.7-61.6	107	40.8	35.1-46.9	9	3.4	1.8-6.4	
No	566	45.0	42.2-47.7	561	44.6	41.8-47.3	132	10.5	8.9-12.3	
Health behaviors factors										
Current smoking										0.57
Yes	56	47.5	38.7-56.4	54	45.8	37.1-54.7	8	6.8	3.5-12.8	
No	655	46.7	44.1-49.3	613	43.7	41.2-46.3	134	9.6	8.1-11.2	

Table 2-5 (continued.)

Characteristics	Non-frail			Pre-frail			Frail			*p* for trend
	n	%	95% CI	n	%	95% CI	n	%	95% CI	
Current alcohol consumption										0.001
Yes	301	50.8	46.7-54.8	254	42.8	38.9-46.9	38	6.41	4.7-8.7	
No	413	44.3	41.1-47.5	416	44.6	41.4-47.8	104	11.2	9.3-13.3	
Going outdoors										<0.001
frequently	697	47.7	45.2-50.3	637	43.6	41.1-46.2	126	8.6	7.3-10.2	
rarely	16	24.6	15.8-36.3	33	50.8	38.9-62.5	16	24.6	15.8-36.3	
Habitual exercise										0.01
Yes	468	49.9	46.7-53.1	386	41.2	38.0-44.3	84	9.0	7.3-11.0	
No	246	41.8	37.9-45.8	285	48.4	44.4-52.4	58	9.9	7.7-12.5	
Engagement in social activities										<0.001
Yes	579	49.5	46.6-52.4	502	42.9	40.1-45.8	89	7.6	6.2-9.3	
No	135	37.8	32.9-43.0	169	47.3	42.2-52.5	53	14.9	11.5-18.9	
Having hobbies										<0.001
Yes	635	49.1	46.4-51.8	557	43.1	40.4-45.8	101	7.8	6.5-9.4	
No	79	33.9	28.1-40.2	113	48.5	42.2-54.9	41	17.6	14.2-23.0	
Function factors										
IADLs limitations (difficulty ≥ 1 tasks)										<0.001
Yes	41	32.5	25.0-41.1	64	50.8	42.2-59.4	21	16.7	11.2-24.1	
No	672	48.0	45.4-50.6	607	43.4	40.8-46.0	121	8.64	7.3-10.2	
Intellectual activity limitations (difficulty ≥ 1 tasks)										<0.001
Yes	166	40.3	35.7-45.1	196	47.6	42.8-52.4	50	12.1	9.3-15.6	
No	548	49.2	46.3-52.1	474	42.6	39.7-45.5	92	8.3	6.8-10.0	
Social role limitations (difficulty ≥ 1 tasks)										<0.001
Yes	224	37.3	33.6-41.3	295	49.2	45.2-53.2	81	13.5	11.0-16.5	
No	488	52.8	49.6-56.0	375	40.6	37.5-43.8	61	6.6	5.2-8.4	
Cognitive impairment (MMSE < 24)										<0.001
Yes	17	23.6	15.3-34.6	36	50.0	38.8-61.3	19	26.4	17.6-37.6	
No	697	47.9	45.4-50.5	635	43.6	41.1-46.2	123	8.4	7.1-10.0	

Note. 95% CI = 95% Confidence Interval; LSNS = Lubben Social Network Scale; IADLs = Instrumental Activities of Daily Living; K6 = Kessler Psychological Distress Scale; MMSE = Mini-Mental State Examination

Table 2-6 Variables showing statistically significant associations with frailty status (n=1459).

Variables	Pre-frail			Frail		
	Univariate OR (95% CI) for pre-frail vs. non-frail	Multivariate OR (95% CI) for pre-frail vs. non-frail		Univariate OR (95% CI) for frail vs. non-frail	Multivariate OR (95% CI) for frail vs. non-frail	
		Model 1	Model 2		Model 1	Model 2
Age , 1 year increment	1.09 (1.07-1.11)*	1.09 (1.07-1.11)*	1.09 (1.07-1.11)*	1.25 (1.21-1.30)*	1.26 (1.22-1.31)*	1.26 (1.21-1.32)*
Living alone (reference: no)	1.56 (1.14-2.15)*	1.47 (1.03-2.10)*	1.57 (1.09-2.25)*	1.65 (0.99-2.73)	1.08 (0.58-2.03)	1.23 (0.63-2.38)
Current alcohol consumption (reference: no)	0.84 (0.68-1.04)	0.91 (0.70-1.20)	0.91 (0.70-1.18)	0.50 (0.34-0.75)*	0.56 (0.33-0.93)*	0.54 (0.32-0.92)*
Engagement in social activities (reference: no)	0.69 (0.54-0.90)*	0.78 (0.58-1.05)	0.78 (0.58-1.05)	0.39 (0.27-0.58)*	0.49 (0.30-0.81)*	0.47 (0.28-0.78)*
Self-perceived health (reference: good/very good)	2.75 (2.04-3.69)*	1.94 (1.40-2.69)*	2.00 (1.42-2.81)*	7.39 (4.92-11.11)*	4.79 (2.90-7.91)*	3.69 (2.17-6.28)*
Depressive and anxiety symptoms (K6), 1 unit increment	1.24 (1.19-1.28)*	1.23 (1.17-1.28)*	1.23 (1.18-1.29)*	1.41 (1.34-1.49)*	1.38 (1.29-1.46)*	1.39 (1.30-1.48)*
Cognitive impairment (reference: MMSE $\geq$ 24)	2.32 (1.29-4.18)*	1.84 (0.95-3.57)	1.81 (0.93-3.54)	6.33 (3.20-12.50)*	2.36 (0.96-5.83)	2.73 (1.09-6.83)*

Note. The sample size decreased from 1527 to 1459 due to missing value of independent variables. *Significant association. OR = Odds ratio, 95% CI = 95% confidence interval, K6 = Kessler Psychological Distress Scale, MMSE = Mini-Mental State Examination. Model 1: Mutually adjusted, adjusted R^2 = 33.6 %; Model 2: further adjusted for co-morbidities, adjusted R^2 = 36.3 %

Table 2-7 Variables showing statistically significant and independent associations with frailty status by gender.

Variables	Pre-frailty Multivariate OR (95% CI) for pre-frailty vs. non-frailty	Frailty Multivariate OR (95% CI) for frailty vs. non-frailty
Female (n=934)		
Age, 1 year increment	1.10 (1.07-1.13)*	1.26 (1.20-1.33)*
Living alone (reference: no)	1.64 (1.09-2.46)*	1.11 (0.52-2.34)
Current alcohol consumption (reference: no)	1.08 (0.76-1.54)	0.34 (0.15-0.81)*
Engagement in social activities (reference: no)	0.74 (0.50-1.09)	0.41 (0.22-0.77)*
Socially isolated (reference: LSNS ≥ 12)	1.47 (0.93-2.32)	2.37 (1.20-4.70)*
Self-perceived health (reference: good/very good)	1.93 (1.26-2.95)*	4.98 (2.60-9.57)*
Psychological distress (K6), 1 unit increment	1.22 (1.16-1.29)*	1.37 (1.26-1.48)*
Cognitive impairment (reference: MMSE ≥ 24)	3.61 (1.28-10.20)*	4.76 (1.32-17.18)*
Male (n=593)		
Age, 1 year increment	1.07 (1.03-1.11)*	1.27 (1.20-1.35)*
Self-perceived health (reference: good/very good)	2.15 (1.28-3.62)*	3.74 (1.64-8.54)*
Psychological distress (K6), 1 unit increment	1.24 (1.15-1.34)*	1.44 (1.29-1.60)*

Chapter 3 - Study 2:

Global Cognitive Performance and Frailty on Non-Demented Community-Dwelling Older Adults

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3-1. Abstract

Background: To investigate associations of global cognitive performance with frailty and pre-frailty in non-demented community-dwelling older adults.

Methods: A cross-sectional study was conducted using data from the baseline survey of the Sasaguri Genkimon Study in 2011. The study sample consisted of 1,565 older adults with complete data and no evidence of dementia. Global cognitive performance was evaluated using the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE). Frailty state was defined using the Cardiovascular Health Study criteria, based on five components: unintentional weight loss, low grip strength, exhaustion, low gait speed, low physical activity.

Results: Total MoCA and MMSE scores and their domain-specific scores decreased across the non-frail, pre-frail and frail groups. Poorer total MoCA and MMSE scores, as well as their domain-specific scores, were associated with the greater likelihood of being frail, but not with pre-frailty after full adjustment. The strength of the association with frailty was greater for total MoCA score than for total MMSE score. Domain-specific scores for visuospatial abilities and attention domains in both of the MoCA and MMSE were consistently associated with the likelihood of pre-frailty and frailty, even after mutually adjusted for all domains.

Conclusions: The MoCA performance is more strongly associated with the odds of frailty

than the MMSE performance in the relatively functional and non-demented older adult population. Our findings may contribute to further exploration of possible common pathways that can be targeted in prevention and management for both of these two conditions.

Key words: aging; cognition; community health; frailty; pre-frailty

3-2. Introduction

Frailty is a clinically recognizable state of increased vulnerability to poor resolution of homoeostasis after a stressor event, which confers increased risk of adverse health outcomes through subtle and progressive physical changes (Fried et al. 2001; Clegg et al. 2013). Recently, there is increasing research focus on the relationship between cognitive impairment and frailty, both of which are common but yet least understood in older adults (Clegg et al. 2013; Robertson et al. 2013). Several longitudinal studies have shown that frailty is a possible early predictor of cognitive decline, mild cognitive impairment, and overall dementia and its subtypes in non-demented older population (Boyle et al. 2010; Buchman et al. 2007; Avila-Funes et al. 2012). On the other hand, cognitive impairment or dementia can predict future incidence of frailty (Robertson et al. 2013; Doba et al. 2012; Raji et al. 2010). These associations raise the possibility of more effective intervention for both cognitive decline and frailty or its intermediate status, the so-called pre-frailty, which could be beneficial to the public health system (Robertson et al. 2013).

Although many previous studies have examined the associations between frailty and cognition, most of them have focused on dementia, or global cognitive impairment assessed with the Mini-Mental State Examination (MMSE) (Robertson et al. 2013; Raji et al. 2010; Samper-Ternent et al. 2008; Mitnitski, Fallah, Rockwood, et al. 2011). Given that different global cognitive tests incorporate different cognitive domains, using different global cognitive tests could contribute to further exploration of the relationship between cognition and frailty, which may indicate possible common pathways that can be targeted in interventions for both of these two conditions. The Montreal Cognitive

Assessment (MoCA), another widely accepted brief screening test for global cognition, has been reported to be sensitive to generalized subtle cognitive changes (Fujiwara et al. 2010). Compared with the MMSE, the MoCA includes more sensitive tests of executive, visuospatial and attention domains (Julayanont et al. 2013). These domains of cognition were reported to be related to frailty (Boyle et al. 2010; O'Halloran et al. 2014), as well as individual components of frailty (Yassuda et al. 2012; Martin et al. 2013). Thus, the MoCA and the MMSE may present different clinical relevance with frailty or pre-frailty. In addition, few studies have examined global cognitive performance in pre-frail individuals, as well as in frail individuals amongst relatively functional and non-demented older populations (Macuco et al. 2012; Robertson et al. 2014).

Therefore, the primary purpose of this study was to investigate the associations of the MoCA scores with frailty status in relatively functional and non-demented older adults, which, to our knowledge, has never been reported. We anticipated that the MoCA scores would be more strongly associated with frailty status than the MMSE scores. In this study, we also examined which domain-specific cognitive scores would be the ones driving the relationship between frailty status and cognition.

3-3. Methods

Study population

Data were from the baseline survey of the Sasaguri Genkimon Study (SGS), which was conducted in 2011. The SGS is an ongoing community-based prospective study, conducted in the Sasaguri Town, located in the east of Fukuoka in Japan, as described elsewhere (Narazaki et al. 2013). Subjects were all inhabitants aged 65 and over without

being certified as needing long-term care (n = 4,979). After excluding those who died or moved out of the district (n = 66), 2,629 responded, presenting a response rate of 53.5 percent. Those who did not respond were older than respondents (74.1 ± 7.1 vs. 73.3 ± 6.2, p = 0.002) but were not different in gender distribution (p = 0.92) from the respondents. Of those, 1,618 had valid data for defining frailty. We further excluded those who did not complete cognitive tests (n = 27), and those who had a history of diagnosis of dementia or Parkinson's disease (n = 4) and depression (n = 11) and missing data of covariates (n = 11). The final sample consisted of 1,565 older adults without evidence of dementia. Comparisons between the excluded and included sample in this study were shown in the Table 3-1.

The SGS protocol was approved by the Institutional Review Board of Institute of Health Science, Kyushu University. Written informed consent was obtained from all participants.

Measures

Frailty

Frailty was defined according to Fried criteria with the following five components: (1) unintentional weight loss of > 2~3 kg in the previous 6 months, which is similar to the original definition of >10 lbs (4.5 kg) in the year prior1; (2) weakness: the lowest 20% of grip strength, measured by a handhold dynamometer (GRIP-D, T.K.K. 5401; Takei Scientific Instruments Co. Ltd., Niigata, Japan), stratified by gender and body mass index (kg/m2); (3) self-reported exhaustion: indicated by positive answer to either or both of the following two questions regarding awareness in the last one month: "Did you feel that everything you did was an effort?" and "Did you feel exhausted without any reason?"; (4)

slowness: the slowest 20% of gait speed in 5-meter walk test at one's maximum walking speed, stratified by gender and standing height; (5) low physical activities: the lowest 20% of energy expenditure of physical activity stratified by gender, assessed for one week with a tri-axial accelerometer (Active Style Pro, HJA350-IT, Omron Healthcare, Inc., Kyoto, Japan). Data were quantified as kcal/kg/day (body weight). A valid day was defined as wearing tri-axial accelerometer for more than 600 minutes. Participants with ≥ 3 valid days were eligible for all analyses. Individuals with ≥ 3 affected components were considered as frail. Individuals with 1 or 2 affected components were considered as pre-frail and those with no affected components were considered as not frail.1 We have reported the satisfactory internal validity of this operational definition of frailty in the SGS cohort somewhere else (Chen et al. 2015).

Global Cognitive Performance

Cognitive performance was evaluated using the Japanese version of the MoCA and MMSE. The Japanese version of the MoCA was translated from the original English version with cross-cultural adaptation, taking the number of syllables, category and frequency of linguistic equivalents into account (Fujiwara et al. 2010). It is a brief test assessing multiple domains: visuospatial abilities, short-term memory, executive function, attention, concentration and working memory, language and orientation. The MMSE consists of 11 subtests with coverage of cognitive domains including orientation, registration, attention, recall, language and visual-constructional ability (Ideno et al. 2012). Both of MMSE and MoCA are paper-and-pencil based tools that require 10 minutes to administer and their total scores range from 0 to 30 points with lower scores indicating poorer cognitive function.

Covariates

Potential confounding variables were selected based on previous literature, including age, gender, education (number of years of formal education), living alone, smoking, drinking, instrumental activities of daily living (IADLs, difficulty in one or more of five tasks from Tokyo Metropolitan Institute of Gerontology Index of Competence (Koyano et al. 1991) and a self-reported history of having ever been diagnosed with hypertension, stroke, chronic heart disease, diabetes mellitus, pulmonary disease, digestive disease, osteoarthritis, and minor trauma fracture.

Statistical Analysis

Characteristics of participants were summarized by frailty groups. The trends for these characteristics across frailty status were tested using the Jonckheere-Terpstra test for continuous variables and the Cochran-Armitage test for categorical variables. Total and domain-specific scores of the MoCA and MMSE were computed in non-frail, pre-frail, and frail groups, and trends across the frailty groups were examined with the Jonckheere-Terpstra test. The marginal mean of global cognitive scores adjusted for age, age squared, gender and education were used to describe the differences between frailty groups and p for trend was assessed using linear contrast tests across frailty categories.

Multinomial logistic regression analyses were performed to examine relationship between total and domain-specific MoCA and MMSE scores, and odds of pre-frailty and frailty. Because the MoCA and MMSE and their domain-specific scores occurred on different scale, these variables were converted into Z scores so as to facilitate comparisons

of the relative effects of each cognitive score on the frailty status. Thus, one unit increment in these variables represented an increase of 1 standard deviation (SD) from the mean. Akaike's Information Criterion (AIC) was used to compare models where global cognitive scores regressed on the frailty status, with lower AIC indicating a better model fit. We further performed Wald test to compare the strength of association of total MMSE and MoCA scores with frailty or pre-frailty. The null hypothesis of the Wald test was that standardized regression coefficients of MMSE and MoCA were equal. We then examined which domain-specific MoCA and MMSE scores were driving those relationships by mutual adjusting for all domain-specific scores along with all covariates.

Quadratic term of age (age squared) was included in adjusted regression models to account for a potential nonlinear effect of age on frailty. Interactions of cognitive scores with age, gender and education were also tested. Model assumptions were assessed graphically and analytically and were adequately met. Multicollinearity between independent variables in all multivariate models was ruled out by variance inflation factor test with value less than 2 indicated as appropriate. All statistical analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, N.C., USA).

3-4. Results

Overall, 1,565 participants were 65 to 93 years of age (mean 73.3 ± 6.0) and 2 to 22 years of education (mean 11.1 ± 2.5) and 40.0 % were men. The rate of pre-frailty and frailty were 43.9 % and 9.5 %, respectively. The cognitive scores were 22.1 ± 3.8 points for the MoCA and 26.6 ± 2.3 points for the MMSE, respectively. On average, frail participants were older, less likely to be current drinker, and had less years of education, higher

frequency of IADLs limitation and a history of stroke, chronic heart disease, diabetes mellitus, pulmonary disease, digestive disease, osteoarthritis, and minor trauma fracture than those who were not frail or pre-frail (Table 3-2).

There were statistically significant decreasing trends in absolute means for total MoCA and MMSE scores and their domain-specific scores across frailty groups (Table 3-3). The marginal mean scores in the frail group were 1.97 points (95 % CI, 1.20 - 2.74) lower on total MoCA score and 0.72 points (95 % CI, 0.23 - 1.22) lower on total MMSE score than those in the non-frail group with adjustment for age, age squared, gender and education.

In fully-adjusted multinomial logistic models, a 1-SD increase in total MoCA and MMSE scores was associated with 47% and 27% decreased odds of being frail respectively, where 'being not frail' was used as the reference category (Table 3-4). Neither the MMSE nor MoCA were significantly associated with pre-frailty. We further changed the reference category from "being non-frail" to 'being pre-frail', and observed that higher total MoCA and MMSE scores was associated with lower odds of being frail (data not shown). The Wald test showed that standardized regression coefficients of MMSE and MoCA differed significantly in differentiating the frail subgroup from the non-frail subgroup (Wald $\chi^2 = 10.4$, $p = 0.001$), indicating that the MoCA score was more strongly associated with odds of being frail than was the MMSE score, although those two coefficients were not different in differentiating the pre-frail subgroup from the non-frail subgroup (Wald $\chi^2 = 0.01$, $p = 0.92$). The AIC for both crude and adjusted models suggested that the MoCA provided better the model fit than the MMSE. No significant interaction terms of the MoCA and MMSE with age, gender, and education were observed.

All the domain-specific MoCA scores except for orientation were significantly correlated with the likelihood of frailty (Table 3-5, model a). Two domain-specific scores for visuospatial abilities and attention, concentration & working memory in the MoCA were significantly correlated with the likelihood of pre-frailty and frailty. These associations remained significant after mutually adjusted for all domain-specific scores. Domain-specific scores for visual-constructional ability and attention in the MMSE were associated with frailty as well, but only attention was associated with pre-frailty in mutually adjusted models (Table 3-5, model b).

3-5. Discussion

In the present study of 1,565 non-demented community-dwelling older adults, we observed that total MMSE and MoCA scores and their domain-specific scores decreased across the non-frail, pre-frail and frail groups, indicating a possible dose-response relationship between cognition and frailty status. Both of total MoCA and MMSE scores, as well as domain-specific MMSE and MoCA scores, were associated with the likelihood of being frail. We found that total MoCA score was more strongly associated with the odds of frailty than total MMSE score. Our results demonstrated that domain-specific scores for visuospatial abilities and attention domains were driving the relationship between frailty status and cognition.

The individuals being pre-frail had better MoCA and MMSE performance than the frail and poorer cognitive performance than the non-frail. The absolute difference in mean scores between the frail and the non-frail, which were 1.4 points in the MMSE and 3.7

points in the MoCA, were relatively smaller than previously reported in Brazil16 but greater than reported in Ireland population (Robertson et al. 2014). However, these mean differences actually represented approximately 0.6 and 1.0 SD respectively with respect to the distribution of global cognitive scores, which was suggestive of significant heterogeneity of cognitive function between frailty groups in this relatively functional population.

We found that poorer MoCA and MMSE scores were both significantly correlated with the higher likelihood of being frail, independent of age, gender, education, drinking, smoking, living alone, IADLs and a history of comorbidities. We also illustrated that the MoCA was more strongly associated with frailty than MMSE. This could be explained by the less variability in the MMSE scores in this population. The MMSE is reported to be less capable of testing for cognitive impairments in domains such as visual spatial/constructional ability, attention and executive function (Nys et al. 2005). For instance, the MMSE test has only one subtest (serial 7 subtractions) for attention while the MoCA test incorporates two additional subtests (digit span and target tapping defined as sustained and focused attention). In addition, the MMSE may be insensitive to subtle cognitive changes (Dong et al. 2010; Haley et al. 2012). Thus it may be difficult to capture small differences in cognition among non-demented and relatively functional population with this test. Practically it is recommended that persons with cognitive complaints and no functional impairment in activity of daily living would be better assessed by the MoCA as first cognitive screening, rather than the MMSE (Julayanont et al. 2013). Therefore, we may speculate that the MoCA may be more suitable to be applied to researches regarding the links between cognition and frailty among relatively functional and

dementia free populations, and to interventions for both of these two conditions in the primacy care practice.

Several common risk factors have been proposed to explain the relationship between cognition and frailty. For instance, vascular risk factors have been reported to be attributed to risk increase in both cognitive decline and frailty (Robertson et al. 2013). Chronic inflammatory and haemostatic abnormalities have been described in the pathogenesis of cognitive decline and frailty (Avila-Funes et al. 2012; Mulero et al. 2011). Other risk factors including hormonal dysfunction, nutrition, depression and social ties have been reported as well to relate to loss of cognition (Robertson et al. 2013; Buchman & Bennett 2012), which contribute to frailty through fatigue and impaired motor function (Han et al. 2014). Nevertheless, our data showed that the association of cognitive performance and frailty remained statistically significant in this older population who were non-demented and relatively functional. There could seemly be other intrinsic pathological pathways to explain this relationship instead of common risk factors mentioned above. This association merits further studies to explore the mechanisms in depth behind the link with taking these possible common risk factors into account.

Our results revealed visual-constructional ability and attention were significantly associated with the likelihood of being frail after mutually adjusted for all domains, suggesting that they were driving the relationship between frailty status and cognition. Inconsistently, prior studies observed significant associations of multiple cognitive domains, such as orientation, memory, registration and executive function, with frailty (Macuco et al. 2012; Robertson et al. 2014; Han et al. 2014). This discrepancy might be

partly explained by that participants in this study were non-demented and relatively functional without evident impairments in those cognitive domains. But our observation still concurs with findings from previous large scale studies that attention and visual construction were associated with frailty and pre-frailty (O'Halloran et al. 2014; Robertson et al. 2014; Han et al. 2014). Impairments in visuospatial function can be detected before any other cognitive deficits are observable for age-related cognitive decline and neurodegenerative disease (Studzinski et al. 2006), which may be a possible explanation of this observation. Visual spatial/constructional and attention (calculation, concentration and digit span) tasks require integration of visual and fine motor sequences and control, visuospatial imaginary and central executive processing and so forth, involving various brain areas such as the frontal lobe, parieto-occipital lobe, prefrontal and fronto-parieto-occipital cortices (Julayanont et al. 2013). Damage (i.e., neuronal loss) to the integrity in any related brain regions may simultaneously lead to visual spatial/constructional, attention and motor function impairment which is a prominent characteristic of physical frailty (Buchman & Bennett 2012). In support of this plausible explanation, prior studies have found that Alzheimer's disease pathology, macroinfarcts and nigral neuronal loss contribute to the simultaneous change in cognition and frailty in older adults (Buchman et al. 2014).

Of note, Fried and colleagues proposed the definition of frailty phenotype without cognition given the consideration of the strong impact of dementia and severe cognitive decline on the clinical presentations of frailty (Fried et al. 2001). Specifically, frailty could potentially be presented as a consequence of dementia or severe cognitive impairment. However, in this non-demented and relatively functional older population, out results

support the relationship between cognition and frailty. This relationship favors the notion that cognitive declines, particularly in some specific cognitive domains, and physical declines seemingly act synergistically in older people (Shatenstein 2011). More importantly, cognitive decline and frailty or pre-frailty are reversible. This relationship merits potentially effective intervention to interrupt the progression of both cognitive decline and frailty.

The strength of this study is its comprehensive physical assessment with objective measurement. The objective measurement of gait speed, and grip strength enabled the lowest quintile approach for cutoff points of frailty criteria in the Sasaguri Genkimon Study, which were very close to and to some extent prior to the original Fried criteria in terms of the objectively-measured energy expenditure of physical activity. The major limitation of this study is that we cannot rule out the possibility of undiagnosed dementia among participants included in the final sample, which may consequently increase the measurement error of self-reported measures. The sample is not nationally representative. The relatively low response rate could have led to overestimation of the lowest quintile values, and selection bias which may to some extent be attributable to the observed stronger association of the MoCA with frailty than the MMSE. Longitudinal studies are needed to observe patterns of changes in global cognitive performance and frailty over time.

3-6. Conclusions

In conclusion, our findings show that there are significant differences in global cognitive performance among the non-frail, pre-frail and frail subpopulations. The MoCA

performance is more strongly associated with frailty than the MMSE performance. Our data reveal that the visuospatial abilities and attention are driving the relationship between cognition and frailty/pre-frailty. Our results may contribute to further exploration of possible common pathways that can be targeted in prevention and management for both of these two conditions.

Table 3-1 Comparisons between the excluded and included sample in this study.

Variable	Excluded	Included	*p* value
Age (yr), mean ± SD	73.7 ± 6.5	73.3 ± 6.0	0.12
Men, %	49.1	40.0	< 0.001
Education (yr), mean ± SD	11.0 ± 2.6	11.1 ± 2.5	0.30
Living alone, %	10.9	13.1	0.09
Current smoker, %	13.1	7.6	< 0.001
Current drinker, %	43.5	39.4	0.04
IADLs limitation (difficulty ≥ 1 task), %	14.4	8.8	< 0.001
Hypertension, %	39.0	38.3	0.72
Stroke, %	4.3	3.6	0.39
Chronic heart disease, %	11.6	13.9	0.08
Diabetes, %	13.4	13.2	0.86
Pulmonary disease, %	5.6	3.6	0.02
Digestive disease, %	7.8	8.8	0.37
Osteoarthritis, %	13.6	18.21	0.002
Minor trauma fracture, %	5.2	4.0	0.14

SD = standard deviation; IADLs = instrumental activities of daily living.

Table 3-2 Characteristics of the sample according to frailty status (*n*=1,565).

Variable	Non-frail (*n*=729)	Pre-frail (*n*=687)	Frail (*n*=149)	*p* for trend
Age (yr), mean ± SD	71.5 ± 5.1	74.0 ± 5.9	79.2 ± 6.1	<0.001
Men, *n* (%)	292 (40.1)	274 (40.0)	59 (39.6)	0.91
Education (yr), mean ± SD	11.5 ± 2.5	10.9 ± 2.4	10.2 ± 2.1	<0.001
Living alone, *n* (%)	79 (10.8)	104 (15.1)	22 (14.8)	0.03
Current smoker, *n* (%)	56 (7.7)	54 (7.9)	9 (6.0)	0.67
Current drinker, *n* (%)	311 (42.6)	267 (38.9)	39 (26.2)	<0.001
IADLs limitation (difficulty ≥ 1 task), *n* (%)	43 (5.9)	72 (10.5)	23 (15.4)	<0.001
Hypertension, *n* (%)	249 (34.2)	289 (42.1)	61 (41.0)	0.007
Stroke, *n* (%)	19 (2.6)	29 (4.2)	9 (6.0)	0.02
Chronic heart disease, *n* (%)	77 (10.6)	98 (14.3)	43 (28.9)	<0.001
Diabetes, *n* (%)	76 (10.4)	99 (14.4)	31 (20.8)	<0.001
Pulmonary disease, *n* (%)	20 (2.7)	25 (3.6)	12 (8.1)	0.007
Digestive disease, *n* (%)	57 (7.8)	59 (8.6)	21 (14.1)	0.04
Osteoarthritis, *n* (%)	106 (14.5)	121 (17.6)	58 (38.9)	<0.001
Minor trauma fracture, *n* (%)	17 (2.3)	30 (4.4)	15 (10.1)	<0.001

SD = standard deviation; IADLs = instrumental activities of daily living.

Table 3-3 Mean scores for cognitive measures by frailty status (*n*=1,565).

Variable	Non-frail (*n*=729)	Pre-frail (*n*=687)	Frail (*n*=149)	*p* for trend†
MoCA score, absolute mean ± SD	22.91 ± 3.50	21.89 ± 3.66	19.24 ± 4.01	<0.001
MoCA score, adjusted marginal mean ± SE‡	22.44 ± 0.13	22.10 ± 0.13	20.49 ± 0.29	<0.001
MoCA subdomains/range, mean ± SD§				
Visuospatial abilities/0-4	3.31 ± 0.75	3.13 ± 0.85	2.74 ± 0.87	<0.001
Short-term memory/0-5	2.27 ± 1.65	2.03 ± 1.65	1.21 ± 1.50	<0.001
Executive function/0-3	2.04 ± 0.89	1.91 ± 0.88	1.52 ± 0.99	<0.001
Attention, concentration, working memory/0-6	5.04 ± 1.03	4.81 ± 1.16	4.40 ± 1.28	<0.001
Language/0-6	4.35 ± 1.08	4.14 ± 1.07	3.64 ± 1.13	<0.001
Orientation/0-6	5.89 ± 0.44	5.87 ± 0.44	5.72 ± 0.70	0.003
MMSE score, absolute mean ± SD	27.96 ± 2.03	27.52 ± 2.25	26.57 ± 2.86	<0.001
MMSE score, adjusted marginal mean ± SE‡	27.75 ± 0.08	27.56 ± 0.08	27.03 ± 0.18	<0.001
MMSE subdomains/range, mean ± SD¶				
Visual-constructional ability/0-1	0.93 ± 0.25	0.91 ± 0.29	0.86 ± 0.35	0.004
Registration/0-3	2.96 ± 0.22	2.96 ± 0.21	2.86 ± 0.48	0.03
Recall/0-3	2.52 ± 0.71	2.44 ± 0.74	2.24 ± 0.93	<0.001
Attention/0-5	3.89 ± 1.24	3.66 ± 1.39	3.42 ± 1.52	<0.001
Language/0-8	7.83 ± 0.44	7.80 ± 0.48	7.68 ± 0.60	0.003
Orientation/0-10	9.81 ± 0.54	9.75 ± 0.61	9.51 ± 0.98	<0.001

SD = standard deviation; SE = standard error; MoCA = Montreal Cognitive Assessment; MMSE = Mini-Mental State Examination.

† *p* for trend across non-frail, pre-frail and frail groups from the Jonckheere-Terpstra test.

‡ Marginal means adjusted for age, age squared, gender and education, with *p* for trend from linear contrast tests across frailty categories

§ MoCA domain-specific score details: Visuospatial abilities/4: clock drawing, copy a cube; Short-term memory/5: 5-word delayed recall; Executive function/3: trail making test-B, verbal abstraction; Attention, Concentration, Working memory/6: target detection using finger tapping, serial 7 subtraction, digits span ; Language/6: naming three items, phonemic fluency, sentence repeating; Orientation/6: year, month, date, day, place, city.

¶ MMSE domain-specific score details: Visual-constructional ability/1: copy overlapping pentagons; Registration/3: repeat 3 words; Recall/3: recall 3 words; Attention/5: serial 7 subtraction; Language/8: naming 2 items, 1 sentence repetition, 3-stage command, visual commands, writing a sentence; Orientation/10: year, month, date, day, place, prefecture, city, town, building, floor.

Table 3-4 Associations of Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) with frailty status based on multinomial logistic regression (n=1,565).

Independent variables		Pre-frail vs. non-frail OR (95% CI)	Frail vs. non-frail OR (95% CI)	AIC of Model†
MoCA Z score	Crude model	0.74 (0.66-0.82) *	0.39 (0.33-0.47) *	2836
	Adjusted model	0.90 (0.79-1.02)	0.53 (0.43-0.66) *	2654
MMSE Z score	Crude model	0.80 (0.71-0.89) *	0.58 (0.50-0.68) *	2907
	Adjusted model	0.90 (0.79-1.01)	0.73 (0.60-0.88) *	2677

Notes. OR = odds ratio; CI = confidence interval; AIC = Akaike's Information Criterion.

* $p < 0.05$. † Smaller AIC indicates a better fitted model. Models were adjusted for age, gender, education (years of schooling), drinking, smoking, living alone, IADLs and a history of having ever been diagnosed with hypertension, stroke, chronic heart disease, diabetes mellitus, pulmonary disease, digestive disease, osteoarthritis, and minor trauma fracture.

Table 3-5 Associations between specific-domain scores (Z scores) of Montreal Cognitive Assessment (MoCA) and Mini-Mental State Examination (MMSE) and frailty status (*n*=1,565).

Independent variables	Pre-frail vs. Non-frail			Frail vs. Non-frail		
	Crude model OR (95% CI)	Adjusted model a OR (95% CI)	Adjusted model b OR (95% CI)	Crude model OR (95% CI)	Adjusted model a OR (95% CI)	Adjusted model b OR (95% CI)
MoCA subdomains						
Visuospatial abilities	0.79 (0.71-0.88)*	0.85 (0.76-0.95)*	0.86 (0.77-0.97)*	0.52 (0.44-0.62)*	0.57 (0.46-0.69)*	0.64 (0.51-0.79)*
Short-term memory	0.86 (0.78-0.96)*	1.04 (0.93-1.18)	1.06 (0.94-1.20)	0.49 (0.40-0.60)*	0.76 (0.60-0.96)*	0.87 (0.68-1.11)
Executive function	0.85 (0.77-0.95)*	0.95 (0.85-1.06)	0.99 (0.88-1.11)	0.57 (0.48-0.68)*	0.66 (0.54-0.81)*	0.81 (0.65-1.01)
Attention, concentration, working memory	0.91 (0.82-1.02)	0.87 (0.78-0.98)*	1.00 (0.89-1.13)	0.68 (0.59-0.78)*	0.66 (0.55-0.80)*	0.77 (0.69-0.90)*
Language	0.81 (0.73-0.91)*	0.95 (0.84-1.07)	0.99 (0.87-1.12)	0.53 (0.44-0.63)*	0.70 (0.57-0.86)*	0.87 (0.69-1.09)
Orientation	0.94 (0.84-1.06)	1.01 (0.89-1.14)	1.04 (0.92-1.18)	0.78 (0.68-0.90)*	0.93 (0.79-1.11)	1.07 (0.89-1.27)
MMSE subdomains						
Visual-constructional ability	0.91 (0.82-1.01)	0.92 (0.82-1.03)	0.93 (0.83-1.04)	0.79 (0.68-0.92)*	0.80 (0.67-0.96)*	0.81 (0.68-0.97)*
Registration	1.01 (0.90-1.14)	1.09 (0.96-1.24)	1.12 (0.98-1.27)	0.79 (0.70-1.90)	0.91 (0.78-1.05)	0.97 (0.82-1.13)
Recall	0.89 (0.80-0.99)*	1.00 (0.89-1.12)	1.01 (0.90-1.14)	0.71 (0.61-0.84)*	0.92 (0.76-1.11)	0.98 (0.81-1.19)
Attention	0.83 (0.75-0.92)*	0.86 (0.77-0.96)*	0.84 (0.68-1.03)	0.71 (0.60-0.84)*	0.77 (0.63-0.94)*	0.85 (0.76-0.96)*
Language	0.94 (0.84-1.04)	1.00 (0.89-1.13)	1.03 (0.92-1.17)	0.77 (0.67-0.89)*	0.85 (0.71-1.01)	0.93 (0.77-1.13)
Orientation	0.87 (0.77-0.97)*	0.96 (0.85-1.09)	0.98 (0.86-1.12)	0.69 (0.60-0.79)*	0.85 (0.72-1.01)	0.93 (0.78-1.12)

Notes. OR = odds ratio; CI = confidence interval. * $p < 0.05$. Model a was adjusted for age, age squared, gender, education (years of schooling), drinking, smoking, living alone, IADLs and a history of having ever been diagnosed with hypertension, stroke, chronic heart disease, diabetes mellitus, pulmonary disease, digestive disease, osteoarthritis, and minor trauma fracture. Model b was mutually adjusted for other MMSE or MoCA subdomains, along with all covariates.

Chapter 4 - General Discussion

The general purpose of this doctoral dissertation research was to provide empirical and methodological evidence of frailty phenotype and its association with cognitive function, using epidemiological observational data from a large cohort of 2,629 community-dwelling older adults. Specifically, this dissertation research (a) facilitated the screening of frailty by defining the low physical activity using a tri-axial accelerometer in the primary care setting and examine the correlates of frailty; and (b) explored the association between frailty and global cognitive performance, and specific cognitive domains among relatively functional and non-demented older adults, which may indicate possible common pathways that can be targeted in interventions for both of frailty and cognitive decline at early stage.

This research has made several important contributions to the better understanding of frailty and its association with cognitive function. With the application of objectively-measured component of low physical activity for screening of frailty phenotype, the comprehensive physical assessment with objective measurement, the examination of potential correlates of frailty, and the use of a large non-demented target population, this research and its findings provide empirical, and methodological contributions to the understanding of frailty and its association with cognitive function. The empirical and methodological contributions will be described as follows.

4-1 Empirical Contributions

In this research, frailty is prevalent in older adults. Overall, the estimated prevalence of frailty was 9.3% (95% confidence intervals, CI, 8.4-11.2); 43.9% were pre-frail (95%

CI, 41.5-46.4). In other words, approximately one out of ten elderly adults aged 65 and over in this community-dwelling population were affected by frailty. The care burden of frailty is the focus of exponentially rising demands for public healthcare resources. Therefore, early detection of frailty before decreased reserves or deficits become more pronounced is of public health importance, which helps to shift towards more appropriate goal-directed and individualized care provision. Of note, more emphasis could be placed on the pre-frail category, the intermediate status, as potentially intervention may be even more effective by reducing the likelihood of progression into the frail state.

Increased age, poorer self-perceived health, depressive and anxiety symptoms, not consuming alcohol, no engagement in social activities, and cognitive impairment were associated with increased odds of frailty status, independent of co-morbidities. Although gender was not independently associated with frailty, the correlates of frailty were different when stratifying the study subjects by gender. Specifically, the associations of living alone, non-drinking, social isolation and no social participation with frailty were significant among women but not among men, indicating that the effect of those correlates of frailty appear to be moderated by gender. The results also showed that socioeconomic status characteristics do not account for the presence of frailty. These findings may contribute to better predicting risk of frailty and developing multidimensional approaches for prevention, evaluation and interventions of frailty among community-dwelling older adults, since frailty is a not an irreversible process.

This research further contributed to elucidate the complex relationship between frailty and cognition amongst non-demented community-dwelling older adults using two

measurements of global cognitive function. Both total MMSE and MoCA scores and their domain-specific scores decreased across the non-frail, pre-frail and frail groups, indicating a possible dose-response relationship between cognition and frailty status. Poorer total MoCA and MMSE scores, as well as their domain-specific scores, were associated with the greater likelihood of being frail. The strength of the association with frailty was greater for total MoCA score than for total MMSE score. Domain-specific scores for visuospatial abilities and attention domains in both of the MoCA and MMSE were consistently associated with the likelihood of pre-frailty and frailty, even after mutually adjusted for all domains. The MoCA performance is more strongly associated with the odds of frailty than the MMSE performance in the relatively functional and non-demented older adult population. The MoCA is able to more easily capture subtle cognitive decline. Therefore community-dwelling non-demented persons without functional impairment in ADL would be better assessed by the MoCA as first cognitive screening to understand the relation between frailty and cognitive decline at early stage. These findings may contribute to further exploration of possible common pathways that can be targeted in prevention and management for both of these two conditions.

The individual components of frailty phenotype have been shown to predict cognitive decline (Robertson et al. 2013). The Swedish Adoption/Twin Study of Aging with a longitudinal follow-up of 6 waves during 20 years reported that weaker grip strength performance was associated with decline in cognitive abilities after age 65 years (Sternang et al. 2015). In a prospective study of 666 cognitively intact older adults aged 70 years or older with a median follow-up of 2.7 years, gait speed, as well as step length and step frequency predicted subsequent cognitive decline. (Taniguchi et al. 2012). A mete-analysis of prospective studies showed that low physical activity was associated

with increased risk of cognitive decline amongst non-demented subjects (Sofi et al. 2011). Weight loss predicted lower MMSE scores in men (Auyeung et al. 2011), and strong links have been found between weight loss with the intermediate, advanced stages of Alzheimer's disease and cognitive symptoms (Sergi et al. 2013). However, when restricted to studies that defined frailty with Frailty Index, it is the number of health deficits (used to define the Frailty Index) that related with cognition rather than the type of health deficits which one measures which predict cognitive decline (Song et al. 2011). Therefore, it is likely that the underlying frailty characterized by decreased reserve with great vulnerability to stressors, not simply the individual symptoms of frailty phenotype, are possibly linked to cognitive decline, regardless of the operational definition models that used to define frailty (Robertson et al. 2013).

The mechanisms underlying the links between cognition and frailty are multifactorial, and vascular, inflammatory, nutritional, and metabolic influences may be of major relevance (Halil et al. 2015; Robertson et al. 2013). Nevertheless, the significant association of frailty and cognitive performance in this older population who were non-demented and relatively functional, as observed in this research, indicated that there could seemly be other intrinsic pathological pathways that do not act through known neuropathology to cause both frailty and cognitive decline. Therefore how frailty and cognitive decline relate to each other in non-demented subjects is noteworthy and merits further studies to explore the mechanisms in depth behind the link with taking these possible common risk factors into account. All taken together, more studies are needed to confirm these findings to disentangle the complex relationship between frailty and cognition.

4-2 Methodological Contributions

The methodological contributions of this research include the use of objective measurement of low physical activity component for operational definition of frailty phenotype, and the incorporation of latent class analysis into statistical analysis as a way to confirm the internal construct validity of the frailty phenotype in the Sasaguri Genkimon Study. The low physical activity domain of the frailty phenotype has been assessed with various self-reported questionnaires, which are prone to possible recall bias and a lack of diagnostic accuracy. Accelerometry, an objective measurement of physical activity, has been growingly diffused in the general populations under free-living conditions and can be administrated by non-professionals. This research conducted objective measurement of physical activity using a device of tri-axial accelerometer, which adopts a simple algorithm for the classification of household and locomotive activities and permits more accurate and immediate estimation of daily physical activity intensities (Ohkawara et al. 2011). Accelerometry may potentially standardize the measurement of low physical activity and improve the diagnostic accuracy of the frailty phenotype criteria.

Latent class analysis is also an important methodological contribution to note. The latent class analysis showed that the objectively-measured low physical activity components aggregated statistically into a syndrome with other components of frailty phenotype. It contributed to confirming the internal construct validity of the frailty phenotype that defined the low energy expenditure domain with the objective measurement of physical activity. Latent class analysis is a statistical technique for the analysis of multivariate categorical data and when observed data take the form of a series of categorical response, it is often of interest to identify and characterize clusters of similar cases, and

approximate the distribution of observations across the many variables of interest (Linzer & Lewis 2011). Given that the components of frailty are age-related factors interacted in a circle as mentioned in the introduction of frailty phenotype, it is important that robust statistical approaches to confirm internal construct validity are incorporated into studies of improving frailty phenotype screening.

4-3 Implications for Research

This research has shown that frailty is associated with cognitive function among community-dwelling non-demented elderly in the cross-sectional analysis. It can be speculated that the relationship between frailty and cognition is likely to be bi-directional or reciprocal. Therefore, in the further studies, one of hypotheses is that low cognitive scores would influence transitions from non-frail state to being pre-frail or frail, and being pre-frail or frail relates to cognitive performance changes over time. Knowing how physical frailty and cognitive decline mutually influence each other over time enables development of intervention strategies for preventing or delaying both conditions so as to break the interacting cycle between physical frailty and cognitive decline.

In addition, existing evidence of the mechanisms behind the link between frailty and cognition cannot explain the association of the two conditions we have observed in the relatively functional and non-demented older adult population. Therefore, there is possibility that common risk/protective factors of frailty and cognitive impairment, such as socioeconomic status, health-related and lifestyle factors, exist. Thus, in the future study, another hypothesis that there are shared risk/protective factors relates to changes of physical frailty and cognitive function over time should be tested. By modifying a

shared set of risk/protective factors, compensatory physical and cognitive reserve may be possibly restored and the onset of physical and cognitive decline may be prevented or delayed, and perhaps, a more unified intervention approach can be taken to prevention of both of the two conditions

In spite of widespread diffusion, this frailty phenotype was argued to place too much emphasis on physical losses of the older people (Gobbens, Luijkx, et al. 2010). Particularly, several investigators proposed cognition as one frailty component on the ground that cognitive impairment has been reported to strongly relate to the circle of frailty and improve the predictive validity of frailty phenotype for adverse health outcomes in different populations (Walston et al. 2006; Avila-Funes et al. 2009). Moreover, recently a concept of cognitive frailty was proposed to define reduced cognitive reserve related to physical frailty with a potential reversibility of clinical representation (Kelaiditi et al. 2013). Nevertheless, there is a lack of consensus on defining the concept of cognitive frailty. The proposed definition also addresses a current gap in the literature of the identification of cognitive frailty and how cognitive frailty relates to health outcomes, such as needs for long-term care and health service utilization. The attempt to identify the novel proposed clinical entity of cognitive frailty and to examine the relationship between cognitive frailty and needs for long-term care and health care utilization would suggest the significance of preventing cognitive frailty for decreasing the healthcare burden on the aging society and families, and may provide a stimulus for new research in the field of aging research.

4-4 Implications for Practice

Although the findings of the research are very limited, some practice implications

related to findings can be suggested by adding the findings to the existing body of evidence. Firstly, the simple, quick, and accurate assessment of physical activity may facilitate wide diffusion of screening for frailty phenotype in community-dwelling older populations. Secondly, early detection and interventions into frailty with cognitive decline need to target non-demented community-dwelling older population before subtle cognitive decline or pre-frailty become more pronounced. In the primary care settings, the evaluation of cognitively impaired older patients with a multidimensional frailty instrument may be useful in identifying possible links among various frailty domains and cognitive impairment, opening new viable routes for the prevention of dementia (Panza et al. 2011). Multi-dimensional interventions focusing on physical, nutritional, cognitive and psychological domains may be helpful with improving the well-being and quality of life in the elderly (Kelaiditi et al. 2013).

The cognitive benefits of physical activity and nutrition have been extensively investigated (Denkinger et al. 2012; Coley et al. 2015). Exercise programme, nutritional supplementation and reduction of polypharmacy improved health outcomes for frail older people (Morley et al. 2013; Clegg et al. 2014; Theou et al. 2011). Multi-factorial interventions were effective on the prevention from development of frailty in older people who are pre-frail (Fairhall et al. 2015). Although evidence for interventions into frailty with cognitive decline is scare, nutrition suggests new viable routes for prevention of both conditions (Panza et al. 2014). Besides, the simultaneous training of cognitive and physical abilities improved cognitive and physical function (Theill et al. 2013; Halil et al. 2015). Physical-cognitive dual-task performance was associated with better cognitive performance in patients with mild Alzheimer's disease (Sobol et al. 2015). Dual-task training may present a promising training method to simultaneously

delay the onset or slow down the progression of cognitive decline and frailty.

4-5 Strengths and Limitations

There are several strength in this research. To our knowledge, the research is the first attempt to date using a tri-axial accelerometer to define energy expenditure of physical activity for the frailty phenotype. This research examined a wide range of potential correlates of frailty covering social, psychological, environmental, and health-related factors. The last but not the least strength of this research is its comprehensive physical assessment. The objective measurement of gait speed, grip strength, and physical activity enabled the lowest quintile approach for cutoff points of frailty criteria in the Sasaguri Genkimon Study, which were very close to and to some extent superior to the original Fried criteria in terms of the objectively-measured physical activity.

This research also has several limitations worth mentioning. The sample of the Sasaguri Genkimon Study was not nationally representative, thus the findings may not be generalizable to different populations. The relatively low response rate could have led to overestimation of the lowest quintile values, and selection bias which may to some extent be attributable to the observed stronger association of the MoCA with frailty than the MMSE. However, given the similar prevalence in the present research and previous studies, it may be extrapolated that potential response or selection biases would not tend to lead to underestimation or over-estimation in the prevalence of frailty. The possibility of undiagnosed dementia among participants included in the final sample cannot be ruled out, which may consequently increase the measurement error of self-reported measures. The cross-sectional design prevents conclusions of directional relationships. Longitudinal studies are needed to confirm the directional relationship.

4-6 Conclusions

This research has contributed to the understanding of frailty and its association with cognition in several ways. The findings of the present research confirmed the internal construct validity of the frailty phenotype that defined the low energy expenditure domain with the objective measurement of physical activity. Accelerometry may potentially standardize the measurement of low physical activity and improve the diagnostic accuracy of the frailty phenotype criteria in primary care setting. The potential role of factors associated with frailty merits further studies to explore their clinical application. In addition, there are significant differences in global cognitive performance among the non-frail, pre-frail and frail subpopulations. The significant association of frailty and cognitive performance in this non-demented and relatively functional population indicated that there could seemly be other intrinsic pathological/etiological pathways behind this link. Further studies are needed to disentangling possible common pathways that can be targeted in prevention and management for both of these two conditions.

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